ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 May 16; 11(14): 3114-3368

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 14 May 16, 2023

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 14 May 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 14 May 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 14 May 16, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Jaw-Yuan Wang, MD, PhD, Professor, Surgical Oncologist, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan. jawyuanwang@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
May 16, 2023

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3114-3127

DOI: 10.12998/wjcc.v11.i14.3114

ISSN 2307-8960 (online)

OPINION REVIEW

Modernising autism spectrum disorder model engineering and treatment *via* CRISPR-Cas9: A gene reprogramming approach

Arushi Sandhu, Anil Kumar, Kajal Rawat, Vipasha Gautam, Antika Sharma, Lekha Saha

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Haggar M, Egypt; Siniscalco D, Italy; Zhu WF, China

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: January 30, 2023
Revised: February 13, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Arushi Sandhu, Anil Kumar, Kajal Rawat, Vipasha Gautam, Antika Sharma, Lekha Saha, Department of Pharmacology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 0172, Chandigarh, India

Corresponding author: Lekha Saha, MBBS, MD, MNAMS, Full Professor, Professor, Department of Pharmacology, Post Graduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh 0172, Chandigarh, India. lekhasaha@rediffmail.com

Abstract

A neurological abnormality called autism spectrum disorder (ASD) affects how a person perceives and interacts with others, leading to social interaction and communication issues. Limited and recurring behavioural patterns are another feature of the illness. Multiple mutations throughout development are the source of the neurodevelopmental disorder autism. However, a well-established model and perfect treatment for this spectrum disease has not been discovered. The rising era of the clustered regularly interspaced palindromic repeats (CRISPR)-associated protein 9 (Cas9) system can streamline the complexity underlying the pathogenesis of ASD. The CRISPR-Cas9 system is a powerful genetic engineering tool used to edit the genome at the targeted site in a precise manner. The major hurdle in studying ASD is the lack of appropriate animal models presenting the complex symptoms of ASD. Therefore, CRISPR-Cas9 is being used worldwide to mimic the ASD-like pathology in various systems like *in vitro* cell lines, *in vitro* 3D organoid models and *in vivo* animal models. Apart from being used in establishing ASD models, CRISPR-Cas9 can also be used to treat the complexities of ASD. The aim of this review was to summarize and critically analyse the CRISPR-Cas9-mediated discoveries in the field of ASD.

Key Words: Autism spectrum disorder; CRISPR-Cas9; Cellular models; Organoids; Animal models; Therapeutic strategies

Core Tip: There are several reviews in the literature explaining the underlying mechanisms contributing to the pathophysiology of autism spectrum disorder by performing several preclinical experiments. Given the significant role of genetics (de novo or inheritable) in the development of autism spectrum disorder, disease specific models should be established for investigating the mechanism involved. Therefore, this review specifically focused on the use of an emerging genomic editing tool, clustered regularly interspaced palindromic repeats/Cas9, for generating different types of preclinical models as well as new therapeutic options, providing a novel insight into the disease.

Citation: Sandhu A, Kumar A, Rawat K, Gautam V, Sharma A, Saha L. Modernising autism spectrum disorder model engineering and treatment *via* CRISPR-Cas9: A gene reprogramming approach. *World J Clin Cases* 2023; 11(14): 3114-3127
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3114.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3114

INTRODUCTION

Identifying the double helix DNA structure and finding technologies to manipulate it ultimately led to an extensive investigation of genomic structure[1]. Manipulation of genomic structure requires various genomic editing techniques including homing-endonucleases or mega nucleases, zinc finger nucleases, transcription activator like effector nucleases and clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9)[2]. Advancement in this field has permitted researchers to alter the DNA of model organisms to obtain the model of interest. In this context, the discovery of the CRISPR-Cas9 system has greatly and enormously expanded the field of study related to the genetic underpinnings of complex and heterogeneous disorders like autism spectrum disorder (ASD)[3]. From bacterial defence systems to genomic engineering tools, CRISPR-Cas9 has been proven beneficial in providing a novel insight into a possible genetic mutation in ASD[4].

The spectrum of disorders under ASD is pervasive. Due to the complexity of this medical condition, it is challenging to determine the diagnostic threshold, making diagnosis difficult. Despite the apparent difficulties connected with identification of ASD aetiologies, intensive genetic investigations have shown that ASD has a substantial genetic basis. Genetic analysis has revealed many susceptibility genes [5]. In addition to this, ASD has been found to be associated with several other disorders such as anxiety, depression, attention-deficit hyperactivity disorder and obsessive-compulsive disorder[6] and with genetic syndromes like Rett syndrome, Angelman syndrome, Timothy epilepsy and Fragile-X syndrome[7,8]. Depending upon the origin of the condition, ASD is diagnosed as syndromic if it is due to specific genetic syndromes with well-defined aetiology, such as Rett syndrome, and it identified as non-syndromic if ASD is diagnosed as the first diagnosis in patients having less-characterized aetiology [9,10].

There are multiple factors involved that contribute to the development of ASD in cases of non-syndromic ASD[10]. Therefore, due to the several aetiologies involved, ASD is considered a heterogeneous group of highly heritable disorders[11,12], and their risk factors could be genetic as well as environmental. A significant role of genetics in the development of the disorder has been known for a long time as confirmed by a meta-analysis of twin studies, which stated that ASD is inherited nearly 64%-91% in monozygotic twins and around 30% in dizygotic twins[13-15].

Modelling of disease at *in vitro, in vivo* and organoid levels are major avenue of research for investigation of abnormal early brain development because several ASD-associated genes have been found to be highly expressed during prenatal brain development of patients[16]. CRISPR-Cas9 has been successfully used to generate genetically engineered models that could mimic the disorder. At the same time, gene therapies are one of the emerging fields in recent years aimed at curing a wide range of diseases including ASD. Moreover, based on the available genetic information, novel gene therapies have also been created, which may help identify the potential ASD therapy candidates. The advent of CRISPR-Cas9 in gene therapy has been helpful in either silencing the gene using non-homologous end joining or correcting the genetic mutation using non-homologous recombination[17]. These developments have given patients new hope regarding rational treatment against the disease. This article provided an overview of the potential use of CRISPR-Cas9 technology for the establishment of appropriate ASD models along with its application in therapeutic strategies at the genomic level.

GENETIC ARCHITECTURE OF ASD

The genetic background contributing to autism aetiology involves copy number variations, somatic mutations, *de novo* mutations, single nucleotide variations, insertions, deletions and chromosomal

abnormalities[18,19]. These factors interfere with the protein-coding genes involved in neuronal development and several other ASD candidate genes related to critical processes like DNA binding, transcription, postsynaptic density and neuroprotection[20]. Any alteration in well-known ASD-associated genes can ultimately result in impaired working of brain areas responsible for cognitive functions[21,22]. Forkhead box protein 1 (*FOXP1*) and fragile X messenger ribonucleoprotein 1 (*FMR1*) are transcription factors and regulating genes. Others, like methyl CpG binding protein 2 (*MECP2*), tuberous sclerosis 1 (*TSC1*), SH3- and multiple ankyrin repeats protein 1 (*SHANK1*), ubiquitin protein ligase E3A and contactin-associated protein-like 2 (*CNTNAP2*), are involved in a wide range of functions like chromatin remodelling, cell proliferation, maintaining synaptic activity, protein ubiquitination and cell adhesion, respectively. Moreover, mutations in *MECP2* and *FMR1* are related to genetic syndromes such as Rett syndrome and fragile X syndrome, respectively[3].

The latest advancements in the development of next-generation sequencing have offered opportunities for genetic analysis to elucidate the underlying genetic mechanisms of ASD[23]. Whole exome sequencing has revealed that some biallelic mutations in proximal assembly proteins, phenylalanine hydrolyses and spectrin repeat containing nuclear envelope protein 1 are associated with familial ASD[24]. These genes also include those that are known to control or be controlled by synaptic activity (*e.g.*, *MECP2*, spectrin repeat containing nuclear envelope protein 1). Genetic analysis using whole genome sequencing has shown that copy number variations and single nucleotide variations result in missense mutations with an overall increase in missense variants, including some ASD risk genes[25]. In addition to this, genome-wide association studies have been able to identify a few potential variants being implicated in the pathogenesis of ASD[26]. Altogether, mutations in specific genes, known to regulate the important biological pathways, neuronal networks, synaptic activity and plasticity, *etc*, contribute to development of ASD and associated clinical symptoms (Figure 1).

STRUCTURE AND FUNCTION OF CRISPR-Cas9

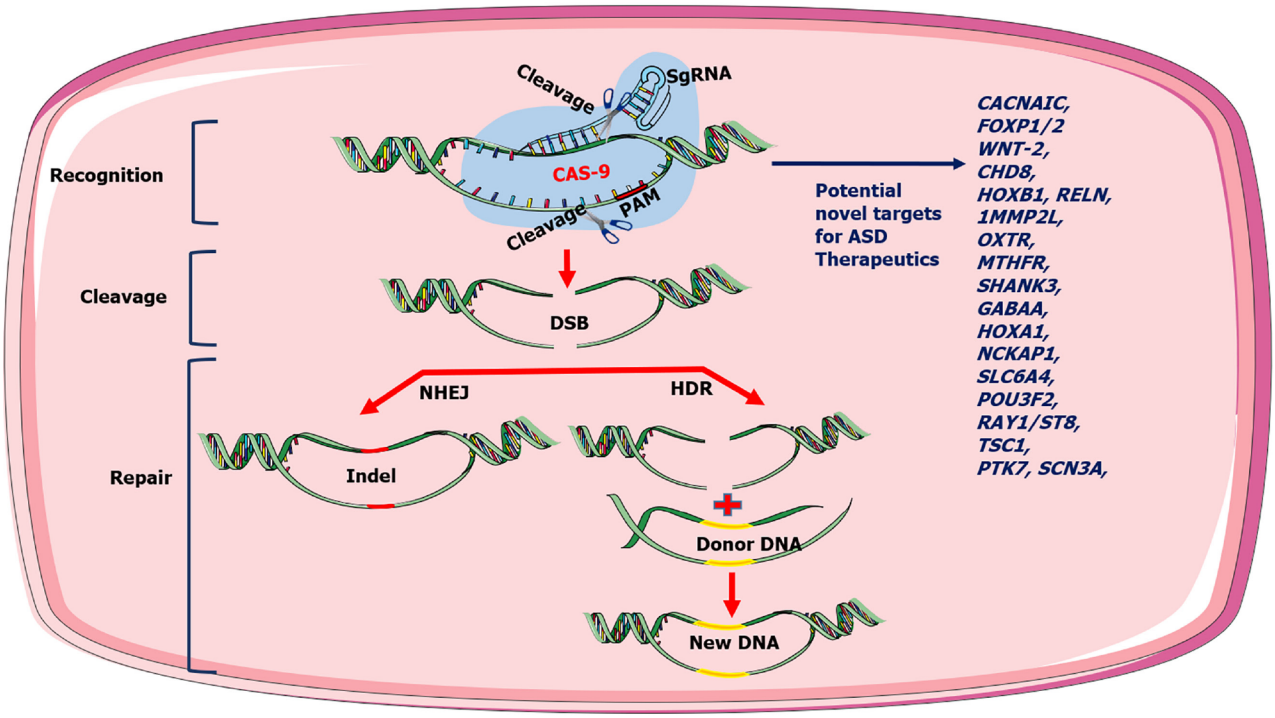
CRISPR-Cas9 is used to cut DNA at predetermined target locations. Although the method has already been revolutionised as a gene editing tool, researchers are constantly exploring new applications. Since being discovered as a bacterial immune system against invading viruses, CRISPR-Cas9 has been adapted as a powerful tool in genomic research. Repeat elements in CRISPR were initially noticed in *Escherichia coli* by Ishino *et al*[27]. Contrary to conventional tandem repeats in the genome, the CRISPR repeat clusters were interestingly separated by non-repeating DNA sequences known as spacers. Complete genome sequencing of bacteria and archaea led researchers to determine that these CRISPR elements are adjacent to well-conserved CRISPR-associated genes (Cas)[28]. This whole structure including palindromic repeats, spacer DNA and Cas gene is known as the CRISPR array. After a decade of research, scientists have finally discovered that the spacer DNA sequences belong to viruses[29,30].

The study by Gasiunas *et al*[31] provided the most significant experimental data about the potential utility of CRISPR systems for bacteria. The concept that the Cas9 enzymes in bacteria can be reprogrammed to target a specific DNA sequence has been the key discovery, which signalled the beginning of CRISPR as a biotechnological gene-editing tool[31,32]. CRISPR RNA and transactivating CRISPR RNA are both vital parts of guide RNA (gRNA) and are required for the functioning of the CRISPR system. Notably, Jinek *et al*[32] demonstrated that CRISPR-Cas9 could also be guided by single gRNA, a chimeric RNA created by joining transactivating CRISPR RNA and CRISPR RNA[32]. These studies were the reason for adopting CRISPR-Cas9 as a gene editing tool.

The ability of the CRISPR-Cas9 system to produce an autism model and its therapeutic potential are the main topics of this review. In 2012, Doudna and Charpentier[32] found that by using the appropriate template, CRISPR-Cas9 could be used to edit any desired DNA. Depending on how Cas proteins act, the CRISPR-Cas9 system has been divided into type I, type II and type III systems. Type II is the most well-studied and simplest for application in genetic engineering[33].

The Cas9 protein performs the function of genetic scissors in the type II system by producing a double-stranded break (DSB) in the DNA[34]. The Cas9 protein contains two structural lobes, one that aids in recognition (REC) and the other that aids in nuclease activity. The REC lobe consists of REC1 and REC2, which are involved in the recognition of gRNA. The nuclease also has a protospacer adjacent motif (PAM) interacting domain responsible for the binding of Cas9 to targeted DNA. The gRNA is used to target viral DNA in prokaryotes, but when utilised as a gene-editing tool, it can be synthetically constructed to target virtually any gene that needs to be changed.

The three phases of the CRISPR-Cas9 genome editing system are recognition, cleavage and repair [35]. Single gRNA binds to a complementary area on the targeted DNA to begin the recognition process. PAM is a 2–5 base pair sequence that has an "NGG" pattern, where "N" stands for any nucleotide followed by two guanine nucleotides. Once the PAM site is identified, double stranded DNA starts melting at the target site followed by an RNA-DNA hybrid formation. Now, the Cas9 protein is ready to make a DSB at the targeted DNA 3 base pairs upstream to PAM[36]. In the last step, the double stranded blunt ended breaks are repaired by non-homologous end joining and homology directed repair by cellular machinery[34,37,38]. By inserting a donor DNA template with sequence homology at the



DOI: 10.12998/wjcc.v11.i14.3114

Figure 1 Schematic diagram describing the structure and functioning of clustered regularly interspaced short palindromic repeats-associated protein 9 technique in autism spectrum disorder. In this schematic, we highlighted the mechanism of clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9) in recognizing a target using protospacer adjacent motifs sequencing and causing cut at specific point. Following cleavage and forming double stand breaks, repair systems like non-homologous end joining and homology directed repair come into play for avoiding any unspecific mutations. Diverse application of CRISPR-Cas9 has been explained in this diagram for investigating the mechanism involved in autism spectrum disorder pathophysiology. Various potential therapeutic targets for autism spectrum disorder could be investigated using CRISPR-Cas9 technology. sgRNA: Single guide RNA; ASD: Autism spectrum disorder; PAM: Protospacer adjacent motifs; DSB: Double strand breaks; NHEJ: Non-homologous end joining; HDR: Homology directed repair.

anticipated DSB site, homology directed repair carries out the precise gene insertion or replacement[39]. The property of CRISPR-Cas9 to either activate genes or to repress genes has been utilised to regulate the transcriptional level of gene expression.

CRISPR-Cas9 MEDIATED GENETIC ENGINEERING OF ASD

Most cases of ASD are idiopathic, with illusive aetiology[40]. The heterogeneous molecular nature of ASD makes it really difficult to understand the associated risk factors and the underlying mechanisms. Modelling ASD is notably challenging due to its multigenic aetiology. Only pertinent and validated disease-specific models could be helpful in discovering novel biomarkers and related therapeutic targets [41].

CRISPR-Cas9 engineered cellular models of ASD

Numerous neurodevelopmental diseases, including ASD are studied using cellular models because of the short experimental period and no ethical concerns and are less expensive. Researchers can create early human brain development, alterations in ASD or any other neurological disorders using *in vitro* models. Induced pluripotent stem cells (iPSCs), which can grow indefinitely *in vitro*, can be created by reprogramming somatic cells. Patient-derived cellular models have been validated and are realistic while preserving the genetic makeup of the donor and are an effective tool for deciphering the pathophysiology of ASD. The emergence of the genomic editing tool, CRISPR-Cas9, is helpful in facilitating more efficient *in vitro* models of ASD considering its genetic background. Using this technique, the researcher can edit primary cultured neural cells or isogenic cell lines by either introducing mutations derived from ASD patients or correcting them. Moreover, this technology reduces genetic background variation and directly correlates the observed symptoms and the associated mutation[42], which further provides information about the role of the particular ASD risk gene in neurodevelopment.

It is known that aberrant neurogenesis and synaptogenesis lead to functional impairments in brain networks in ASD[41]. Therefore, early molecular events during ASD development can be replicated in a model system in neurogenin 2-directed induced iPSCs (for excitatory neurons) that are further differentiated into forebrain glutamatergic neurons. Using that information and based on the whole exome sequencing results of some selected ASD-associated risk genes, the CRISPR-Cas9 approach was used to generate knockout (KO) iPSCs for the functional studies of the following genes: Anosmin 1; *FMR2*; calcium voltage-gated channel subunit alpha1 C; astrotactin 2; alpha-thalassemia/mental retardation, X-linked; chromodomain helicase DNA binding protein 8 (*CHD8*); disks large-associated protein 2; teneurin transmembrane protein 1; potassium voltage-gated channel subfamily q member 2; and sodium voltage-gated channel alpha subunit 2 (*SCN2A*). They revealed that ASD genes could result in similar electrophysiological phenotypes and transcriptional rewiring in the human iPSC-derived excitatory neurons model system[43].

Apart from the role of the *SHANK3* gene in synaptogenesis, one of the other consequences of its haploinsufficiency is hyperpolarization-activated cation channelopathy, which contributes to ASD pathogenesis. This impairment was analysed by generating *SHANK3* deletion by CRISPR in human embryonic stem cells[44]. Findings also highlighted that iPSC-derived glutamatergic neurons deficient in at least one allele of *CNTN5*/euchromatic histone lysine methyltransferase 2 resulting in ASD-associated phenotypes presented the increased synaptic activity of excitatory neurons *in vitro*[45]. In addition, CRISPR mediated inactivation of euchromatic histone lysine methyltransferase 1 in human neurons, which is directly associated with n-methyl-D-aspartate receptor hyperfunction and is implicated in ASD pathophysiology[46].

The major obstacle in the treatment of ASD is testing different drug candidates because of its aetiological heterogeneity. Therefore, an *in vitro* study has been done using the CRISPR tool for introducing mutations in activity-dependent neuroprotective protein, dead-box helicase 3 X-linked and *FOXP1* genes to create a relevant ASD model[47]. Similarly, hemizygous *CHD8* (*CHD8*+/−) iPSC lines were designed to investigate the role of *CHD8* in embryo development at the molecular and cellular levels. According to transcriptomic profiling, *CHD8* regulates several other genes connected to the development of ASD[48]. In addition to ASD-associated genes, the role of long noncoding RNAs, such as patched domain containing 1-antisense RNA[49]and molybdenum cofactor sulfurase[50], in ASD development was studied using CRISPR technology in human induced pluripotent stem cells (hiPSCs). Cellular models are briefly summarized in Table 1. These aforementioned findings indicate that these ASD associated genes may be a therapeutic target for the treatment of ASD.

CRISPR-Cas9 engineered organoids of ASD

The lack of suitable ASD models has always been a hindrance in ASD research because neither 2D cell culture nor animal models can accurately mimic the aetiology of ASD. Therefore, 3D *in vitro* models like organoids have recently emerged in the field of research. They have been shown to reproduce the gene expression profile, transcriptome, epigenome and disease dynamics of both idiopathic and syndromic ASD[51]. Like other cellular models, iPSC-derived organoids are being used because of no ethical concerns and are preferred over 2D culture and animal models as they can generate more disease-specific models.

This methodology has become even more reliable due to the integration of CRISPR-Cas9 to produce isogenic controls, significantly reducing genetic background differences. Idiopathic ASD has been connected to abnormalities in several genes, and genetic research has found multiple mutations that are linked to this condition[52]. Enhanced neurogenesis in idiopathic ASD has been studied through CRISPR engineered organoid models to create mutations in histone methyltransferase *SUV420H1*, the tumour suppressor phosphatase and TENsin homolog[53], *CHD8* and the GTPase-encoding RAS-related protein Rab-39B[54]. These genes are linked to macrocephalic ASD, and CRISPR-mediated deletion resulted in larger haploinsufficient cerebral organoids in comparison to isogenic control due to overactivation of the P13K-AKT-mTOR pathway[54].

Modelling of syndromic ASD is also being achieved using cerebral organoids to investigate the underlying genetic mechanism. One of the important ASD-associated genes *MECP2* is considered critical for early brain development, but its loss-of-function mutations are a common underlying aetiology of Rett syndrome[55], causing severe impairment in human interneurons and ultimately neurogenesis. Human *MECP2*-KO neurons and cortical organoids were used using CRISPR to investigate its neuropathological function[56,57]. Mutation (deletion) in *UBE3A* is also related to the pathology of syndromic ASD, and an organoid model derived from human iPSCs demonstrated hyperexcitability in brains contributing to network dysfunction[58].

Similarly, cerebral organoids are used for studying other syndromic ASD, such as a mutation in *TSC1/TSC2* genes in CRISPR-engineered human cortical spheroid model[59]. It caused synaptic imbalances, with an increase in γ-aminobutyric acid synapses[60]. Human corticostriatal organoids were studied using CRISPR-generated *SHANK3* gene deletion for modelling autism[61]. hiPSC-derived brain organoids with CRISPR-Cas9 induced *FMR1*-KO, which caused an abnormal increase in astrocyte number, was utilized to model FXS, a syndromic ASD[62]. Various organoid models of syndromic as well as idiopathic ASD is summarized in Table 1.

Table 1 Summary of clustered regularly interspaced palindromic repeats-associated protein 9 engineered models of autism spectrum disorder

Ref.	Model	Gene mutation/syndrome	Observed alterations
Cellular			
[32]	ES cells	*SHANK3*/Phelan-McDermid syndrome	Altered neuronal morphology and synaptic connectivity; impaired Ih channels
[33]	iPSCs	*CNTN5* or *EHMT2*/idiopathic ASD	Increased synaptic excitatory neuron activity
[34]	iPSCs	*EHMT1*/Kleefstra syndrome	Upregulation of NMDAR1; neuronal network impairments
[35]	iPSCs	*ADNP, DDX3X* and *FOXP1*/idiopathic ASD	Increased neurogenesis
[36]	iPSCs	*CHD8*/idiopathic ASD	Dysregulated expression of genes associated with human brain volume or head size
[37]	iPSCs	*PTCHD1-AS*/idiopathic ASD	Impaired excitatory synaptic function (NMDAR hypofunction); synaptic impairment
[38]	iPSCs	*COSMOC*/idiopathic ASD	Destabilization of lipid and energy metabolism; affected neuronal maturation
Organoids			
[41]	Cerebral	*PTEN*/idiopathic ASD, *CHD8*/idiopathic ASD, *SUV420H1*/ idiopathic ASD	Increased upper layer colossal neurons, cycling progenitor neuron; high outer radial glial cells; increased cortical interneurons; increased newly born deep layer projection neurons
[42]	Cerebral	*RAB39b*/ idiopathic ASD	Increased NPC proliferation
[44]	Cortical and neurons	*MECP2*/Rett syndrome	Dysregulation in genes of neuronal and glial cells
[46]	Cortical	*UBE3A*/ Angelman syndrome	Dysfunction in big potassium channel dysfunction causing increased neuronal excitability
[47]	Cortical	*TSC1 or 2*/Tuberous sclerosis complex	Affected cortical neurons and glial cell development
[49]	Cortico-striatal organoids	*SHANK3*/ Phelan-McDermid syndrome	Enhanced neuronal excitability; dysregulated expression of protocadherins and zinc-finger genes
[50]	Cortical	*FMR1*/Fragile X syndrome	Increased number of glial cells and bigger organoid size
Animal Models			
[52]	Cynomolgus macaques	*SHANK3*/ Phelan-McDermid syndrome	Sleep disturbances; increased repetitive behaviour, motor deficit; social and learning impairment; aberrant neural circuit connectivity
[53]	Mice	*ARID1B*/idiopathic ASD	Social behaviour impairment; altered vocalization; anxiety-like behaviour; neuroanatomical abnormalities; growth impairment
[54]	Mice	*CHD8*/idiopathic ASD	Cognitive impairment; disrupted pathways involved in neurogenesis, neuroimmune signalling, synaptic processes
[55]	Mice	*ASH1L*/idiopathic ASD	Dysregulated epigenetic modification; upregulation of neurexin-1α
[56]	Rat	*CYFIP1*/idiopathic ASD	Extensive changes in white matter; myelin sheath thinning in corpus callosum; abnormal oligodendrocytes; behavioural inflexibility
[57]	Rat	*TCF4*/idiopathic ASD	Attenuated action potential output; alteration in electrophysiological properties in neurons
[58]	Rat	*UBE3A*/idiopathic ASD	Deficits in motor coordination as well as learning and memory
[59]	Zebra fish	*CHD8*/idiopathic ASD	Increased head size; reduction in post mitotic enteric neurons
[60]	Zebra fish	*FMR1*/Fragile X syndrome	Abnormal behaviour; learning memory deficits; impaired craniofacial cartilage development
[61]	Zebra fish	*NR3C2*/idiopathic ASD	Disruption in sleep and social functions

[62]	Zebra fish	*SHANK3*/ Phelan-McDermid syndrome	Reduced social nitration and locomotory activity; repetitive swimming behaviour; reduced levels of post synaptic homer1 and presynaptic synaptophysin

ADNP: Activity-dependent neuroprotective protein; *ARID1B*: AT-rich interaction domain 1B; ASD: Autism spectrum disorder; *ASH1L*: ASH1-like histone lysine methyltransferase; *CHD8*: Chromodomain helicase DNA binding protein 8; *CNTN5*: Contactin-associated protein-like 5; *COSMOC*: Molybdenum cofactor sulfurase; *CYFIP1*: Cytoplasmic FMR1 interacting protein; *DDX3X*: Dead-box helicase 3 X-linked; *EHMT1/2*: Euchromatic histone lysine methyltransferase 1/2; *FMR1*: Fragile X messenger ribonucleoprotein 1; *FOXP1*: Forkhead box protein 1; ES: Embryonic stem; Ih: Hyperpolarization-activated cation; iPSC: Induced pluripotent stem cell; *MECP2*: Methyl CpG binding protein 2; *NMDAR1*: N-methyl-D-aspartate receptor 1; NPC: Neural progenitor cell; *NR3C2*: Nuclear receptor subfamily 3 group c member 2; *PTCHD1-AS*: Patched domain containing 1-antisense RNA; *PTEN*: Phosphatase and TENsin homolog; *RAB39b*: RAS-related protein Rab-39B; *SHANK3*: SH3- and multiple ankyrin repeats protein 3; *TSC1/2*: Tuberous sclerosis 1/2; *TCF4*: Transcription factor 4.

CRISPR-Cas9 engineered animal models of ASD

Despite the capabilities of *in vitro* models to recapitulate the basic aetiology of ASD, animal models are preferred as a more fundamental tool to fully understand the complexity involved in ASD. Animal models allow a researcher to investigate behavioural and developmental features in addition to molecular parameters. However, generating an ASD animal model is a time-consuming procedure and involves ethical concerns, but it is helpful in studying neurodevelopmental disorders. Moreover, in the case of ASD, it is helpful in validating the implication of critical genes in the development of ASD.

The emerging CRISPR-Cas9 approach has been a great help in creating various genetic animal models (KO, Knock-in, overexpression and point mutation) to study various ASD-associated genes identified in an individual with ASD. ASD models can be studied in multiple species like rodents including mice, rats, monkeys, fruit flies and zebrafish, depending upon the requirement and purpose of the experiment [63]. CRISPR-mediated generation of mutations in the *SHANK3* gene by creating insertions and deletions (indels) in exon 21 led to the development of an ASD model in monkeys and their F1 offspring, showing atypical autistic phenotypes like increased repetitive behaviour along with social and learning deficits[64].

Studies have reported that a CRISPR-mediated mutation in ASD-associated genes such as AT-rich interaction domain 1B[65], *CHD8*[66] and ASH1-like histone lysine methyltransferase[67] showed ASD-like symptoms in mice. To investigate genes implicated in ASD such as cytoplasmic FMR1 interacting protein[68], transcription factor 4[69] and *UBE3A*[70] in a rat model created with CRISPR engineered technology was studied. The rats showed autistic phenotypes like alteration in behavioural flexibility, learning ability and memory difficulties.

Similarly, a zebrafish model of ASD using the CRISPR strategy has been used to study the functional role of genes in the development of ASD such as *CHD8*[71], *FMR1*[72], nuclear receptor subfamily 3 group c member 2[73]and *SHANK3*[74]. Major ASD-linked phenotypes observed in these zebrafish models are macrocephaly, hyperactivity, anxiety, impaired social behaviour, sleep disturbances and altered neuronal development (summarized in Table 1).

CRISPR-Cas9-BASED THERAPEUTIC STRATEGIES AND POTENTIAL TARGETS

Over the years, the CRISPR-Cas9 genome editing tool has evolved as a specific delivery tool for delivering genes to the target cells including neural and brain cells. One such benchmark was set by Staahl *et al*[75], where the engineered variants of the Cas9 ribonucleoprotein complex were delivered to the mice hippocampus, striatum and cortex region and demonstrated the *in vivo* neuronal gene editing [75]. The advances in the genome editing tool have opened the door for eradicating the genetic mutations underlying severe neurological diseases like ASD.

Several genes that are linked to ASD can be targeted for correction using the CRISPR-Cas9 approach to reduce the disease burden (summarized in Figure 1). The genes that undergo mutations in ASD and ASD-associated monogenic syndromes include calcium voltage-gated channel subunit alpha1 C, *FOXP1/2*, wingless-related integration site-2, *CHD8*, homeobox B1, reelin, inner mitochondrial membrane peptidase subunit 2, oxytocin receptor gene, methylenetetrahydrofolate reductase, *SHANK2/3*, γ-aminobutyric acid type A receptor subunit, homeobox A1, *UBE3A*, NCK associated protein 1, human serotonin transporter gene, POU class 3 homeobox 2, reduced arabinose yariv1/suppression of tumorigenicity 8, *FMR1*[76-77], *MECP2, TSC1, PTK7, SCN3A* and *CNTNAP2*[78-82]. Some of these genes for monogenic syndromes associated with ASD are targeted using the CRISPR-Cas9 tool *in vitro* and *in vivo*; however, many others remain to be explored.

The lack of target specificity or the polygenic form of ASD limits the use of the CRISPR-Cas9 tool as a therapeutic strategy in ASD. The CRISPR-Cas9-based therapeutic strategies that had been explored are summarized in Table 2; They primarily consist of the monogenic form of ASD. One of the studies by Lee *et al*[83] demonstrated that gold nanoparticle delivery of CRISPR-Cas9 ribonucleoprotein rescued the

Table 2 Summary of clustered regularly interspaced palindromic repeats-associated protein 9 edited therapeutic targets of autism spectrum disorder

Ref.	*In vitro*/*in vivo*	Gene mutation/editing method	Observed alterations
[80-82]	BTBR T + tf/J (BTBR), *Fmr1* knockout, C57BL/6 mice	*mGluR5*	Rescued the exaggerated repetitive behaviours in mice caused by fragile X syndrome
[83]	HEK293 cell and Human iPSC (BCRT cell line)	*MECP2*	Reversal of ASD-associated Rett syndrome-like symptoms
[84]	RX41X iPSC and NOD/SCID female mice	*SHANK2*	Positive impact on nerve cells was reported like an increase in synapse number, dendritic complexity and length
[85]	C57BL/6 mice, Ube3a$^{m-/p+}$ mice and Ube3a$^{m-/pYFP}$ mice on the C57Bl/6	Antisense transcript of *UBE3A*	Rescued the anatomical and behavioural phenotypes in a mouse model of Angelman syndrome
[86]	HEK293FT cells	*FMR1*	Fragile X syndrome improved by knocking out the CGG
[89]	Mef2c L35P knock-in mouse	*MEF2C*	Reversal of autistic-like behaviour

ASD: Autism spectrum disorder; CGG: Cytosine-guanine-guanine; *FMR1*/*Fmr1*: Fragile X messenger ribonucleoprotein 1; iPSC: Induced pluripotent stem cell; *MECP2*: Methyl CpG binding protein 2; *MEF2C*: Myocyte-specific enhancer factor 2C; *mGluR5*: Metabotropic glutamate receptor subtype 5; *SHANK2*: SH3- and multiple ankyrin repeats protein 2.

exaggerated repetitive behaviours in mice caused by fragile X syndrome[83]. The study demonstrated minimal off-target effects, and the editing target used was the metabotropic glutamate receptor subtype 5 gene, one of the overexpressed targets in ASD-associated syndromes[83-85].

In another study, the CRISPR-Cas9 tool was used to correct the *MECP2* mutations responsible for ASD-associated Rett syndrome *via* homology directed repair in hiPSCs[86]. Loss-of-function mutations in the *SHANK2* gene has been associated with monogenic ASD. CRISPR-Cas9-mediated correction of a nonsense mutation on *SHANK2* was demonstrated in iPSCs, and the positive impacts on nerve cells were reported, including an increase in synapse number and dendritic complexity and length[87].

In Angelman syndrome (monogenic form of ASD) caused by deletion of the maternally inherited *UBE3A* allele, the CRISPR-Cas9 approach was used to knock out the antisense transcript of *UBE3A* in cultured human neurons and a mouse model. The antisense transcript of *UBE3A* is a long non-coding RNA that silences the paternal copy of the *UBE3A* allele and leads to the neurodevelopmental syndrome. The CRISPR-Cas9 approach was used to terminate the long non-coding RNA termed as antisense transcript of *UBE3A*, which led to the copy of the *UBE3A* allele available for transcription (activation of *UBE3A*) and hence rescued the anatomical and behavioural phenotypes in the mouse model of Angelman syndrome[88].

In another study, the CRISPR-Cas9 approach was used to improve fragile X syndrome by knocking out the cytosine-guanine-guanine (CGG) repeats expansion, recovering *FMR1* expression *in vitro*. *FMR1* encodes fragile X mental retardation protein, which undergoes epigenetic silencing because of the addition of CGG repeats and excessive DNA methylation, thus the CRISPR-Cas9 approach was used to excise the CGG expansion in the iPSCs[89]. A recent study used the CRISPR-Cas9 tool to activate the extracellular matrix receptor b3 integrin. The study also validated the involvement of b3 integrin haploinsufficiency in the pathophysiology of ASD and ASD-associated fragile X syndrome[90].

All CRISPR-Cas9-based therapeutic strategies established so far mainly comprise the proof of principle studies and have used the conventional homology-directed repair pathway to correct the mutations in the monogenic form of ASD. However, with the advancements in CRISPR-Cas9 genome editing tools, the most recently introduced concept of the base editing technique for more specific genome editing has been explored in fewer studies. One such study used CRISPR-Cas9-based cytidine base editors and the fourth generation base editor system to selectively modify the disco-interacting protein 2a and 2c genes in cell culture. Both of these genes are highly expressed in the central neuron system and known to be associated with ASD[91].

In another study, the CRISPR-mediated cytidine base editor system was used to restore the impairments in social interactions and repetitive behaviours in a knock-in mice model of autism. The *de novo* mutation in the gene myocyte-specific enhancer factor 2C was introduced in the mice brain, which displayed autistic-like behaviour. With the help of the base editing system the myocyte-specific enhancer factor 2C mutation was eradicated, and the reversal of symptoms was reported in mice[92]. A study demonstrated the use of CRISPR-Cas9 for correcting the mutation in *CNTNAP2* in an organoid model derived from patients with syndromic ASD by rescuing the phenotype of organoid overgrowth. This *CNTNAP2*-organoid model provided an opportunity for further mechanistic inquiry and development of new therapeutic strategies for ASD[93]. Another finding has shown the use of a CRISPR activation-based approach for rescuing abnormalities in *SCN2A* haploinsufficiency-associated ASD[94].

The CRISPR-Cas9 mediated base editing system is just the beginning of an era of targeted gene modification, which can bring a breakthrough in the treatment of ASD.

A plethora of studies is being conducted worldwide using several targets in cultured cells or in animal models. However, the extrapolation to patients has not been achieved yet. The advances in the techniques leading to improved specificity, targeted delivery and personalized therapeutics will definitely help in the bench-to-bedside conversion of these CRISPR-Cas9 based therapies and help in reducing the disease burden.

CONCLUSION

Understanding brain function and its complexities have only been made possible by emerging genomic engineering tools like transcription activator like effector nucleases, zinc finger nucleases and CRISPR-Cas9. Opportunities for manipulating the genome have created the possibility to generate models for understanding a complex neurological disorder like ASD. Among these genomic editing tools, CRISPR-Cas9 is being considered the most extensive and effective, with the advantages of low mutation rate, high target efficiency and cost-efficient. CRISPR has enabled the creation of models that reproduce exactly the same causal mutations identified in patients, which has made it possible to determine an appropriate and disease-specific drug therapy.

Owing to the heterogeneous nature of ASD, it is difficult to identify the exact cause of ASD in patients as it could be genetic or environmental. No standard medication has been developed for treating ASD, except for aripiprazole and risperidone for irritability and aggressiveness. Thus, creating a reliable model, establishing a causal factor and representing all the characteristics of the disease is difficult. *In vitro* modelling of ASD has been a great benefit for understanding the underlying mechanism involved in the pathogenesis of ASD. However, it does come with limitations like high heterogeneity among hiPSCs lines. Therefore, reprogramming strategies need to be optimized. CRISPR-Cas9 potentially overcome such limitations by generating isogenic cell lines and increasing the reproducibility of experiments.

To further investigate the pathogenesis of ASD, the genome of animals can be successfully edited to construct a validated KO and knock-in models using CRISPR. These animal models have been reported to present phenotypes, including neuroanatomical, behavioural and morphological characteristics, caused by ASD-associated genes. In that regard, such models are helpful in determining the aetiology of the condition as well as screening appropriate drugs to restore the altered phenotype. Advancement in genomic editing systems is an encouraging indication that could restore the wild-type sequence and potentially be effective in human treatment trials. Utilization of the CRISPR-Cas9 tool is not only limited to the modelling of ASD but also has been helpful in targeting the mutated genes and correcting them.

Based on the available genetic information, ASD-associated genes have been widely explored, but their therapeutic potential is limited to monogenic forms of ASD and remains unexplored in polygenic form of ASD. Also, due to lack of target specificity, genetic therapy using CRISPR-Cas9 is unable to target every ASD- associated gene. Other approaches, such as CRISPR-mediated activation of a gene in which nuclease-deficient Cas9 was fused with a transcriptional activator or the CRISPR-mediated base editor system in gene therapy, have been helpful in restoring and normalizing gene dosage in ASD. However, this method has not been explored well, and optimization of this procedure is necessary before utilization.

Despite advancements in CRISPR-Cas9 tools, there are certain numbers of limitations like off-targeting, delivery method and immunogenicity and associated risks that make it challenging to use in clinical trials. A high frequency of off-targets is a prime concern while using CRISPR for gene therapy because it can lead to further mutations in undesired genomic locations. However, emergence of bioinformatic tools have been helpful in reducing the off-target effects while predicting the off-target modifications. Another major concern is immunogenicity caused by the introduction of Cas9 and delivery methods using viral vectors. Cas9 is derived from *Streptococcus pyogenes*, which is responsible for various human infections. Therefore, many patients would already harbour pre-existing anti-Cas9 antibodies. Therefore, when it is introduced for therapy purposes in humans, it will be recognised as a foreign antigen. An immune response may develop and cause degradation of Cas9, which would prevent it from gene editing. Another safety concern is the DSBs induced by CRISPR, which often trigger apoptosis. In addition to this, induced DSBs have also resulted in unnecessary massive deletions and rearrangements of sequences, suggesting a significant safety concern for the clinical use of DSB-inducing CRISPR therapy.

Given the challenges involved in using these gene editing techniques, gene therapy is still a distant therapeutic approach. Considering all limitations and the need for improvising CRISPR technology, studies using genomic editing tools is limited to cultured cells or animal models. Extrapolation of such experiments in patients has not been yet achieved. Therefore, the application of results from preclinical studies to the clinical treatment of ASD will require extreme care.

FOOTNOTES

Author contributions: Sandhu A contributed to conceptualization, writing-original draft preparation, visualization and investigation, reviewing and editing; Kumar A, Rawat K and Sharma A wrote the original draft; Gautam V wrote the original draft and proofread; Saha L contributed to conceptualization, supervision, reviewing and editing.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

Country/Territory of origin: India

ORCID number: Lekha Saha 0000-0001-5925-7159.

S-Editor: Li L
L-Editor: Filipodia
P-Editor: Yu HG

REFERENCES

1 **Hsu PD**, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. *Cell* 2014; **157**: 1262-1278 [PMID: 24906146 DOI: 10.1016/j.cell.2014.05.010]
2 **Akram F**, Sahreen S, Aamir F, Haq IU, Malik K, Imtiaz M, Naseem W, Nasir N, Waheed HM. An Insight into Modern Targeted Genome-Editing Technologies with a Special Focus on CRISPR/Cas9 and its Applications. *Mol Biotechnol* 2023; **65**: 227-242 [PMID: 35474409 DOI: 10.1007/s12033-022-00501-4]
3 **Domadenik A**. Overview of current mouse models of autism and strategies for their development using CRISPR/Cas9 technology. *Acta Agric Slov* 2018; **112**: 19 [DOI: 10.14720/aas.2018.112.1.3]
4 **Singh V**, Gohil N, Ramírez García R, Braddick D, Fofié CK. Recent Advances in CRISPR-Cas9 Genome Editing Technology for Biological and Biomedical Investigations. *J Cell Biochem* 2018; **119**: 81-94 [PMID: 28544016 DOI: 10.1002/jcb.26165]
5 **Havdahl A**, Niarchou M, Starnawska A, Uddin M, van der Merwe C, Warrier V. Genetic contributions to autism spectrum disorder. *Psychol Med* 2021; **51**: 2260-2273 [PMID: 33634770 DOI: 10.1017/S0033291721000192]
6 **Yin J**, Schaaf CP. Autism genetics – an overview. *Prenat Diagn* 2017; **37**: 14-30 [PMID: 27743394 DOI: 10.1002/pd.4942]
7 **Peters SU**, Beaudet AL, Madduri N, Bacino CA. Autism in Angelman syndrome: implications for autism research. *Clin Genet* 2004; **66**: 530-536 [PMID: 15521981 DOI: 10.1111/j.1399-0004.2004.00362.x]
8 **Bey AL**, Jiang YH. Overview of mouse models of autism spectrum disorders. *Curr Protoc Pharmacol* 2014; **66**: 5.66.1-5.66.26 [PMID: 25181011 DOI: 10.1002/0471141755.ph0566s66]
9 **Schaefer GB**, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med* 2013; **15**: 399-407 [PMID: 23519317 DOI: 10.1038/gim.2013.32]
10 **Mitchell KJ (ed)**. The genetics of neurodevelopmental disorders. Hoboken, New Jersey: Wiley-Blackwell
11 **Bailey A**, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med* 1995; **25**: 63-77 [PMID: 7792363 DOI: 10.1017/s0033291700028099]
12 **Steffenburg S**, Gillberg C, Hellgren L, Andersson L, Gillberg IC, Jakobsson G, Bohman M. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry* 1989; **30**: 405-416 [PMID: 2745591 DOI: 10.1111/j.1469-7610.1989.tb00254.x]
13 **Tick B**, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry* 2016; **57**: 585-595 [PMID: 26709141 DOI: 10.1111/jcpp.12499]
14 **Folstein SE**, Rosen-Sheidley B. Genetics of autism: complex aetiology for a heterogeneous disorder. *Nat Rev Genet* 2001; **2**: 943-955 [PMID: 11733747 DOI: 10.1038/35103559]
15 **Rosenberg RE**, Law JK, Yenokyan G, McGready J, Kaufmann WE, Law PA. Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Arch Pediatr Adolesc Med* 2009; **163**: 907-914 [PMID: 19805709 DOI: 10.1001/archpediatrics.2009.98]
16 **Gordon A**, Geschwind DH. Human in vitro models for understanding mechanisms of autism spectrum disorder. *Mol Autism* 2020; **11**: 26 [PMID: 32299488 DOI: 10.1186/s13229-020-00332-7]
17 **Maeder ML**, Gersbach CA. Genome-editing Technologies for Gene and Cell Therapy. *Mol Ther* 2016; **24**: 430-446 [PMID: 26755333 DOI: 10.1038/mt.2016.10]
18 **Ramaswami G**, Geschwind DH. Genetics of autism spectrum disorder. *Handb Clin Neurol* 2018; **147**: 321-329 [PMID: 29325621 DOI: 10.1016/B978-0-444-63233-3.00021-X]
19 **Lupski JR**, Stankiewicz P. Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. *PloS Genet* 2005; **1**: e49 [PMID: 16444292 DOI: 10.1371/journal.pgen.0010049]

20 **Cook EH Jr**, Scherer SW. Copy-number variations associated with neuropsychiatric conditions. *Nature* 2008; **455**: 919-923 [PMID: 18923514 DOI: 10.1038/nature07458]

21 **Canitano R**, Bozzi Y. Editorial: Autism Spectrum Disorders: Developmental Trajectories, Neurobiological Basis, Treatment Update. *Front Psychiatry* 2017; **8**: 125 [PMID: 28751868 DOI: 10.3389/fpsyt.2017.00125]

22 **Giovedí S**, Corradi A, Fassio A, Benfenati F. Involvement of synaptic genes in the pathogenesis of autism spectrum disorders: the case of synapsins. *Front Pediatr* 2014; **2**: 94 [PMID: 25237665 DOI: 10.3389/fped.2014.00094]

23 **Perenthaler E**, Yousefi S, Niggl E, Barakat TS. Beyond the Exome: The Non-coding Genome and Enhancers in Neurodevelopmental Disorders and Malformations of Cortical Development. *Front Cell Neurosci* 2019; **13**: 352 [PMID: 31417368 DOI: 10.3389/fncel.2019.00352]

24 **Yu TW**, Chahrour MH, Coulter ME, Jiralerspong S, Okamura-Ikeda K, Ataman B, Schmitz-Abe K, Harmin DA, Adli M, Malik AN, D'Gama AM, Lim ET, Sanders SJ, Mochida GH, Partlow JN, Sunu CM, Felie JM, Rodriguez J, Nasir RH, Ware J, Joseph RM, Hill RS, Kwan BY, Al-Saffar M, Mukaddes NM, Hashmi A, Balkhy S, Gascon GG, Hisama FM, LeClair E, Poduri A, Oner O, Al-Saad S, Al-Awadi SA, Bastaki L, Ben-Omran T, Teebi AS, Al-Gazali L, Eapen V, Stevens CR, Rappaport L, Gabriel SB, Markianos K, State MW, Greenberg ME, Taniguchi H, Braverman NE, Morrow EM, Walsh CA. Using whole-exome sequencing to identify inherited causes of autism. *Neuron* 2013; **77**: 259-273 [PMID: 23352163 DOI: 10.1016/j.neuron.2012.11.002]

25 **Turner TN**, Coe BP, Dickel DE, Hoekzema K, Nelson BJ, Zody MC, Kronenberg ZN, Hormozdiari F, Raja A, Pennacchio LA, Darnell RB, Eichler EE. Genomic Patterns of De Novo Mutation in Simplex Autism. *Cell* 2017; **171**: 710-722.e12 [PMID: 28965761 DOI: 10.1016/j.cell.2017.08.047]

26 **Weiss LA**, Arking DE; Gene Discovery Project of Johns Hopkins & the Autism Consortium, Daly MJ, Chakravarti A. A genome-wide linkage and association scan reveals novel loci for autism. *Nature* 2009; **461**: 802-808 [PMID: 19812673 DOI: 10.1038/nature08490]

27 **Ishino Y**, Shinagawa H, Makino K, Amemura M, Nakata A. Nucleotide sequence of the iap gene, responsible for alkaline phosphatase isozyme conversion in Escherichia coli, and identification of the gene product. *J Bacteriol* 1987; **169**: 5429-5433 [PMID: 3316184 DOI: 10.1128/jb.169.12.5429-5433.1987]

28 **Jansen R**, Embden JD, Gaastra W, Schouls LM. Identification of genes that are associated with DNA repeats in prokaryotes. *Mol Microbiol* 2002; **43**: 1565-1575 [PMID: 11952905 DOI: 10.1046/j.1365-2958.2002.02839.x]

29 **Bolotin A**, Quinquis B, Sorokin A, Ehrlich SD. Clustered regularly interspaced short palindrome repeats (CRISPRs) have spacers of extrachromosomal origin. *Microbiology (Reading)* 2005; **151**: 2551-2561 [PMID: 16079334 DOI: 10.1099/mic.0.28048-0]

30 **Mojica FJ**, Díez-Villaseñor C, García-Martínez J, Soria E. Intervening sequences of regularly spaced prokaryotic repeats derive from foreign genetic elements. *J Mol Evol* 2005; **60**: 174-182 [PMID: 15791728 DOI: 10.1007/s00239-004-0046-3]

31 **Gasiunas G**, Barrangou R, Horvath P, Siksnys V. Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. *Proc Natl Acad Sci U S A* 2012; **109**: E2579-E2586 [PMID: 22949671 DOI: 10.1073/pnas.1208507109]

32 **Jinek M**, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 2012; **337**: 816-821 [PMID: 22745249 DOI: 10.1126/science.1225829]

33 **Liu Z**, Dong H, Cui Y, Cong L, Zhang D. Application of different types of CRISPR/Cas-based systems in bacteria. *Microb Cell Fact* 2020; **19**: 172 [PMID: 32883277 DOI: 10.1186/s12934-020-01431-z]

34 **Mei Y**, Wang Y, Chen H, Sun ZS, Ju XD. Recent Progress in CRISPR/Cas9 Technology. *J Genet Genomics* 2016; **43**: 63-75 [PMID: 26924689 DOI: 10.1016/j.jgg.2016.01.001]

35 **Shao M**, Xu TR, Chen CS. The big bang of genome editing technology: development and application of the CRISPR/Cas9 system in disease animal models. *Dongwuxue Yanjiu* 2016; **37**: 191-204 [PMID: 27469250 DOI: 10.13918/j.issn.2095-8137.2016.4.191]

36 **Ceasar SA**, Rajan V, Prykhozhij SV, Berman JN, Ignacimuthu S. Insert, remove or replace: A highly advanced genome editing system using CRISPR/Cas9. *Biochim Biophys Acta* 2016; **1863**: 2333-2344 [PMID: 27350235 DOI: 10.1016/j.bbamcr.2016.06.009]

37 **Liu M**, Rehman S, Tang X, Gu K, Fan Q, Chen D, Ma W. Methodologies for Improving HDR Efficiency. *Front Genet* 2018; **9**: 691 [PMID: 30687381 DOI: 10.3389/fgene.2018.00691]

38 **Jiang F**, Doudna JA. CRISPR-Cas9 Structures and Mechanisms. *Annu Rev Biophys* 2017; **46**: 505-529 [PMID: 28375731 DOI: 10.1146/annurev-biophys-062215-010822]

39 **Yang H**, Ren S, Yu S, Pan H, Li T, Ge S, Zhang J, Xia N. Methods Favoring Homology-Directed Repair Choice in Response to CRISPR/Cas9 Induced-Double Strand Breaks. *Int J Mol Sci* 2020; **21** [PMID: 32899704 DOI: 10.3390/ijms21186461]

40 **Russo FB**, Freitas BC, Pignatari GC, Fernandes IR, Sebat J, Muotri AR, Beltrão-Braga PCB. Modelling the Interplay Between Neurons and Astrocytes in Autism Using Human Induced Pluripotent Stem Cells. *Biol Psychiatry* 2018; **83**: 569-578 [PMID: 29129319 DOI: 10.1016/j.biopsych.2017.09.021]

41 **Marchetto MC**, Belinson H, Tian Y, Freitas BC, Fu C, Vadodaria K, Beltrao-Braga P, Trujillo CA, Mendes APD, Padmanabhan K, Nunez Y, Ou J, Ghosh H, Wright R, Brennand K, Pierce K, Eichenfield L, Pramparo T, Eyler L, Barnes CC, Courchesne E, Geschwind DH, Gage FH, Wynshaw-Boris A, Muotri AR. Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. *Mol Psychiatry* 2017; **22**: 820-835 [PMID: 27378147 DOI: 10.1038/mp.2016.95]

42 **Engle SJ**, Blaha L, Kleiman RJ. Best Practices for Translational Disease Modeling Using Human iPSC-Derived Neurons. *Neuron* 2018; **100**: 783-797 [PMID: 30465765 DOI: 10.1016/j.neuron.2018.10.033]

43 **Deneault E**, White SH, Rodrigues DC, Ross PJ, Faheem M, Zaslavsky K, Wang Z, Alexandrova R, Pellecchia G, Wei W, Piekna A, Kaur G, Howe JL, Kwan V, Thiruvahindrapuram B, Walker S, Lionel AC, Pasceri P, Merico D, Yuen RKC, Singh KK, Ellis J, Scherer SW. Complete Disruption of Autism-Susceptibility Genes by Gene Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons. *Stem Cell Reports* 2018; **11**: 1211-1225 [PMID: 30392976

DOI: 10.1016/j.stemcr.2018.10.003]

44 **Yi F**, Danko T, Botelho SC, Patzke C, Pak C, Wernig M, Südhof TC. Autism-associated SHANK3 haploinsufficiency causes Ih channelopathy in human neurons. *Science* 2016; **352**: aaf2669 [PMID: 26966193 DOI: 10.1126/science.aaf2669]

45 **Deneault E**, Faheem M, White SH, Rodrigues DC, Sun S, Wei W, Piekna A, Thompson T, Howe JL, Chalil L, Kwan V, Walker S, Pasceri P, Roth FP, Yuen RK, Singh KK, Ellis J, Scherer SW. CNTN5(-)(/+)or EHMT2(-)(/+)human iPSC-derived neurons from individuals with autism develop hyperactive neuronal networks. *Elife* 2019; **8** [PMID: 30747104 DOI: 10.7554/eLife.40092]

46 **Frega M**, Linda K, Keller JM, Gümüş-Akay G, Mossink B, van Rhijn JR, Negwer M, Klein Gunnewiek T, Foreman K, Kompier N, Schoenmaker C, van den Akker W, van der Werf I, Oudakker A, Zhou H, Kleefstra T, Schubert D, van Bokhoven H, Nadif Kasri N. Neuronal network dysfunction in a model for Kleefstra syndrome mediated by enhanced NMDAR signaling. *Nat Commun* 2019; **10**: 4928 [PMID: 31666522 DOI: 10.1038/s41467-019-12947-3]

47 **Rao SR**, Kostic A, Baillargeon P, Fernandez-Vega V, de Anda MR, Fletcher K, Shumate J, Scampavia L, Buxbaum JD, Spicer TP. Screening for modulators of autism spectrum disorder using induced human neurons. *SLAS Discov* 2022; **27**: 128-139 [PMID: 35123134 DOI: 10.1016/j.slasd.2022.01.004]

48 **Wang P**, Lin M, Pedrosa E, Hrabovsky A, Zhang Z, Guo W, Lachman HM, Zheng D. CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in neurodevelopment. *Mol Autism* 2015; **6**: 55 [PMID: 26491539 DOI: 10.1186/s13229-015-0048-6]

49 **Ross PJ**, Zhang WB, Mok RSF, Zaslavsky K, Deneault E, D'Abate L, Rodrigues DC, Yuen RKC, Faheem M, Mufteev M, Piekna A, Wei W, Pasceri P, Landa RJ, Nagy A, Varga B, Salter MW, Scherer SW, Ellis J. Synaptic Dysfunction in Human Neurons With Autism-Associated Deletions in PTCHD1-AS. *Biol Psychiatry* 2020; **87**: 139-149 [PMID: 31540669 DOI: 10.1016/j.biopsych.2019.07.014]

50 **Rontani P**, Perche O, Greetham L, Jullien N, Gepner B, Féron F, Nivet E, Erard-Garcia M. Impaired expression of the COSMOC/MOCOS gene unit in ASD patient stem cells. *Mol Psychiatry* 2021; **26**: 1606-1618 [PMID: 32327736 DOI: 10.1038/s41380-020-0728-2]

51 **Rabeling A**, Goolam M. Cerebral organoids as an in vitro model to study autism spectrum disorders. *Gene Ther* 2022 [PMID: 35790793 DOI: 10.1038/s41434-022-00356-z]

52 **Englund C**, Fink A, Lau C, Pham D, Daza RA, Bulfone A, Kowalczyk T, Hevner RF. Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J Neurosci* 2005; **25**: 247-251 [PMID: 15634788 DOI: 10.1523/JNEUROSCI.2899-04.2005]

53 **Paulsen B**, Velasco S, Kedaigle AJ, Pigoni M, Quadrato G, Deo A, Adiconis X, Uzquiano A, Kim K, Simmons SK, Tsafou K, Albanese A, Sartore R, Abbate C, Tucewicz A, Smith S, Chung K, Lage K, Regev A, Levin JZ, Arlotta P. Human brain organoids reveal accelerated development of cortical neuron classes as a shared feature of autism risk genes. *Developmental Biology* [DOI: 10.1101/2020.11.10.376509]

54 **Zhang W**, Ma L, Yang M, Shao Q, Xu J, Lu Z, Zhao Z, Chen R, Chai Y, Chen JF. Cerebral organoid and mouse models reveal a RAB39b-PI3K-mTOR pathway-dependent dysregulation of cortical development leading to macrocephaly/autism phenotypes. *Genes Dev* 2020; **34**: 580-597 [PMID: 32115408 DOI: 10.1101/gad.332494.119]

55 **Amir RE**, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999; **23**: 185-188 [PMID: 10508514 DOI: 10.1038/13810]

56 **Trujillo CA**, Adams JW, Negraes PD, Carromeu C, Tejwani L, Acab A, Tsuda B, Thomas CA, Sodhi N, Fichter KM, Romero S, Zanella F, Sejnowski TJ, Ulrich H, Muotri AR. Pharmacological reversal of synaptic and network pathology in human MECP2-KO neurons and cortical organoids. *EMBO Mol Med* 2021; **13**: e12523 [PMID: 33501759 DOI: 10.15252/emmm.202012523]

57 **Xiang Y**, Tanaka Y, Patterson B, Hwang SM, Hysolli E, Cakir B, Kim KY, Wang W, Kang YJ, Clement EM, Zhong M, Lee SH, Cho YS, Patra P, Sullivan GJ, Weissman SM, Park IH. Dysregulation of BRD4 Function Underlies the Functional Abnormalities of MeCP2 Mutant Neurons. *Mol Cell* 2020; **79**: 84-98.e9 [PMID: 32526163 DOI: 10.1016/j.molcel.2020.05.016]

58 **Sun AX**, Yuan Q, Fukuda M, Yu W, Yan H, Lim GGY, Nai MH, D'Agostino GA, Tran HD, Itahana Y, Wang D, Lokman H, Itahana K, Lim SWL, Tang J, Chang YY, Zhang M, Cook SA, Rackham OJL, Lim CT, Tan EK, Ng HH, Lim KL, Jiang YH, Je HS. Potassium channel dysfunction in human neuronal models of Angelman syndrome. *Science* 2019; **366**: 1486-1492 [PMID: 31857479 DOI: 10.1126/science.aav5386]

59 **Blair JD**, Hockemeyer D, Bateup HS. Genetically engineered human cortical spheroid models of tuberous sclerosis. *Nat Med* 2018; **24**: 1568-1578 [PMID: 30127391 DOI: 10.1038/s41591-018-0139-y]

60 **Dooves S**, van Velthoven AJH, Suciati LG, Heine VM. Neuron-Glia Interactions in Tuberous Sclerosis Complex Affect the Synaptic Balance in 2D and Organoid Cultures. *Cells* 2021; **10** [PMID: 33445520 DOI: 10.3390/cells10010134]

61 **Wang Y**, Chiola S, Yang G, Russell C, Armstrong CJ, Wu Y, Spampanato J, Tarboton P, Ullah HMA, Edgar NU, Chang AN, Harmin DA, Bocchi VD, Vezzoli E, Besusso D, Cui J, Cattaneo E, Kubanek J, Shcheglovitov A. Modeling human telencephalic development and autism-associated SHANK3 deficiency using organoids generated from single neural rosettes. *Nat Commun* 2022; **13**: 5688 [PMID: 36202854 DOI: 10.1038/s41467-022-33364-z]

62 **Brighi C**, Salaris F, Soloperto A, Cordella F, Ghirga S, de Turris V, Rosito M, Porceddu PF, D'Antoni C, Reggiani A, Rosa A, Di Angelantonio S. Novel fragile X syndrome 2D and 3D brain models based on human isogenic FMRP-KO iPSCs. *Cell Death Dis* 2021; **12**: 498 [PMID: 33993189 DOI: 10.1038/s41419-021-03776-8]

63 **Doi M**, Li M, Usui N, Shimada S. Genomic Strategies for Understanding the Pathophysiology of Autism Spectrum Disorder. *Front Mol Neurosci* 2022; **15**: 930941 [PMID: 35813066 DOI: 10.3389/fnmol.2022.930941]

64 **Zhou Y**, Sharma J, Ke Q, Landman R, Yuan J, Chen H, Hayden DS, Fisher JW 3rd, Jiang M, Menegas W, Aida T, Yan T, Zou Y, Xu D, Parmar S, Hyman JB, Fanucci-Kiss A, Meisner O, Wang D, Huang Y, Li Y, Bai Y, Ji W, Lai X, Li W, Huang L, Lu Z, Wang L, Anteraper SA, Sur M, Zhou H, Xiang AP, Desimone R, Feng G, Yang S. Atypical behaviour and connectivity in SHANK3-mutant macaques. *Nature* 2019; **570**: 326-331 [PMID: 31189958 DOI: 10.1038/s41586-019-1278-0]

65 **Celen C**, Chuang JC, Luo X, Nijem N, Walker AK, Chen F, Zhang S, Chung AS, Nguyen LH, Nassour I, Budhipramono A, Sun X, Bok LA, McEntagart M, Gevers EF, Birnbaum SG, Eisch AJ, Powell CM, Ge WP, Santen GW, Chahrour M, Zhu H. Arid1b haploinsufficient mice reveal neuropsychiatric phenotypes and reversible causes of growth impairment. *Elife* 2017; **6** [PMID: 28695822 DOI: 10.7554/eLife.25730]

66 **Gompers AL**, Su-Feher L, Ellegood J, Copping NA, Riyadh MA, Stradleigh TW, Pride MC, Schaffler MD, Wade AA, Catta-Preta R, Zdilar I, Louis S, Kaushik G, Mannion BJ, Plajzer-Frick I, Afzal V, Visel A, Pennacchio LA, Dickel DE, Lerch JP, Crawley JN, Zarbalis KS, Silverman JL, Nord AS. Germline Chd8 haploinsufficiency alters brain development in mouse. *Nat Neurosci* 2017; **20**: 1062-1073 [PMID: 28671691 DOI: 10.1038/nn.4592]

67 **Zhu T**, Liang C, Li D, Tian M, Liu S, Gao G, Guan JS. Histone methyltransferase Ash1L mediates activity-dependent repression of neurexin-1α. *Sci Rep* 2016; **6**: 26597 [PMID: 27229316 DOI: 10.1038/srep26597]

68 **Silva AI**, Haddon JE, Ahmed Syed Y, Trent S, Lin TE, Patel Y, Carter J, Haan N, Honey RC, Humby T, Assaf Y, Owen MJ, Linden DEJ, Hall J, Wilkinson LS. Cyfip1 haploinsufficient rats show white matter changes, myelin thinning, abnormal oligodendrocytes and behavioural inflexibility. *Nat Commun* 2019; **10**: 3455 [PMID: 31371763 DOI: 10.1038/s41467-019-11119-7]

69 **Rannals MD**, Page SC, Campbell MN, Gallo RA, Mayfield B, Maher BJ. Neurodevelopmental models of transcription factor 4 deficiency converge on a common ion channel as a potential therapeutic target for Pitt Hopkins syndrome. *Rare Dis* 2016; **4**: e1220468 [PMID: 28032012 DOI: 10.1080/21675511.2016.1220468]

70 **Dodge A**, Peters MM, Greene HE, Dietrick C, Botelho R, Chung D, Willman J, Nenninger AW, Ciarlone S, Kamath SG, Houdek P, Sumová A, Anderson AE, Dindot SV, Berg EL, O'Geen H, Segal DJ, Silverman JL, Weeber EJ, Nash KR. Generation of a Novel Rat Model of Angelman Syndrome with a Complete Ube3a Gene Deletion. *Autism Res* 2020; **13**: 397-409 [PMID: 31961493 DOI: 10.1002/aur.2267]

71 **Bernier R**, Golzio C, Xiong B, Stessman HA, Coe BP, Penn O, Witherspoon K, Gerdts J, Baker C, Vulto-van Silfhout AT, Schuurs-Hoeijmakers JH, Fichera M, Bosco P, Buono S, Alberti A, Failla P, Peeters H, Steyaert J, Vissers LELM, Francescatto L, Mefford HC, Rosenfeld JA, Bakken T, O'Roak BJ, Pawlus M, Moon R, Shendure J, Amaral DG, Lein E, Rankin J, Romano C, de Vries BBA, Katsanis N, Eichler EE. Disruptive CHD8 mutations define a subtype of autism early in development. *Cell* 2014; **158**: 263-276 [PMID: 24998929 DOI: 10.1016/j.cell.2014.06.017]

72 **Hu J**, Chen L, Yin J, Yin H, Huang Y, Tian J. Hyperactivity, Memory Defects, and Craniofacial Abnormalities in Zebrafish fmr1 Mutant Larvae. *Behav Genet* 2020; **50**: 152-160 [PMID: 32048109 DOI: 10.1007/s10519-020-09995-7]

73 **Ruzzo EK**, Pérez-Cano L, Jung JY, Wang LK, Kashef-Haghighi D, Hartl C, Singh C, Xu J, Hoekstra JN, Leventhal O, Leppä VM, Gandal MJ, Paskov K, Stockham N, Polioudakis D, Lowe JK, Prober DA, Geschwind DH, Wall DP. Inherited and De Novo Genetic Risk for Autism Impacts Shared Networks. *Cell* 2019; **178**: 850-866.e26 [PMID: 31398340 DOI: 10.1016/j.cell.2019.07.015]

74 **Liu CX**, Li CY, Hu CC, Wang Y, Lin J, Jiang YH, Li Q, Xu X. CRISPR/Cas9-induced shank3b mutant zebrafish display autism-like behaviors. *Mol Autism* 2018; **9**: 23 [PMID: 29619162 DOI: 10.1186/s13229-018-0204-x]

75 **Staahl BT**, Benekareddy M, Coulon-Bainier C, Banfal AA, Floor SN, Sabo JK, Urnes C, Munares GA, Ghosh A, Doudna JA. Efficient genome editing in the mouse brain by local delivery of engineered Cas9 ribonucleoprotein complexes. *Nat Biotechnol* 2017; **35**: 431-434 [PMID: 28191903 DOI: 10.1038/nbt.3806]

76 **Warrier V**, Chee V, Smith P, Chakrabarti B, Baron-Cohen S. A comprehensive meta-analysis of common genetic variants in autism spectrum conditions. *Mol Autism* 2015; **6**: 49 [PMID: 26322220 DOI: 10.1186/s13229-015-0041-0]

77 **Wiśniowiecka-Kowalnik B**, Nowakowska BA. Genetics and epigenetics of autism spectrum disorder-current evidence in the field. *J Appl Genet* 2019; **60**: 37-47 [PMID: 30627967 DOI: 10.1007/s13353-018-00480-w]

78 **Guo H**, Zhang Q, Dai R, Yu B, Hoekzema K, Tan J, Tan S, Jia X, Chung WK, Hernan R, Alkuraya FS, Alsulaiman A, Al-Muhaizea MA, Lesca G, Pons L, Labalme A, Laux L, Bryant E, Brown NJ, Savva E, Ayres S, Eratne D, Peeters H, Bilan F, Letienne-Cejudo L, Gilbert-Dussardier B, Ruiz-Arana IL, Merlini JM, Boizot A, Bartoloni L, Santoni F, Karlowicz D, McDonald M, Wu H, Hu Z, Chen G, Ou J, Brasch-Andersen C, Fagerberg CR, Dreyer I, Chun-Hui Tsai A, Slegesky V, McGee RB, Daniels B, Sellars EA, Carpenter LA, Schaefer B, Sacoto MJG, Begtrup A, Schnur RE, Punj S, Wentzensen IM, Rhodes L, Pan Q, Bernier RA, Chen C, Eichler EE, Xia K. NCKAP1 Disruptive Variants Lead to a Neurodevelopmental Disorder with Core Features of Autism. *Am J Hum Genet* 2020; **107**: 963-976 [PMID: 33157009 DOI: 10.1016/j.ajhg.2020.10.002]

79 **Levitt P**, Campbell DB. The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders. *J Clin Invest* 2009; **119**: 747-754 [PMID: 19339766 DOI: 10.1172/JCI37934]

80 **Muhle R**, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics* 2004; **113**: e472-e486 [PMID: 15121991 DOI: 10.1542/peds.113.5.e472]

81 **Shailesh H**, Gupta I, Sif S, Ouhtit A. Towards understanding the genetics of Autism. *Front Biosci (Elite Ed)* 2016; **8**: 412-426 [PMID: 27100348 DOI: 10.2741/e776]

82 **Huang K**, Wu Y, Shin J, Zheng Y, Siahpirani AF, Lin Y, Ni Z, Chen J, You J, Keles S, Wang D, Roy S, Lu Q. Transcriptome-wide transmission disequilibrium analysis identifies novel risk genes for autism spectrum disorder. *PloS Genet* 2021; **17**: e1009309 [PMID: 33539344 DOI: 10.1371/journal.pgen.1009309]

83 **Lee B**, Lee K, Panda S, Gonzales-Rojas R, Chong A, Bugay V, Park HM, Brenner R, Murthy N, Lee HY. Nanoparticle delivery of CRISPR into the brain rescues a mouse model of fragile X syndrome from exaggerated repetitive behaviours. *Nat Biomed Eng* 2018; **2**: 497-507 [PMID: 30948824 DOI: 10.1038/s41551-018-0252-8]

84 **Silverman JL**, Smith DG, Rizzo SJ, Karras MN, Turner SM, Tolu SS, Bryce DK, Smith DL, Fonseca K, Ring RH, Crawley JN. Negative allosteric modulation of the mGluR5 receptor reduces repetitive behaviors and rescues social deficits in mouse models of autism. *Sci Transl Med* 2012; **4**: 131ra51 [PMID: 22539775 DOI: 10.1126/scitranslmed.3003501]

85 **Tao J**, Wu H, Coronado AA, de Laittre E, Osterweil EK, Zhang Y, Bear MF. Negative Allosteric Modulation of mGluR5 Partially Corrects Pathophysiology in a Mouse Model of Rett Syndrome. *J Neurosci* 2016; **36**: 11946-11958 [PMID: 27881780 DOI: 10.1523/JNEUROSCI.0672-16.2016]

86 **Le TTH**, Tran NT, Dao TML, Nguyen DD, Do HD, Ha TL, Kühn R, Nguyen TL, Rajewsky K, Chu VT. Efficient and

Precise CRISPR/Cas9-Mediated MECP2 Modifications in Human-Induced Pluripotent Stem Cells. *Front Genet* 2019; **10**: 625 [PMID: 31333716 DOI: 10.3389/fgene.2019.00625]

87 **Zaslavsky K**, Zhang WB, McCready FP, Rodrigues DC, Deneault E, Loo C, Zhao M, Ross PJ, El Hajjar J, oom A, Thompson T, Piekna A, Wei W, Wang Z, Khattak S, Mufteev M, Pasceri P, Scherer SW, Salter MW, Ellis J. SHANK2 mutations associated with autism spectrum disorder cause hyperconnectivity of human neurons. *Nat Neurosci* 2019; **22**: 556-564 [PMID: 30911184 DOI: 10.1038/s41593-019-0365-8]

88 **Wolter JM**, Mao H, Fragola G, Simon JM, Krantz JL, Bazick HO, Oztemiz B, Stein JL, Zylka MJ. Cas9 gene therapy for Angelman syndrome traps Ube3a-ATS long non-coding RNA. *Nature* 2020; **587**: 281-284 [PMID: 33087932 DOI: 10.1038/s41586-020-2835-2]

89 **Xie N**, Gong H, Suhl JA, Chopra P, Wang T, Warren ST. Reactivation of FMR1 by CRISPR/Cas9-Mediated Deletion of the Expanded CGG-Repeat of the Fragile X Chromosome. *PloS One* 2016; **11**: e0165499 [PMID: 27768763 DOI: 10.1371/journal.pone.0165499]

90 **Jaudon F**, Thalhammer A, Zentilin L, Cingolani LA. CRISPR-mediated activation of autism gene Itgb3 restores cortical network excitability *via* mGluR5 signaling. *Mol Ther Nucleic Acids* 2022; **29**: 462-480 [PMID: 36035754 DOI: 10.1016/j.omtn.2022.07.013]

91 **Adlat S**, Hayel F, Yang P, Chen Y, Oo ZM, Myint MZZ, Sah RK, Bahadar N, Al-Azab M, Bah FB, Zheng Y, Feng X. CRISPR-mediated base editing in mice using cytosine deaminase base editor 4. *Electron J Biotechn* 2021; **52**: 59-66 [DOI: 10.1016/j.ejbt.2021.04.010]

92 **Li W**, Chen J, Peng W, Yuan B, Han W, Yuan Y, Xue Z, Wang J, Chen Z, Shan S, Zhu S, Xu M, Cheng T, Qiu Z. Whole-brain in vivo base editing reverses autistic-like behaviors in mice. *Neuroscience* [DOI: 10.1101/2022.01.25.477781]

93 **de Jong JO**, Llapashtica C, Genestine M, Strauss K, Provenzano F, Sun Y, Zhu H, Cortese GP, Brundu F, Brigatti KW, Corneo B, Migliori B, Tomer R, Kushner SA, Kellendonk C, Javitch JA, Xu B, Markx S. Cortical overgrowth in a preclinical forebrain organoid model of CNTNAP2-associated autism spectrum disorder. *Nat Commun* 2021; **12**: 4087 [PMID: 34471112 DOI: 10.1038/s41467-021-24358-4]

94 **Tamura S**, Nelson AD, Spratt PWE, Kyoung H, Zhou X, Li Z, Zhao J, Holden SS, Sahagun A, Keeshen CM, Lu C, Hamada EC, Ben-Shalom R, Pan JQ, Paz JT, Sanders SJ, Matharu N, Ahituv N, Bender KJ. CRISPR activation rescues abnormalities in SCN2A haploinsufficiency-associated autism spectrum disorder. *Neuroscience* [DOI: 10.1101/2022.03.30.486483]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3128-3139

DOI: 10.12998/wjcc.v11.i14.3128

ISSN 2307-8960 (online)

REVIEW

Burden of disability in type 2 diabetes mellitus and the moderating effects of physical activity

Olufemi O Oyewole, Ayotunde O Ale, Michael O Ogunlana, Thavanesi Gurayah

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Balbaa ME, Egypt; Lee S, South Korea; Long P, China

Received: December 3, 2022
Peer-review started: December 3, 2022
First decision: February 8, 2023
Revised: March 2, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Olufemi O Oyewole, Department of Physiotherapy, Olabisi Onabanjo University Teaching Hospital, Sagamu 201101, Ogun, Nigeria

Olufemi O Oyewole, Michael O Ogunlana, College of Health Sciences, University of KwaZulu-Natal, Durban 3629, South Africa

Ayotunde O Ale, Department of Medicine, Olabisi Onabanjo University, Sagamu 121101, Ogun, Nigeria

Ayotunde O Ale, Department of Endocrinology, Diabetes and Metabolism Unit, Medicine, Olabisi Onabanjo University Teaching Hospital, Sagamu 121101, Ogun, Nigeria

Michael O Ogunlana, Department of Physiotherapy, Federal Medical Centre, Abeokuta 110101, Ogun, Nigeria

Thavanesi Gurayah, Occupational Therapy, School of Health Sciences, University of Kwazulu Natal, Private Bag X54001, Durban, 4000

Corresponding author: Olufemi O Oyewole, PhD, Physiotherapist, Department of Physiotherapy, Olabisi Onabanjo University Teaching Hospital, Hospital Road, Sagamu 201101, Ogun, Nigeria. oyewoleyeo1@ukzn.ac.za

Abstract

The growing diabetic epidemic has created a substantial burden, not only on the people with diabetes but also on society at large. This mini-review discussed the limitations and patterns of disability in type 2 diabetes mellitus and put forward a case for the moderating effects of physical activity (PA) in the management of diabetes. The limitations and impairments associated with diabetes include vascular, neurological, cardiac, and renal impairments. Moreover, individuals participate less in their daily lives and in their instrumental activities of daily living, which negatively impacts the quality of life of individuals with diabetes. This often leads to a loss of quality of life due to disabilities, resulting in an increased rate of disability-adjusted life years among people with type 2 diabetes mellitus. Moreover, there are psychosocial sequelae of diabetes mellitus. This necessitates looking for moderating factors that may reduce the burden of the disease. PA has been shown to be one of the factors that can mitigate these burdens. PA does this in several ways, including through the benefits it confers, such as a reduction of hemoglobin A1c, a reduction of excess fat in the liver and pancreas, and the reduction of cardiovascular risk factors, all of which favorably

affect glycemic parameters. Specifically, PA regulates or moderates diabetes disability through two mechanisms: The regulation of glucolipid metabolism disorders and the optimization of body mass index and systemic conditions. Therefore, efforts should be directed at PA uptake through identified strategies. This will not only prevent diabetes or diabetes complications but will reduce its burden.

Key Words: Type 2 diabetes mellitus; Disability burden; Physical activity; Moderating effect

Core Tip: There has been a growing epidemic of diabetes resulting in a substantial burden, not only on the people with diabetes but on society at large. This mini-review focused on the burden of disability in type 2 diabetes mellitus and discussed how physical activity moderates the burden.

Citation: Oyewole OO, Ale AO, Ogunlana MO, Gurayah T. Burden of disability in type 2 diabetes mellitus and the moderating effects of physical activity. *World J Clin Cases* 2023; 11(14): 3128-3139
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3128.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3128

INTRODUCTION

Diabetes remains a public health concern globally, with the epidemic growing in the last decade[1]. It is one of the leading causes of death globally[2]. In 2017, the global prevalence of diabetes was estimated to be 476 million people, which is projected to reach 570.9 million by 2025[2] and 693 million people by 2045[3]. There was a prevalence rate of 6059 cases per 100000 in 2017, projected to rise to 7079 cases per 100000 by 2030[4]. Diabetes, coupled with its complications, imposes several burdens on individuals affected by the disease, including economic and psychological limitations[5-7].

The cost of treating diabetes and its complications is a great burden globally[8-10]. Globally, the annual average cost (both direct and indirect) per person for treating type 2 diabetes mellitus (T2DM) ranged from USD 29.91 to USD 237.38 (direct costs USD 106.53-USD 293.79 and indirect costs USD 1.92-USD 73.4)[11]. This amounts to USD 25.51 billion in economic loss in Africa[12]. Similar economic loss was reported in other parts of the world, including Asia and Europe[6,7,13-16].

Diabetes and its complications cause severe disabilities in individuals with the condition and often lead to the loss of a healthy life due to disability[17]. Disability-adjusted life years (DALYs), an indicator to measure the burden of disease, have been reported to have increased among people with T2DM[17,18]. Globally, the age-standardized DALY rates increased by 5.07% from 2007 to 2017[18]. In 2017, 67.9 million DALYs were associated with diabetes, with a projection to 79.3 million by 2025[2].

To address the psychosocial issues that may arise from these burdens[5,19], it is necessary to look for moderating factors that may reduce the burden of the disease. Physical activity (PA) has been shown to be one of the factors that can mitigate these burdens[20]. PA does this in several ways through the benefits it confers, such as a reduction of excess fat in the liver and pancreas[21], the reduction of cardiovascular risk factors, and by favorably affecting glycemic parameters[20], thereby ultimately improving hemoglobin A1c[20,22]. Patient education is another key factor in reducing the burden of diabetes. Individuals with T2DM who are well-informed and motivated are more successful in maintaining good control of their risk factors and can eventually reduce their cardiovascular risk and slow the progression of microvascular disease[23]. This communication should be client-centered as it moderates the relationship between the burden of diabetes and diabetes distress[24]. Thus, this mini-review discussed the burden of disability in T2DM and the moderating effects of PA.

PROFILE AND PATTERNS OF DISABILITY IN DIABETES

Diabetes was ranked ninth in the 2019 WHO global estimates of the leading causes of mortality, showing a 70% increase since the year 2000[25]. Moreover, it is one of the five leading conditions impacting years lived with disability in the Americas[26]. Diabetes is also implicated in the etiology of other conditions. Table 1 shows the percentages of comorbid conditions associated with diabetes in the National Burden of Disease study in South Africa[27].

There are numerous indicators and markers of disability in individuals with T2DM. One of these markers is weight management. It has been found that a significant proportion (around 85%) of diabetic

Table 1 Percentages of comorbid conditions associated with diabetes in the National Burden of Disease Study[27]

Diabetic-related comorbid conditions	Percent contribution to national burden of diseases in South Africa
Ischemic heart disease	14%
Stroke	10%
Hypertension	12%
Renal disease	12%

adults are overweight[28], having a body mass index (BMI) of 25.0 to 29.9; while others are obese, with a BMI over 30. Individuals with a BMI over 40 at baseline were found to gain weight over a 10-year period. Moreover, there was a high proportion of insulin users in this group, confirming the link between insulin use and weight accumulation[29,30].

Keeping an individual's weight stable and within the normal range acts to slow the increase of limitations in diabetic adults[31]. A study by Ferraro *et al*[32] found that the risk of disability was higher for obese individuals but not always for overweight individuals. Research has shown that 13.6% of patients with T2DM will develop some limitation in at least one activity of daily living (ADL) 6 years post diagnosis; and 38.3% will develop a functional decline at a rate of 1.0% mean decline in function per year[33,34].

It has been suggested that complications related to diabetes are avoidable[35]. This is contingent upon maintaining optimal hemoglobin A1c control in the range between 6.5% and 7.0% (48-53 mmol/mol)[36]. However late diagnosis, failure meeting the targeted DM treatment goals, and non-compliance with treatment can lead to severe complications such as nephropathy, neuropathy, retinopathy, amputations, and stroke[37]. A recurring finding is the physical limitations in both sexes, relating to the loss of function in the lower limbs, which impacts mobility, and is a predictor of the loss of autonomy[38,39].

The global epidemic of T2DM has been characterized by the early onset of the disease, typically in people below 40 years of age, who are obese, and who belong to an ethnic minority group. These characteristics are associated with decreased physical fitness and reduced muscle mass[40]. Moreover, there are specific markers of accelerated metabolic aging in T2DM, which leads to a ripple effect of functional decline, reduced physical capacity, and increased falls and fractures, typically seen in elderly people[41]. This leads to poorer functional outcomes and prognosis and a decreased quality of life. Specific limitations are discussed below and are shown in Table 2.

Reduction in body structure and function

Muscle wasting is a condition associated with aging and diabetes and is negatively associated with physical functioning[42]. As there is vascular and neurological impairment in diabetes, there may also be a vulnerability to depressive symptoms and dementia. Cognitive impairment has been shown to be increased in diabetic individuals[43]. In tandem with physical frailty, cognitive impairment is associated with a higher risk of mortality in diabetic individuals[44].

Frailty has been defined as the increased vulnerability to physical and psychological stressors due to decreased physiological reserves in multiple organ systems, which impact the body's ability to maintain homeostasis[45]. Frailty can be diagnosed by confirming three of the following five criteria: Unintentional weight loss; low energy expenditure; slowness; weakness; and exhaustion[46]. While frailty is associated with elderly people, the frailty phenotype in T2DM is typically a younger obese individual with multiple comorbidities[47]. Frailty, accompanied by decreased physical function, has emerged as the third complication of T2DM after the micro- and macrovascular complications[48]. This is confirmed by the increased prevalence of frailty in 32% to 48% of individuals with diabetes aged 65 years and older, compared to only 5% to 10% of individuals in the general population[49].

Activity limitation

Regular PA is one of the key factors in maintaining optimum blood sugar control in diabetic individuals[22]. However, individuals with cardiovascular conditions may avoid PA out of fear of hurting themselves[50]. This may be attributed to diabetic-related complications and comorbidities such as peripheral neuropathy, foot or leg pains, poor vision, and impaired renal function[51]. However, most individuals in the diabetic population lead sedentary lifestyles[52,53], which may have been exacerbated during the coronavirus disease 2019 pandemic as people's movements were restricted.

Participation restriction

It has been found that individuals with T2DM experience musculoskeletal pains twice as often as people in the general population[54]. Meanwhile, common reasons cited for the lack of regular exercise include having little time, bad weather, health problems, a lack of social support and professional coaching, safety considerations, limited access, prohibitive costs of a gym membership, and decreased self-efficacy

Table 2 Types of disability in diabetes

Ref.	Type of disability	Summary/remark
Dhamoon *et al*[33], 2014	Decline in function	1% mean decline in function per year was reported
Sakurai *et al*[34], 2012	ADL, IADL disability and functional impairment	After 6 years of follow-up, 13.6% of patients had developed a new ADL disability, and 38.3% had developed a new functional impairment
Gregg *et al*[70], 2000	Physical disability	Among subjects ≥ 60 yr of age with diabetes, 32% of females and 15% of males reported an inability to walk one-fourth of a mile, climb stairs, or do housework compared with 14% of females and 8% of males without diabetes
Gregg *et al*[38], 2002	Functional disability	The yearly incidence of any functional disability was 9.8% among females with diabetes and 4.8% among females without diabetes
Volpato *et al*[39,41], 2002; Volpato *et al*[41], 2010	Functional/lower extremity disability	Females with diabetes showed a greater prevalence of mobility disability, disabilities in ADLs, and severe walking limitation; their summary mobility performance score (0-12 scale, based on balance, gait speed, chair stands) was 1.4 points lower than in nondiabetic women
Maggi *et al*[42], 2004	ADLs and physical performance	The association between severe and/or total disability on the basis of physical performance tests and diabetes was strong in both sexes
Thein *et al*[44], 2018	ADL and IADL disability	Diabetes was associated with a significantly higher prevalence of CI and/or PF. PF and/or CI were associated with a considerably higher prevalence of IADL
Ahmad *et al*[47], 2022	Impaired physical function	Impaired physical function is a growing problem
Wong *et al*[48], 2013	Physical disability	Diabetes is associated with a strong increase in the risk of physical disability
Godino *et al*[63], 2017	Functional disability	Diabetes patients had a significantly greater burden of functional disability compared to those without diabetes
Malavige and Levy [64], 2009	Erectile dysfunction	A prevalence of erectile dysfunction from 35% to 90% among diabetic males was reported
Omidvar *et al*[67], 2013	Sexual dysfunction	The prevalence of sexual dysfunction was 32.3%. Low sexual desire was seen in 81.8%, disorders of arousal in 78.3%, orgasm disorder in 47.5%, and 35.1% had disorders in resolution areas

ADL: Activity of daily living; IADL: Instrumental activity of daily living; CI: Cognitive impairment; PF: Physical frailty.

[55,56]. Furthermore, the fear of stigma regarding their weight and feelings of shame, inferiority, and inadequacy may be a barrier to regular PA[57]. Obese individuals may be hypersensitive to people looking at them or making comments regarding their weight, while others feel they are too obese to exercise or experience discomfort related to their obesity, such as chafing of their thighs or becoming breathless[58].

Functional limitations and disability

There are likely to be greater functional limitations and disabilities in individuals with diabetes due to the comorbidities associated with diabetes. They are usually reported as limitations and impairments in ADLs, which relate to self-care activities such as feeding, bathing, toileting, and grooming. Impairments in ADLs are reported in research studies as they are predictors of morbidity and mortality[38,39]. The ability to perform ADLs and instrumental ADLs (IADL) is contingent upon the interplay of multiple physiological and organ systems, such as the musculoskeletal, neurological, vascular, and cardiorespiratory systems[59]. Being capable of independence in self-care, or ADLs and IADLs, is essential for independent community living and is directly associated with an individual's quality of life[59,60]. Diabetes in Africa usually affects people between the ages of 40 years and 60 years, impacting their working lives negatively, and resulting in absenteeism, sick days, and decreased productivity[61].

An exploratory study by Huang *et al*[62] of the self-reported goals of individuals with T2DM who were 65 years and older revealed that they rated being independent and maintaining their functionality in terms of ADLs (71.0%) higher than maintaining their optimal blood glucose levels (3.5%), avoidance of symptoms (3.5%), or losing weight (14.0%). A cross-sectional study by Godino *et al*[63] revealed a pattern of diabetic-related disability across four domains in decreasing order, namely ADL, followed by IADL, lower limb mobility, and decreased physical function.

Limitations in sexual functioning

There are many changes that occur in the autonomic nervous systems of diabetic individuals, including the genitourinary system. There is a higher incidence of erectile dysfunction in the diabetic population, affecting 35% to 90% of men[64]. Pathophysiology has implicated multiple factors, including endothelial dysfunction, diabetic comorbidities, and psychological factors[65]. Moreover, erectile dysfunction may be an important marker of silent coronary heart disease and can predict future cardiovascular events in

both diabetic and non-diabetic individuals[65]. As erectile dysfunction can affect self-esteem and trigger anxiety and depression, it is important to address the psychological factors as part of a holistic intervention program.

In females with diabetes, the patterns of sexual dysfunction are more varied and appear less prevalent[66]. However, they may still present with a low level of arousal and sexual drive, decreased vaginal lubrication, orgasmic dysfunction, dyspareunia, or painful intercourse[67]. These problems have been attributed to neuropathy, vascular impairment, and psychological factors. Other studies have identified all the aforementioned factors, as well as anxiety, decreased sexual satisfaction, and recurrent vaginal infections, which may negatively affect the sexual experiences of females with diabetes[68].

EFFECT OF DISABILITY, QUALITY-ADJUSTED LIFE YEARS, AND DALY ON QUALITY OF LIFE

Disability in diabetes can be visible or hidden. Disability is the experience of any condition that makes it more difficult for a person to do certain activities or have equitable access within a given society. Diabetes is considered a disability under the federal law of the United States of America[69]. This is because it limits the functioning of the endocrine system. Hence, diabetes may be described as a hidden disability when its complications are not obvious.

Certain disabilities may predispose people to diabetes[69]. It is thought that disability could contribute to diabetes risk through an increase in sedentary behavior, muscle disuse, and a change in the ratio of lean-to-fat mass affecting insulin sensitivity in vulnerable adults[69]. However, it is commonly reported that diabetes leads to several disabilities that are said to be sex-specific[70]. Obesity, congestive heart diseases, lower extremity diseases, stroke, and depression appear to be the most prominent conditions that heighten the disability risk among people with and without diabetes[41].

All health interventions for people with diabetes aim to improve their quality of life as a health outcome. People with diabetes have a poorer quality of life than people with no chronic illnesses but a better quality of life than people with most other serious chronic diseases. Complications of diabetes are the most important disease-specific determinant of quality of life[71]. The complications of diabetes are the major pointers to the nature of disability that are visible and are important for describing the burden of diabetic disease. Jing *et al*[72], in a systematic review and meta-analysis, classified the factors associated with the quality of life of individuals with diabetes as characteristics related to the disease (the presence of complications, comorbidities like hypertension, the duration of diabetes, and insulin use), lifestyles (frequency of physical exercise, dietary controls including consumption of red meat, and the frequency of glucose checks), and mental factors (the presence of depression, anxiety, and worries).

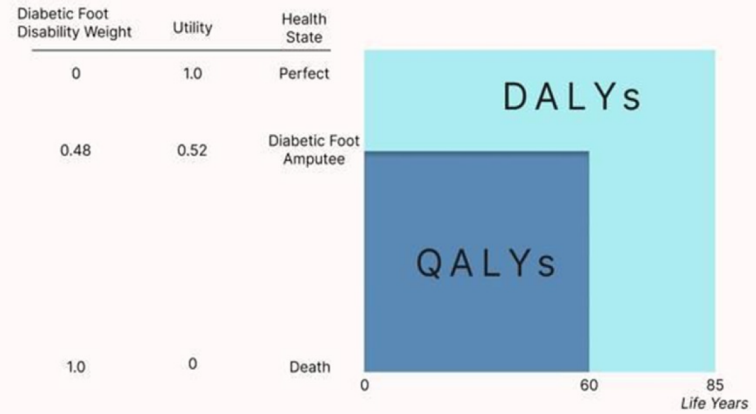
The global burden of disease estimates that the use of information on mortality and morbidity, which are described as quality-adjusted life years and DALY, has been useful in quantifying the extent of disability in a disease like diabetes (Figure 1). These two constructs are used in estimating the burden of diseases like diabetes, and they are widely accepted as a reference standard in cost-effectiveness analyses[18,73].

EFFECT OF PA ON DIABETES AND ITS COMPLICATION

PA is a core element in DM management and in mitigating its complications. PA plays a key role in maintaining good glycemic control and other associated metabolic parameters. PA, coupled with diet and medical therapy, has been shown to reduce the complications of DM and improve quality of life. PA is defined as any bodily movement that substantially increases energy expenditure[22]. The American College of Sports Medicine recommended at least 150 min of moderately intensive aerobic activity or at least 75 min per week of vigorous aerobic activity or a combination of both, preferably spread throughout the week[22].

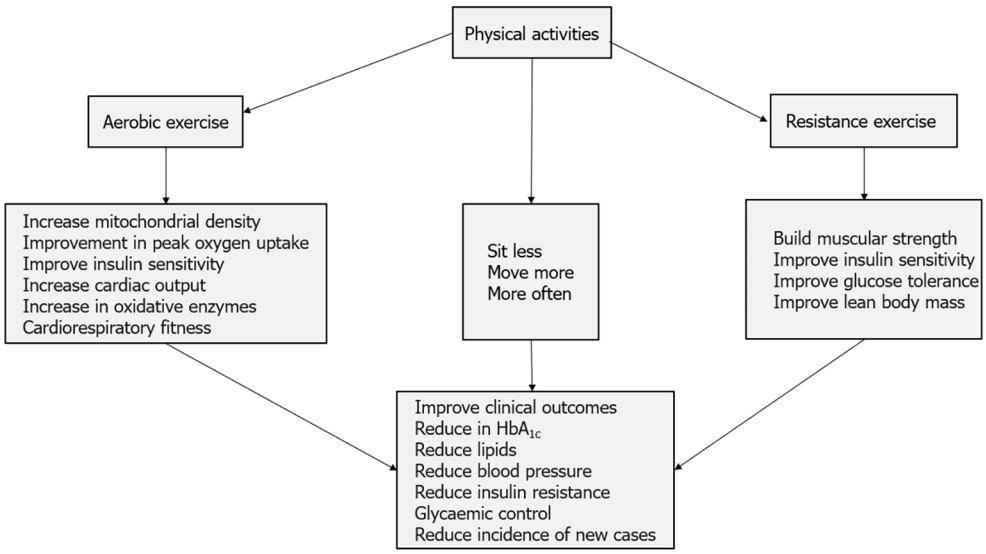
A high prevalence of physical inactivity has been reported worldwide among diabetic individuals, ranging from 31.0% to 61.0% in the United States, 30.7% in Brazil, 31.9% in Malaysia, and 38.4% in Saudi Arabia[74-76]. Nigeria reported a prevalence between 31% and 62%[77,78]. Many benefits are derived from regular PA (Figure 2). PA improves not only physical health but also metabolic control and mental and social-economic well-being. PA is an effective tool in DM management and aids in reducing the incidence of T2DM in people with impaired glucose tolerance, improving glucose control, blood pressure, lipids, and weight control in T2DM, and promoting better bone health. Increased fitness and function, enhanced feelings of well-being, a reduced risk of depression, and a reduction in morbidity and mortality culminate in lower healthcare expenditure[22,79-81]. In contrast, low PA levels lead to an increased risk of overall and cardiovascular disease mortality in people with diabetes[81].

The mechanism by which PA improves or confers these benefits has been explained through the regulation of glycolipid metabolism disorder. Mechanisms resulting from PA, which improve glucolipid metabolism, include an increase of glucose uptake and utilization in metabolic tissues, such as the



DOI: 10.12998/wjcc.v11.i14.3128

Figure 1 Years of healthy life lived and lost in diabetes. DALYs: Disability-adjusted life years; QALYs: Quality-adjusted life years.



DOI: 10.12998/wjcc.v11.i14.3128

Figure 2 Benefits of physical activity in type 2 diabetes. HbA1c: Hemoglobin A1c.

skeletal muscle, liver, and adipose tissues, thereby enhancing insulin sensitivity, protecting pancreatic β cell function, increasing lipid hydrolysis oxidation, alleviating systemic inflammation, and optimizing BMI and systemic condition[82].

Studies have shown that pain, poor health, lack of willpower, lack of energy, lack of skills, lack of social support, and the fear of injury are the top obstacles to PA among DM individuals[83]. Identification with and acceptance of the new lifestyle, social support, support from healthcare professionals, achievement of results, and coping with ongoing challenges have been identified as motivation to maintain PA[84].

MODERATING EFFECT OF PA ON THE RELATIONSHIP BETWEEN DISABILITY AND QUALITY OF LIFE

The importance of PA in the prevention and management of T2DM cannot be overemphasized[85]. Evidence has shown that reducing and frequently breaking up prolonged sitting with light-intensity PA

and standing are among the practical strategies for improving T2DM prevention and management[86]. Thus, moderately intense PA (60 min to 75 min per day) eliminates the increased risk of death associated with prolonged sitting time[87]. Individuals with T2DM are more likely to experience a decline in physical function, especially in mid-life[88]. Regular PA has been shown to reduce the decline in function among the population of T2DM individuals[88].

PA has a direct influence on disability and quality of life. It decreases the self-reported levels of disability and maintains health-related quality of life (HRQoL)[89]. Fatigue, a common disabling clinical complaint among people with T2DM, is also documented to be positively influenced when sitting is regularly interrupted by brief activity breaks[90]. Beyond the effect of PA on an individual's disability and HRQoL, PA has demonstrated a moderating effect on the relationship between disability and HRQoL among older adults[91]. For older adults with high levels of PA, the moderating effects on physical disability and HRQoL are significant, suggesting that improved PA reduces the negative impact of a poor quality of life and disability[91].

Although the moderating effects of PA on the relationship between disability and quality of life[91, 92] have been studied in the older adult population, there are few or limited studies exploring the moderating and mediating effect of PA on the relationship between disability and quality of life in the T2DM population. This may suggest the focus or direction of future research into PA among people with T2DM. It will be of interest to explore the dose-response of PA on the relationship between disability and quality of life as well other factors that may enhance this moderating effect.

IMPROVING PA AMONG PEOPLE WITH DIABETES

Despite expanded data on the benefits of diet, lifestyle modification, and PA in diabetes prevention and management, routine PA has declined in recent decades among individuals with diabetes[93]. Therefore, efforts should be directed at increasing PA uptake among this population. The Centers for Disease Control and Prevention identified ten strategies to improve PA in the community to prevent non-communicable diseases that may predispose individuals to developing diabetes[94]. These strategies include community-wide campaigns, point-of-decision prompts to encourage the use of stairs, individually adapted health behavior change program, enhanced school-based physical education, social support interventions in community settings, the creation of, or enhanced, access to places for PA combined with informational outreach activities, street-scale urban design and land-use policies and community-scale urban design and land-use policies, active transport to school and transportation and travel policies and practices[94]. It is essential to approach these strategies with a predictive, preventive, personalized, and participatory novel approach[93]. In another commentary, strategies to increase PA included measuring PA as a vital sign, encouraging individuals to be physically active at least 150 min per week, creating healthy environments by making it easier to be physically active where we live, learn, work, play, and pray, monitoring the disease incidence in individuals who are physically active compared to those who are not physically active, and spread best practices[95].

Point-of-decision prompts for increasing PA

Evidence abounds regarding increasing the active use of stairs with point-of-decision prompts[94,96, 97]. "Point-of-decision prompts are motivational signs placed on or near stairwells or at the base of elevators and escalators encouraging people to use the stairs"[97]. It is a community-based intervention for behavioral change that has increased PA[96]. It has been established that ascending stairs is a vigorous-intensity activity, while descending stairs is moderately intense, based on mean heart rate and perceived exertion responses to self-chosen, continuous stair use[98]. Thus, making use of stairs through point-of-decision prompts may help satisfy the daily recommendation for moderate or vigorous activity. Emerging data is also suggesting that climbing escalators may have similar health benefits or consequences as climbing stairs when compared to standing on escalators[99]. Thus, promoting point-of-decision prompts to encourage escalator climbing rather than standing on the escalator could promote energy expenditure. However, psychological barriers such as anxiety and depression, which have been associated with the perceived difficulty in using stairs, must be addressed for maximum PA uptake[98].

Technology use to increase PA

Attractive, personalized, and tailored smartphone-based mHealth PA interventions have been shown to increase PA uptake[100-103]. They positively affect an individual's engagement and perception. Smartphone apps and self-monitoring devices are evolving technologies that promote PA uptake[104, 105]. It has been suggested that video games that require gross motor activity, such as Exergames on Nintendo Wii, Xbox, and PlayStation promote healthy weight and PA in the general population[104, 106]. The use of social media to jumpstart PA has also been documented[104,105].

Education and counselling to increase PA uptake

One of the strategies to improve PA uptake is education and counseling[95]. An assessment of PA at each visit to a physician or health provider will facilitate proper education and counseling. Asking a client the number of minutes per week she or he participated in PA will reinforce the notion that exercise is a vital part of health just like other vital signs of health, such as blood pressure[95]. A conversation about the importance of PA in health can begin if the individual does not meet exercise goals. The focus should be on letting them understand what is expected of them and teaching them how to change their behavior from inactivity to daily PA. Lehr *et al*[107] proposed the ABCD of lifestyle counseling to improve individual health, including daily PA uptake. The acronym ABCD represents assess, barriers, commit, and demonstrate. The ABCD framework for lifestyle counselling starts with: (1) Assessing a patient's readiness for change; (2) identifying potential barriers to change; (3) encouraging patients to commit to measurable goals; and (4) helping them demonstrate progress by selecting an appropriate self-monitoring strategy[107].

CONCLUSION

This article explored the limitations and complications that can result from poorly managed T2DM. These limitations relate to obesity, cardiac complications, renal, vascular, and neurological problems, sexual dysfunction, and decreased participation in ADL, IADL, and work. However, PA, in tandem with a healthy diet, appears to be an effective strategy in reducing the long-term complications of T2DM. It will also curb spending in terms of non-communicable diseases, including diabetes. Specifically, PA regulates or moderates diabetes disability through two mechanisms: The regulation of glucose and lipid metabolism disorders and the optimization of BMI and systemic condition. It is, therefore, imperative to include a prescription of regular, moderate physical exercise/activity in the treatment regimen of all people with T2DM to improve their medical and functional prognosis and quality of life. Exercise can also be used as a health promotion and prevention strategy in population-level interventions.

FOOTNOTES

Author contributions: Oyewole OO, Ale AO, Ogunlana MO, and Gurayah T helped with literature acquisition and contributed to writing the original daft and editing the draft; Oyewole OO helped in the conceptualization and data validation; All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country/Territory of origin: Nigeria

ORCID number: Olufemi O Oyewole Olufemi Oyewole.

S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Yu HG

REFERENCES

1 **Lovic D**, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The Growing Epidemic of Diabetes Mellitus. *Curr Vasc Pharmacol* 2020; **18**: 104-109 [PMID: 30961501 DOI: 10.2174/1570161117666190405165911]
2 **Lin X**, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren Y, Shan PF. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020; **10**: 14790 [PMID: 32901098 DOI: 10.1038/s41598-020-71908-9]
3 **Cho NH**, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018; **138**: 271-281 [PMID: 29496507 DOI: 10.1016/j.diabres.2018.02.023]
4 **Khan MAB**, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes-Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health* 2020; **10**: 107-111 [PMID: 32175717 DOI:

10.2991/jegh.k.191028.001]
5 **Kangethe A**, Lawrence DF, Touya M, Chrones L, Polson M, Evangelatos T. Incremental burden of comorbid major depressive disorder in patients with type 2 diabetes or cardiovascular disease: a retrospective claims analysis. *BMC Health Serv Res* 2021; **21**: 778 [PMID: 34362353 DOI: 10.1186/s12913-021-06802-9]
6 **Köster I**, Huppertz E, Hauner H, Schubert I. Direct costs of diabetes mellitus in Germany-CoDiM 2000-2007. *Exp Clin Endocrinol Diabetes* 2011; **119**: 377-385 [PMID: 21264804 DOI: 10.1055/s-0030-1269847]
7 **Sortsø C**, Green A, Jensen PB, Emneus M. Societal costs of diabetes mellitus in Denmark. *Diabet Med* 2016; **33**: 877-885 [PMID: 26414087 DOI: 10.1111/dme.12965]
8 **Alzaid A**, Ladrón de Guevara P, Beillat M, Lehner Martin V, Atanasov P. Burden of disease and costs associated with type 2 diabetes in emerging and established markets: systematic review analyses. *Expert Rev Pharmacoecon Outcomes Res* 2021; **21**: 785-798 [PMID: 32686530 DOI: 10.1080/14737167.2020.1782748]
9 **Cannon A**, Handelsman Y, Heile M, Shannon M. Burden of Illness in Type 2 Diabetes Mellitus. *J Manag Care Spec Pharm* 2018; **24**: S5-S13 [PMID: 30156443 DOI: 10.18553/jmcp.2018.24.9-a.s5]
10 **Andersson E**, Persson S, Hallén N, Ericsson Å, Thielke D, Lindgren P, Steen Carlsson K, Jendle J. Costs of diabetes complications: hospital-based care and absence from work for 392,200 people with type 2 diabetes and matched control participants in Sweden. *Diabetologia* 2020; **63**: 2582-2594 [PMID: 32968866 DOI: 10.1007/s00125-020-05277-3]
11 **Afroz A**, Alramadan MJ, Hossain MN, Romero L, Alam K, Magliano DJ, Billah B. Cost-of-illness of type 2 diabetes mellitus in low and lower-middle income countries: a systematic review. *BMC Health Serv Res* 2018; **18**: 972 [PMID: 30558591 DOI: 10.1186/s12913-018-3772-8]
12 **Mapa-Tassou C**, Katte JC, Mba Maadjhou C, Mbanya JC. Economic Impact of Diabetes in Africa. *Curr Diab Rep* 2019; **19**: 5 [PMID: 30680578 DOI: 10.1007/s11892-019-1124-7]
13 **Catic T**, Popovic SP, Asimi ZV, Hlavinkova L. Costs of Diabetes Mellitus and Its Complications in Bosnia and Herzegovina. *Mater Sociomed* 2022; **34**: 149-154 [PMID: 36199846 DOI: 10.5455/msm.2022.34.149-154]
14 **Eshwari K**, Kamath VG, Rao CR, Kamath A. Economic burden of type 2 diabetes mellitus management: Epidemiological determinants from a coastal community of Southern India. *WHO South East Asia J Public Health* 2021; **10**: 84-89 [PMID: 35532600 DOI: 10.4103/WHO-SEAJPH.WHO-SEAJPH_20_21]
15 **Ganasegeran K**, Hor CP, Jamil MFA, Loh HC, Noor JM, Hamid NA, Suppiah PD, Abdul Manaf MR, Ch'ng ASH, Looi I. A Systematic Review of the Economic Burden of Type 2 Diabetes in Malaysia. *Int J Environ Res Public Health* 2020; **17** [PMID: 32784771 DOI: 10.3390/ijerph17165723]
16 **Al-Maskari F**, El-Sadig M, Nagelkerke N. Assessment of the direct medical costs of diabetes mellitus and its complications in the United Arab Emirates. *BMC Public Health* 2010; **10**: 679 [PMID: 21059202 DOI: 10.1186/1471-2458-10-679]
17 **Kotwas A**, Karakiewicz B, Zabielska P, Wieder-Huszla S, Jurczak A. Epidemiological factors for type 2 diabetes mellitus: evidence from the Global Burden of Disease. *Arch Public Health* 2021; **79**: 110 [PMID: 34158120 DOI: 10.1186/s13690-021-00632-1]
18 **Yu M**, Zhan X, Yang Z, Huang Y. Measuring the global, regional, and national burden of type 2 diabetes and the attributable risk factors in all 194 countries. *J Diabetes* 2021; **13**: 613-639 [PMID: 33486878 DOI: 10.1111/1753-0407.13159]
19 **Hussain S**, Habib A, Singh A, Akhtar M, Najmi AK. Prevalence of depression among type 2 diabetes mellitus patients in India: A meta-analysis. *Psychiatry Res* 2018; **270**: 264-273 [PMID: 30273857 DOI: 10.1016/j.psychres.2018.09.037]
20 **Amanat S**, Ghahri S, Dianatinasab A, Fararouei M, Dianatinasab M. Exercise and Type 2 Diabetes. *Adv Exp Med Biol* 2020; **1228**: 91-105 [PMID: 32342452 DOI: 10.1007/978-981-15-1792-1_6]
21 **Taylor R**, Valabhji J, Aveyard P, Paul D. Prevention and reversal of Type 2 diabetes: highlights from a symposium at the 2019 Diabetes UK Annual Professional Conference. *Diabet Med* 2019; **36**: 359-365 [PMID: 30597609 DOI: 10.1111/dme.13892]
22 **Kanaley JA**, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, Kirwan JP, Zierath JR. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. *Med Sci Sports Exerc* 2022; **54**: 353-368 [PMID: 35029593 DOI: 10.1249/MSS.0000000000002800]
23 **Rachmani R**, Slavachevski I, Berla M, Frommer-Shapira R, Ravid M. Teaching and motivating patients to control their risk factors retards progression of cardiovascular as well as microvascular sequelae of Type 2 diabetes mellitus- a randomized prospective 8 years follow-up study. *Diabet Med* 2005; **22**: 410-414 [PMID: 15787665 DOI: 10.1111/j.1464-5491.2005.01428.x]
24 **Peimani M**, Garmaroudi G, Stewart AL, Yekaninejad M, Shakibazadeh E, Nasli-Esfahani E. Type 2 Diabetes Burden and Diabetes Distress: The Buffering Effect of Patient-centred Communication. *Can J Diabetes* 2022; **46**: 353-360 [PMID: 35589533 DOI: 10.1016/j.jcjd.2021.11.007]
25 **World Health Organization**. The top 10 causes of death. 2020. [cited 7 March 2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
26 **Pan American Health Organization**. Leading causes of mortality and health loss at regional, subregional, and country levels in the Region of the Americas. 2021. [cited 7 March 2023]. Available from: https://www.paho.org/en/enlace/Leading-causes-death-and-disability
27 **Bradshaw D**, Norman R, Pieterse D, Levitt NS; South African Comparative Risk Assessment Collaborating Group. Estimating the burden of disease attributable to diabetes in South Africa in 2000. *S Afr Med J* 2007; **97**: 700-706 [PMID: 17952227]
28 **Powell A**. Obesity? Diabetes? We've been set up. Harvard Gazette. March 7, 2012. [cited 7 March 2023]. Available from: https://news.harvard.edu/gazette/story/2012/03/the-big-setup/
29 **Chaudhry ZW**, Gannon MC, Nuttall FQ. Stability of body weight in type 2 diabetes. *Diabetes Care* 2006; **29**: 493-497 [PMID: 16505494 DOI: 10.2337/diacare.29.03.06.dc05-1703]
30 **Russell-Jones D**, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes Metab* 2007; **9**: 799-812 [PMID: 17924864 DOI: 10.1111/j.1463-1326.2006.00686.x]

31 **Chiu CJ**, Wray LA, Lu FH, Beverly EA. BMI change patterns and disability development of middle-aged adults with diabetes: a dual trajectory modeling approach. *J Gen Intern Med* 2013; **28**: 1150-1156 [PMID: 23463456 DOI: 10.1007/s11606-013-2399-z]

32 **Ferraro KF**, Su YP, Gretebeck RJ, Black DR, Badylak SF. Body mass index and disability in adulthood: a 20-year panel study. *Am J Public Health* 2002; **92**: 834-840 [PMID: 11988456 DOI: 10.2105/ajph.92.5.834]

33 **Dhamoon MS**, Moon YP, Paik MC, Sacco RL, Elkind MS. Diabetes predicts long-term disability in an elderly urban cohort: the Northern Manhattan Study. *Ann Epidemiol* 2014; **24**: 362-368.e1 [PMID: 24485410 DOI: 10.1016/j.annepidem.2013.12.013]

34 **Sakurai T**, Iimuro S, Sakamaki K, Umegaki H, Araki A, Ohashi Y, Ito H; Japanese Elderly Diabetes Intervention Trial Study Group. Risk factors for a 6-year decline in physical disability and functional limitations among elderly people with type 2 diabetes in the Japanese Elderly Diabetes Intervention Trial. *Geriatr Gerontol Int* 2012; **12** Suppl 1: 117-126 [PMID: 22435947 DOI: 10.1111/j.1447-0594.2011.00819.x]

35 **Andrade CS**, Ribeiro GS, Santos CAST, Neves RCS, Moreira ED Jr. Factors associated with high levels of glycated haemoglobin in patients with type 1 diabetes: a multicentre study in Brazil. *BMJ Open* 2017; **7**: e018094 [PMID: 29247092 DOI: 10.1136/bmjopen-2017-018094]

36 **American Diabetes Association**. 5. Glycemic Targets. *Diabetes Care* 2016; **39** Suppl 1: S39-S46 [PMID: 26696679 DOI: 10.2337/dc16-S008]

37 **Fox KM**, Gerber Pharmd RA, Bolinder B, Chen J, Kumar S. Prevalence of inadequate glycemic control among patients with type 2 diabetes in the United Kingdom general practice research database: A series of retrospective analyses of data from 1998 through 2002. *Clin Ther* 2006; **28**: 388-395 [PMID: 16750453 DOI: 10.1016/j.clinthera.2006.03.005]

38 **Gregg EW**, Mangione CM, Cauley JA, Thompson TJ, Schwartz AV, Ensrud KE, Nevitt MC; Study of Osteoporotic Fractures Research Group. Diabetes and incidence of functional disability in older women. *Diabetes Care* 2002; **25**: 61-67 [PMID: 11772902 DOI: 10.2337/diacare.25.1.61]

39 **Volpato S**, Blaum C, Resnick H, Ferrucci L, Fried LP, Guralnik JM; Women's Health and Aging Study. Comorbidities and impairments explaining the association between diabetes and lower extremity disability: The Women's Health and Aging Study. *Diabetes Care* 2002; **25**: 678-683 [PMID: 11919124 DOI: 10.2337/diacare.25.4.678]

40 **Magliano DJ**, Sacre JW, Harding JL, Gregg EW, Zimmet PZ, Shaw JE. Young-onset type 2 diabetes mellitus-implications for morbidity and mortality. *Nat Rev Endocrinol* 2020; **16**: 321-331 [PMID: 32203408 DOI: 10.1038/s41574-020-0334-z]

41 **Volpato S**, Maraldi C, Fellin R. Type 2 diabetes and risk for functional decline and disability in older persons. *Curr Diabetes Rev* 2010; **6**: 134-143 [PMID: 20380626 DOI: 10.2174/157339910791162961]

42 **Maggi S**, Noale M, Gallina P, Marzari C, Bianchi D, Limongi F, Crepaldi G; ILSA Group. Physical disability among older Italians with diabetes. The ILSA study. *Diabetologia* 2004; **47**: 1957-1962 [PMID: 15599698 DOI: 10.1007/s00125-004-1555-8]

43 **Gregg EW**, Engelgau MM, Narayan V. Complications of diabetes in elderly people. *BMJ* 2002; **325**: 916-917 [PMID: 12399324 DOI: 10.1136/bmj.325.7370.916]

44 **Thein FS**, Li Y, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Physical frailty and cognitive impairment is associated with diabetes and adversely impact functional status and mortality. *Postgrad Med* 2018; **130**: 561-567 [PMID: 29949390 DOI: 10.1080/00325481.2018.1491779]

45 **Bergman H**, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, Wolfson C. Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007; **62**: 731-737 [PMID: 17634320 DOI: 10.1093/gerona/62.7.731]

46 **Fried LP**, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146-M156 [PMID: 11253156 DOI: 10.1093/gerona/56.3.m146]

47 **Ahmad E**, Sargeant JA, Yates T, Webb DR, Davies MJ. Type 2 Diabetes and Impaired Physical Function: A Growing Problem. *Diabetology* 2022; **3**: 30-45 [DOI: 10.3390/diabetology3010003]

48 **Wong E**, Backholer K, Gearon E, Harding J, Freak-Poli R, Stevenson C, Peeters A. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2013; **1**: 106-114 [PMID: 24622316 DOI: 10.1016/S2213-8587(13)70046-9]

49 **Morley JE**, Malmstrom TK, Rodriguez-Mañas L, Sinclair AJ. Frailty, sarcopenia and diabetes. *J Am Med Dir Assoc* 2014; **15**: 853-859 [PMID: 25455530 DOI: 10.1016/j.jamda.2014.10.001]

50 **Rogerson MC**, Murphy BM, Bird S, Morris T. "I don't have the heart": a qualitative study of barriers to and facilitators of physical activity for people with coronary heart disease and depressive symptoms. *Int J Behav Nutr Phys Act* 2012; **9**: 140 [PMID: 23194091 DOI: 10.1186/1479-5868-9-140]

51 **McCarthy MM**, Davey J, Wackers FJ, Chyun DA. Predictors of physical inactivity in men and women with type 2 diabetes from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Educ* 2014; **40**: 678-687 [PMID: 24942531 DOI: 10.1177/0145721714540055]

52 **Loprinzi PD**, Hager KK, Ramulu PY. Physical activity, glycemic control, and diabetic peripheral neuropathy: a national sample. *J Diabetes Complications* 2014; **28**: 17-21 [PMID: 24090951 DOI: 10.1016/j.jdiacomp.2013.08.008]

53 **Zhao G**, Ford ES, Li C, Balluz LS. Physical activity in U.S. older adults with diabetes mellitus: prevalence and correlates of meeting physical activity recommendations. *J Am Geriatr Soc* 2011; **59**: 132-137 [PMID: 21226683 DOI: 10.1111/j.1532-5415.2010.03236.x]

54 **Molsted S**, Tribler J, Snorgaard O. Musculoskeletal pain in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2012; **96**: 135-140 [PMID: 22244365 DOI: 10.1016/j.diabres.2011.12.022]

55 **Buckworth J**, Lee RE, Regan G, Schneider LK, DiClemente CC. Decomposing intrinsic and extrinsic motivation for exercise: Application to stages of motivational readiness. *Psychol Sport Exerc* 2007; **8**: 441-461 [DOI: 10.1016/j.psychsport.2006.06.007]

56 **Moschny A**, Platen P, Klaassen-Mielke R, Trampisch U, Hinrichs T. Barriers to physical activity in older adults in Germany: a cross-sectional study. *Int J Behav Nutr Phys Act* 2011; **8**: 121 [PMID: 22047024 DOI:

10.1186/1479-5868-8-121]
57 **Lidegaard LP**, Schwennesen N, Willaing I, Faerch K. Barriers to and motivators for physical activity among people with Type 2 diabetes: patients' perspectives. *Diabet Med* 2016; **33**: 1677-1685 [PMID: 27279343 DOI: 10.1111/dme.13167]
58 **Bombak AE**. Obese persons' physical activity experiences and motivations across weight changes: a qualitative exploratory study. *BMC Public Health* 2015; **15**: 1129 [PMID: 26577260 DOI: 10.1186/s12889-015-2456-0]
59 **Garber CE**, Greaney ML, Riebe D, Nigg CR, Burbank PA, Clark PG. Physical and mental health-related correlates of physical function in community dwelling older adults: a cross sectional study. *BMC Geriatr* 2010; **10**: 6 [PMID: 20128902 DOI: 10.1186/1471-2318-10-6]
60 **Painter P**, Stewart AL, Carey S. Physical functioning: definitions, measurement, and expectations. *Adv Ren Replace Ther* 1999; **6**: 110-123 [PMID: 10230878 DOI: 10.1016/s1073-4449(99)70028-2]
61 **Peer N**, Kengne AP, Motala AA, Mbanya JC. Diabetes in the Africa Region: an update. *Diabetes Res Clin Pract* 2014; **103**: 197-205 [PMID: 24315460 DOI: 10.1016/j.diabres.2013.11.006]
62 **Huang ES**, Gorawara-Bhat R, Chin MH. Self-reported goals of older patients with type 2 diabetes mellitus. *J Am Geriatr Soc* 2005; **53**: 306-311 [PMID: 15673357 DOI: 10.1111/j.1532-5415.2005.53119.x]
63 **Godino JG**, Appel LJ, Gross AL, Schrack JA, Parrinello CM, Kalyani RR, Windham BG, Pankow JS, Kritchevsky SB, Bandeen-Roche K, Selvin E. Diabetes, hyperglycemia, and the burden of functional disability among older adults in a community-based study. *J Diabetes* 2017; **9**: 76-84 [PMID: 26847713 DOI: 10.1111/1753-0407.12386]
64 **Malavige LS**, Levy JC. Erectile dysfunction in diabetes mellitus. *J Sex Med* 2009; **6**: 1232-1247 [PMID: 19210706 DOI: 10.1111/j.1743-6109.2008.01168.x]
65 **Phé V**, Rouprêt M. Erectile dysfunction and diabetes: a review of the current evidence-based medicine and a synthesis of the main available therapies. *Diabetes Metab* 2012; **38**: 1-13 [PMID: 22056307 DOI: 10.1016/j.diabet.2011.09.003]
66 **Jackson G**. Sexual dysfunction and diabetes. *Int J Clin Pract* 2004; **58**: 358-362 [PMID: 15161120 DOI: 10.1111/j.1368-5031.2004.00180.x]
67 **Omidvar S**, Niaki MT, Amiri FN, Kheyrkhah F. Sexual dysfunction among women with diabetes mellitus in a diabetic center in Amol. *J Nat Sci Biol Med* 2013; **4**: 321-324 [PMID: 24082725 DOI: 10.4103/0976-9668.116992]
68 **White L**, Duncan G. Medical-surgical nursing: an integrated approach. 2nd ed. February 8, 2012. [cited 7 March 2023]. Available from: https://archive.org/details/medicalsurgicaln0000whit
69 **Bardenheier BH**, Gregg EW, Zhuo X, Cheng YJ, Geiss LS. Association of functional decline with subsequent diabetes incidence in U.S. adults aged 51 years and older: the Health and Retirement Study 1998-2010. *Diabetes Care* 2014; **37**: 1032-1038 [PMID: 24550218 DOI: 10.2337/dc13-2216]
70 **Gregg EW**, Beckles GL, Williamson DF, Leveille SG, Langlois JA, Engelgau MM, Narayan KM. Diabetes and physical disability among older U.S. adults. *Diabetes Care* 2000; **23**: 1272-1277 [PMID: 10977018 DOI: 10.2337/diacare.23.9.1272]
71 **Rubin RR**, Peyrot M. Quality of life and diabetes. *Diabetes Metab Res Rev* 1999; **15**: 205-218 [PMID: 10441043 DOI: 10.1002/(sici)1520-7560(199905/06)15:3<205::aid-dmrr29>3.0.co;2-o]
72 **Jing X**, Chen J, Dong Y, Han D, Zhao H, Wang X, Gao F, Li C, Cui Z, Liu Y, Ma J. Related factors of quality of life of type 2 diabetes patients: a systematic review and meta-analysis. *Health Qual Life Outcomes* 2018; **16**: 189 [PMID: 30231882 DOI: 10.1186/s12955-018-1021-9]
73 **Nord E**, Daniels N, Kamlet M. QALYs: some challenges. *Value Health* 2009; **12** Suppl 1: S10-S15 [PMID: 19250125 DOI: 10.1111/j.1524-4733.2009.00516.x]
74 **Nelson KM**, Reiber G, Boyko EJ; NHANES III. Diet and exercise among adults with type 2 diabetes: findings from the third national health and nutrition examination survey (NHANES III). *Diabetes Care* 2002; **25**: 1722-1728 [PMID: 12351468 DOI: 10.2337/diacare.25.10.1722]
75 **Duarte CK**, Almeida JC, Merker AJ, Brauer Fde O, Rodrigues Tda C. Physical activity level and exercise in patients with diabetes mellitus. *Rev Assoc Med Bras (1992)* 2012; **58**: 215-221 [PMID: 22569617]
76 **Nor Shazwani MN Jr**, Suzana S, Hanis Mastura Y, Lim CJ, Teh SC, Mohd Fauzee MZ, Lim HC, Dahlia S, Norliza M. Assessment of Physical Activity Level among Individuals with Type 2 Diabetes Mellitus at Cheras Health Clinic, Kuala Lumpur. *Malays J Nutr* 2010; **16**: 101-112 [PMID: 22691857]
77 **Oyewole OO**, Odusan O, Oritogun KS, Idowu AO. Physical activity among type-2 diabetic adult Nigerians. *Ann Afr Med* 2014; **13**: 189-194 [PMID: 25287033 DOI: 10.4103/1596-3519.142290]
78 **Oguntibeju OO**, Odunaiya N, Oladipo B, Truter EJ. Health behaviour and quality of life of patients with type 2 diabetes attending selected hospitals in south western Nigeria. *West Indian Med J* 2012; **61**: 619-626 [PMID: 23441358]
79 **Codogno JS**, Fernandes RA, Sarti FM, Freitas Júnior IF, Monteiro HL. The burden of physical activity on type 2 diabetes public healthcare expenditures among adults: a retrospective study. *BMC Public Health* 2011; **11**: 275 [PMID: 21542924 DOI: 10.1186/1471-2458-11-275]
80 **Chimen M**, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia* 2012; **55**: 542-551 [PMID: 22189486 DOI: 10.1007/s00125-011-2403-2]
81 **Sigal RJ**, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; **29**: 1433-1438 [PMID: 16732040 DOI: 10.2337/dc06-9910]
82 **Yang D**, Yang Y, Li Y, Han R. Physical Exercise as Therapy for Type 2 Diabetes Mellitus: From Mechanism to Orientation. *Ann Nutr Metab* 2019; **74**: 313-321 [PMID: 31013502 DOI: 10.1159/000500110]
83 **Thomas N**, Alder E, Leese GP. Barriers to physical activity in patients with diabetes. *Postgrad Med J* 2004; **80**: 287-291 [PMID: 15138320 DOI: 10.1136/pgmj.2003.010553]
84 **Schmidt SK**, Hemmestad L, MacDonald CS, Langberg H, Valentiner LS. Motivation and Barriers to Maintaining Lifestyle Changes in Patients with Type 2 Diabetes after an Intensive Lifestyle Intervention (The U-TURN Trial): A Longitudinal Qualitative Study. *Int J Environ Res Public Health* 2020; **17** [PMID: 33066239 DOI: 10.3390/ijerph17207454]

85 **Gao S**, Yu L, Yi G, Li T, Chen Z, Ding J. Exercise Intervention as a Therapy in Patients with Diabetes Mellitus and Sarcopenia: A Meta-Analysis. *Diabetes Ther* 2022; **13**: 1311-1325 [PMID: 35648376 DOI: 10.1007/s13300-022-01275-3]

86 **Dempsey PC**, Owen N, Yates TE, Kingwell BA, Dunstan DW. Sitting Less and Moving More: Improved Glycaemic Control for Type 2 Diabetes Prevention and Management. *Curr Diab Rep* 2016; **16**: 114 [PMID: 27699700 DOI: 10.1007/s11892-016-0797-4]

87 **Ekelund U**, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, Bauman A, Lee IM; Lancet Physical Activity Series 2 Executive Committe; Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet* 2016; **388**: 1302-1310 [PMID: 27475271 DOI: 10.1016/S0140-6736(16)30370-1]

88 **Fritschi C**, Bronas UG, Park CG, Collins EG, Quinn L. Early declines in physical function among aging adults with type 2 diabetes. *J Diabetes Complications* 2017; **31**: 347-352 [PMID: 27450624 DOI: 10.1016/j.jdiacomp.2016.06.022]

89 **Brazo-Sayavera J**, López-Torres O, Martos-Bermúdez Á, Rodriguez-Garcia L, González-Gross M, Guadalupe-Grau A. Effects of Power Training on Physical Activity, Sitting Time, Disability, and Quality of Life in Older Patients With Type 2 Diabetes During the COVID-19 Confinement. *J Phys Act Health* 2021; **18**: 660-668 [PMID: 33883291 DOI: 10.1123/jpah.2020-0489]

90 **Dempsey PC**, Dunstan DW, Larsen RN, Lambert GW, Kingwell BA, Owen N. Prolonged uninterrupted sitting increases fatigue in type 2 diabetes. *Diabetes Res Clin Pract* 2018; **135**: 128-133 [PMID: 29129482 DOI: 10.1016/j.diabres.2017.11.001]

91 **Hao W**, Li J, Fu P, Zhao D, Jing Z, Wang Y, Yu C, Yuan Y, Zhou C. Physical frailty and health-related quality of life among Chinese rural older adults: a moderated mediation analysis of physical disability and physical activity. *BMJ Open* 2021; **11**: e042496 [PMID: 33419914 DOI: 10.1136/bmjopen-2020-042496]

92 **Hu W**, Chu J, Chen X, Liu S, Sun N, Han Q, Li T, Feng Z, He Q, Shen Y. The role of depression and physical activity in the association of between sleep quality, and duration with and health-related quality of life among the elderly: a UK Biobank cross-sectional study. *BMC Geriatr* 2022; **22**: 338 [PMID: 35436848 DOI: 10.1186/s12877-022-03047-x]

93 **Arena R**, Sagner M, Byrne NM, Williams AD, McNeil A, Street SJ, Hills AP. Novel approaches for the promotion of physical activity and exercise for prevention and management of type 2 diabetes. *Eur J Clin Nutr* 2017; **71**: 858-864 [PMID: 28443607 DOI: 10.1038/ejcn.2017.53]

94 **Centers for Disease Control and Prevention**. Strategies to Prevent Obesity and Other Chronic Diseases: The CDC Guide to Strategies to Increase Physical Activity in the Community. 2011. [cited 7 March 2023]. Available from: http://www.cdc.gov/obesity

95 **Tuso P**. Strategies to Increase Physical Activity. *Perm J* 2015; **19**: 84-88 [PMID: 26517440 DOI: 10.7812/TPP/14-242]

96 **Kaczynski AT**, Wilhelm Stanis SA, Hipp JA. Point-of-decision prompts for increasing park-based physical activity: a crowdsource analysis. *Prev Med* 2014; **69**: 87-89 [PMID: 25204987 DOI: 10.1016/j.ypmed.2014.08.029]

97 **Soler RE**, Leeks KD, Buchanan LR, Brownson RC, Heath GW, Hopkins DH; Task Force on Community Preventive Services. Point-of-decision prompts to increase stair use. A systematic review update. *Am J Prev Med* 2010; **38**: S292-S300 [PMID: 20117614 DOI: 10.1016/j.amepre.2009.10.028]

98 **Gay JL**, Cherof SA, LaFlamme CC, O'Connor PJ. Psychological Aspects of Stair Use: A Systematic Review. *Am J Lifestyle Med* 2022; **16**: 109-121 [PMID: 35185433 DOI: 10.1177/1559827619870104]

99 **Bellettiere J**, Nguyen B, Liles S, Berardi V, Adams MA, Dempsey P, Benporat Y, Kerr J, LaCroix AZ, Hovell M. Prompts to increase physical activity at points-of-choice between stairs and escalators: what about escalator climbers? *Transl Behav Med* 2019; **9**: 656-662 [PMID: 30099542 DOI: 10.1093/tbm/iby080]

100 **Domin A**, Spruijt-Metz D, Theisen D, Ouzzahra Y, Vögele C. Smartphone-Based Interventions for Physical Activity Promotion: Scoping Review of the Evidence Over the Last 10 Years. *JMIR Mhealth Uhealth* 2021; **9**: e24308 [PMID: 34287209 DOI: 10.2196/24308]

101 **Coughlin SS**, Whitehead M, Sheats JQ, Mastromonico J, Smith S. A Review of Smartphone Applications for Promoting Physical Activity. *Jacobs J Community Med* 2016; **2** [PMID: 27034992]

102 **Stuckey MI**, Carter SW, Knight E. The role of smartphones in encouraging physical activity in adults. *Int J Gen Med* 2017; **10**: 293-303 [PMID: 28979157 DOI: 10.2147/IJGM.S134095]

103 **Jee H**. Review of researches on smartphone applications for physical activity promotion in healthy adults. *J Exerc Rehabil* 2017; **13**: 3-11 [PMID: 28349027 DOI: 10.12965/jer.1732928.464]

104 **Chaddha A**, Jackson EA, Richardson CR, Franklin BA. Technology to Help Promote Physical Activity. *Am J Cardiol* 2017; **119**: 149-152 [PMID: 27889045 DOI: 10.1016/j.amjcard.2016.09.025]

105 **Tate DF**, Lyons EJ, Valle CG. High-tech tools for exercise motivation: use and role of technologies such as the internet, mobile applications, social media, and video games. *Diabetes Spectr* 2015; **28**: 45-54 [PMID: 25717278 DOI: 10.2337/diaspect.28.1.45]

106 **Woessner MN**, Tacey A, Levinger-Limor A, Parker AG, Levinger P, Levinger I. The Evolution of Technology and Physical Inactivity: The Good, the Bad, and the Way Forward. *Front Public Health* 2021; **9**: 655491 [PMID: 34123989 DOI: 10.3389/fpubh.2021.655491]

107 **Lehr AL**, Driver SL, Stone NJ. The ABCDs of Lifestyle Counseling. *JAMA Cardiol* 2016; **1**: 505-506 [PMID: 27439176 DOI: 10.1001/jamacardio.2016.1419]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3140-3147

DOI: 10.12998/wjcc.v11.i14.3140

ISSN 2307-8960 (online)

MINIREVIEWS

Postoperative hypoxemia for patients undergoing Stanford type A aortic dissection

Hai-Yuan Liu, Shuai-Peng Zhang, Cheng-Xin Zhang, Qing-Yun Gao, Yu-Yong Liu, Sheng-Lin Ge

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Papazafiropoulou A, Greece; Ueda H, Japan

Received: November 24, 2022
Peer-review started: November 24, 2022
First decision: February 28, 2023
Revised: March 6, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 16, 2023

Hai-Yuan Liu, Shuai-Peng Zhang, Cheng-Xin Zhang, Qing-Yun Gao, Department of Cardiovascular Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui Province, China

Yu-Yong Liu, Sheng-Lin Ge, First Affiliated Hospital of Anhui Medical University, Anhui Medical University, Hefei 230032, Anhui Province, China

Corresponding author: Sheng-Lin Ge, Doctor, Professor, First Affiliated Hospital of Anhui Medical University, Anhui Medical University, No. 218 Jixi Road, Shushan District, Hefei 230032, Anhui Province, China. wenxian84@126.com

Abstract

Clinically, it is widely recognized that surgical treatment is the preferred and reliable option for Stanford type A aortic dissection. Stanford type A aortic dissection is an emergent and serious cardiovascular disease characterized with an acute onset, poor prognosis, and high mortality. However, the incidences of postoperative complications are relatively higher due to the complexity of the disease and its intricate procedure. It has been considered that hypoxemia, one of the most common postoperative complications, plays an important role in having a worse clinical prognosis. Therefore, the effective intervention of postoperative hypoxemia is significant for the improved prognosis of patients with Stanford type A aortic dissection.

Key Words: Stanford type A aortic dissection; Hypoxemia; Risk factors; Intervention; Mortality

Core Tip: Surgically, it has been considered that in patients suffering with Stanford type A dissection, postoperative complications are the main risk factors that lead to higher mortality and worse outcome. As one of the most common postoperative complications, the importance of prevention and intervention on the postoperative hypoxemia should be fully emphasized with the aim to decrease the mortality and improve the outcome.

Citation: Liu HY, Zhang SP, Zhang CX, Gao QY, Liu YY, Ge SL. Postoperative hypoxemia for patients undergoing Stanford type A aortic dissection. *World J Clin Cases* 2023; 11(14): 3140-3147
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3140.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3140

INTRODUCTION

Stanford type A aortic dissection is described as the unstable and fatal rupture of aortic wall involving the ascending aorta and arch. The physio-pathological alteration of Stanford type A aortic dissection is mainly summarized as the separation from media layers leading to false lumen within the wall under the influence of two critical factors, weakness and increased tension of the aortic wall[1]. Once confirmed, among different clinical protocols, the surgical strategy should be predominated and under the guide of strict assessment, the long-term clinical outcome of patients will be improved positively[2, 3]. On the other hand, limited by huge difficulty and complexity of surgical procedure as well as various individual uncertainty of patients, the incidences of postoperative complications are relatively higher. Additionally, hypoxemia caused by multifactors is closely associated with longer mechanical ventilation and hospital stay, progressive respiratory failure, and increased mortality[4].

Therefore, the aim of this study is to provide clinical recommendations for the improvement of postoperative hypoxemia of patients with Stanford type A aortic dissection based on risk factors and intervention of hypoxemia.

RISK FACTORS OF POSTOPERATIVE HYPOXEMIA

Organic disorder

Postoperative stable organic function is positively associated with the inhibition of an inflammatory response. Hence, under the consequence of organic disorder, both internal environment disturbance and inflammatory response are activated. In a retrospective study aiming to explore the independent predictors of hypoxemia, it was found that renal disorder is an independent factor associated with hypoxemia. Activated inflammatory response, unregulated production of erythropoietin, and abnormal delivery of oxygen are also considered possible mechanisms. However, there is no significant correlation between renal insufficiency and mild hypoxemia[5]. Moreover, according to Guo *et al*[6], it has been demonstrated that complicated hypertension is found in the majority of patients with Stanford type A aortic dissection, which leads to atherosclerosis, is negatively associated with pulmonary circulation, and may further induce postoperative hypoxemia. In addition, impairment of the respiratory system by the cascade reactions, originating from aortic dissection, is thought to be pro-inflammatory, which increases the permeability of both endothelial and epithelial cells. Pulmonary vascular pressure affects the physiological function of alveolar surfactant and eventually disturbs normal oxygenation processes[7]. Meanwhile, it has been indicated that angiotensin II is related to the apoptosis of pulmonary microvascular endothelial cells and the upregulated expression of monocyte chemoattractant protein-1 (MCP-1). Angiotensin II is widely considered the key factor during the development of dissection. It exaggerates elastin fragmentation and damages the structure of adventitial layer through activation of caspase-3 and imbalance of the B-cell lymphoma-2 (Bcl-2)/Bcl-2-associated X protein ratio. As a result, both angiotensin II and MCP-1 are critical factors for the inactivated alveolus-capillary barrier and increased pulmonary vascular permeability[8,9].

Obesity

Clinically, during the postoperative stage, the respiratory function of obese patients with Stanford type A aortic dissection is less stable and insufficient to maintain the physiological demands due to limited rehabilitation processes. The lung compliance of obese patients is generally weaker, which means that both breathing difficulties and respiratory resistance are more frequent among the obese population. Obesity is also a driving factor for oxidative stress and reactive oxygen products causing direct deterioration of lung function even hypoxemia[10]. In a retrospective study conducted by Sheng *et al*[11], it has been found that 25 kg/m^2 of body mass index (BMI) is the threshold value; if exceeded, the assessment of lung function becomes worse and the possibility of complications with postoperative hypoxemia is greater. In another study focusing on the Japanese population, the obese threshold of BMI was set to 30 kg/m^2, while 25.5-29.0 kg/m^2 was defined as overweight. It was found that, compared with patients with normal weight, the incidences of ventilation > 48 h for the overweight and obese patients were 60.1% and 78.3%, respectively[12]. Shi *et al*[13] indicated that elevated free fatty acid in obese patients is associated with early postoperative lung damage through the process of endothelial activation and is inversely related to the lowest oxygen level 24 h after cardiac surgery. Furthermore, the level of malondialdehyde is significantly increased in obese patients with aortic dissection, which

indicates that the balance between oxidation and antioxidation is destroyed and sequentially larger secretions and synthesis of inflammatory factors are activated[14]. Meanwhile, patients with obesity are at high risk for obstructive sleep apnea (OSA), and of note, OSA is the risk factor of the development for aortic dissection and postoperative hypoxemia. First, based on findings from a study conducted by Wang *et al*[15], aortic root diameter is positively correlated with the severity of OSA. Consequently, due to the negative effects of adverse apnea events causing failure of the oxidative system, the cascade of inflammatory reactions and release of cytokines such as interleukin (IL)-2, IL-4, and IL-6 are apparent among patients with OSA[16]. Similarly, in a retrospective study focusing on the Chinese patients, the predictive value of OSA on hypoxemia after Stanford type A aortic dissection should be emphasized although the exact mechanism remains unknown[17].

Transfusion of blood products

Since the surgical treatment of Stanford type A aortic dissection is time consuming, considerable blood lost is inevitable during the procedure. Transfusion is necessary to maintain the relative normal level of hemoglobin. However, on the other hand, transfusion-related adverse events including allergy, immune response, infection, circulatory overload, and even organic injury should not be ignored and evaluated with caution. Currently, transfusion-related acute lung injury (TRALI) is the most frequent adverse event that possibly may induce secondary severe postoperative hypoxemia. In a large cohort study enrolling a total of 8944 patients, with the aim of decreasing the incidence of TRALI, it was demonstrated that the mortality of TRALI in the intensive care unit (ICU) was 70%, which is significantly higher than that in other medical units. Hence, it is especially challenging to patients undergoing surgery for Stanford type A aortic dissection, and some improvements have also been observed through the use of solvent/detergent plasma; nevertheless, there are no significant clinical differences[18]. Recently, enhanced coagulation and anticoagulation, as well as damaged fibrinolysis, have been found in the TRALI animal model, through which sequential increased fibrin accumulation in lungs led to platelet capture, the potential risk factor of hypercoagulable state and formation of pulmonary thrombin [19]. Neutrophil extracellular trap (NET), to some extent, is thought to be related to the clinical advancement of TRALI through the impairment of both lung tissue and endothelial cells. Le *et al*[20] found that the inhibition of protective factor, Krüppel-like Factor 2, is induced by microRNA 144 (miR-144) and further activates the nuclear factor-kappa B (NF-κB)/C-X-C motif chemokine receptor 1 signaling pathway, which are possibly responsible for the generation of NET. As another newer mechanism concentrating on the soluble antigen by Bayat *et al*[21], the binding between soluble cluster of differentiation 177/proteinase 3 and platelet endothelial cell adhesion molecule-1 activates endothelial cells and even overrides respiratory functional barrier. In addition to TRALI, transfusion-associated circulatory overload is another potential risk factor to pulmonary edema with clinical presentations including dyspnea, jugular vein engorgement, and elevated systolic blood pressure due to increased pulmonary vascular permeability[22].

Cardiopulmonary bypass

Cardiopulmonary bypass (CPB), an indispensable assisted platform during the surgical procedure of Stanford type A aortic dissection, is critically responsible for the maintenance and protection of normal cardiopulmonary physiological function. Nevertheless, CPB-related adverse events, which are gradually presented following the duration of surgery, include the immune response originating from extracorporeal blood circuit and injury of blood components by compression of the mechanical pump. Lung injury by CPB is mainly concluded as two significant points: ischemia-reperfusion injury and systematic inflammatory reaction. There is a synergistic effect for both, of which, vessels, tissue, and parenchyma of pulmonary are seriously affected. Therefore, a series of pathological alterations of the lungs, predicting postoperative hypoxemia and CPB duration association are observed such as impaired permeability, interstitial edema, fluid accumulation, reduced surface-active substances, and gas exchange disorder [23]. In an observatory study of a rat model, established by Deng *et al*[24], it was shown that high-mobility cassette-1/Toll-like receptor 4 (TLR4)/NF-κB is a reliable signaling pathway that induces CPB-related lung injury and activates a pro-inflammatory effect. Moreover, recently, the association between ferroptosis and CPB-related lung injury was first demonstrated based on the finding that the level of labeled indicators for ferroptosis, glutathione peroxidase 4, and acyl-coenzyme A synthetase long-chain family member 4 is regulated significantly within lung tissue after CPB[25]. As is well known, deep hypothermic circulatory arrest (DHCA) is a special and important period during the entire surgical procedure of Stanford type A aortic dissection, within which a relative bloodless field is provided to increase the possibility of a successful surgery. On the other hand, DHCA is also a risk factor for some postoperative complications including hypoxemia due to ischemia and hypoxia. Kong *et al*[26] suggested that activated autophagy by DHCA is associated with lung injury and its presentation with time-dependent dynamic change characterized as activity decreasing at 3 h after surgery while increasing at 6 h after surgery. Metabolically, especially within the dorsocaudal lung region, CPB/DHCA also affects the regulation pathway of metabolites including amino acids, carbohydrates, lipids, steroids, and vitamins[27].

Other factors

Severe pain and older age, to some extent, are closely correlated with postoperative hypoxemia, whereas reduced muscular strength with a grip < 15 s, due to inadequate evaluation of muscle reversal, is a higher significant predictor contributing to the hypoxemia[28]. Besides, smoking history, chronic respiratory disease, lower oxygenation with arterial oxygen saturation < 96% should be emphasized during the comprehensive assessment for postoperative hypoxemia, and interestingly, different from the obesity mentioned above, the possibility of postoperative hypoxemia for patients with relatively lower BMI < 18.5 kg/m^2 is also higher than that for those with normal BMI, possibly suggesting that malnourishment and/or other complicated chronic diseases are equally significant for the pathogenesis [29]. In an animal model of acute lung injury, Wu *et al*[30] indicated that the pulmonary edema, alveolar protein leaking, and inflammatory response were found in rats treated with hyperglycemia, which was associated with the upregulated serum-glucocorticoid kinase 1-NKCC1 pathway inhibiting excessive fluid removal and activating the inflammatory response. Morey *et al*[31] demonstrated that the synergy effect between hyperglycemia and hypoxemia is significant for persistent inflammation state delaying or even worsening the clinical outcome.

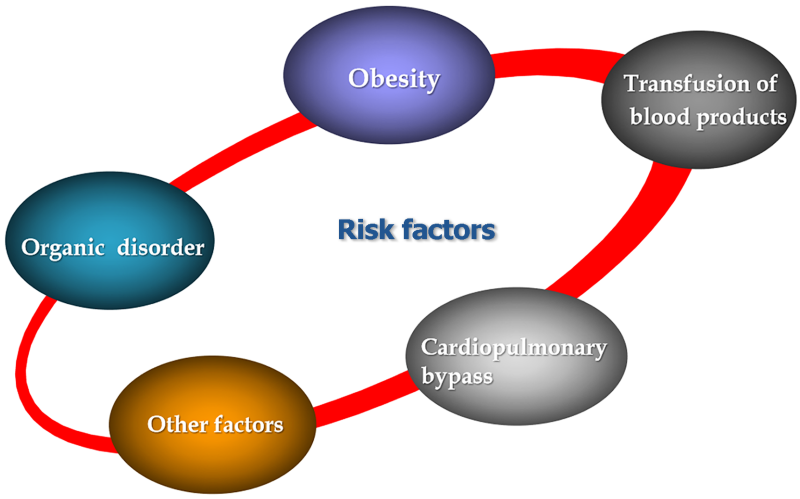
THE INTERVENTION OF POSTOPERATIVE HYPOXEMIA

Medicine intervention

To date, conventionally, medicine intervention should be necessary and compulsory when postoperative hypoxemia occurs. It should predominantly include ulinastatin and sevoflurane, which mainly suppress inflammatory response and improve lung injury. Clinically, ulinastatin, as a regular trypsin inhibitor, is extracted from human urine and used in the treatment of acute or critical inflammatory response and organ functional failure. In accordance with the result of study conducted by Jiang *et al*[32], it has been indicated that the improvement of pulmonary edema by ulinastatin is presented through reduced permeability and enhanced alveolar fluid clearance, whose mechanism may involve two pathways, activated phosphoinositide 3-kinase/Akt and suppressed TLR4/ myeloid differentiation primary response 88/NF-κB. Meanwhile, enhanced autophagy is also another medical target for relief of lung injury by ulinastatin *via* the upregulation of transforming growth factor-β1 and light chain 3 and the downregulation of α-smooth muscle actin, matrix metalloproteinase (MMP)-2 and MMP-9[33]. Sevoflurane is used as a classic agent against acute lung injury through multiple pathways. Notably, the suppression of oxidative stress by sevoflurane is firstly elaborated in the mice model of acute lung injury, which is dependent on the pathway of Kelch-like ECH-associated protein 1/nuclear factor erythroid 2–related factor 2[34]. In a similar study, the LINC00839/miR-223/NLR family pyrin domain containing 3 axis was newly confirmed as the driven regulator involving the development of acute lung injury, through which sevoflurane can also be responsible for lung protection[35]. Nitric oxide (NO) has been currently adapted widely for the treatment of respiratory system failure and critical illness such as acute respiratory distress syndrome (ARDS), pulmonary hypertension, and lung transplantation. In a retrospective study focusing on postoperative hypoxemia, the incidence of postoperative hypoxemia for patients who underwent low-dose NO therapy (5-10 ppm) after surgery for Stanford type A aortic dissection decreased and the length of ICU stay as well as duration of mechanical ventilation significantly improved. Of note, the only concern about this unique therapy was prolonged bleeding time due to restrained platelet aggregation and adhesion with endothelium by NO[36]. Furthermore, it has been suggested that NO therapy is especially adaptive to the improvement of postoperative refractory hypoxemia within 72 h after surgery[37,38]. Moreover, some promising results from other attempts have also been evaluated and verified. Prophylactic usage of erythropoietin is valuable in the prevention of lung injury with the exact mechanism, for example, decreasing the levels of negative inflammatory factors such as IL-1β, tumor necrosis factor-α and NF-κB; enhancing lung compliance, optimizing gas exchange; and reducing airway pressure[39]. On the other hand, the highly selective and potent α2 adrenergic agonist, dexmedetomidine, is an effective agent against oxidative stress injury with the aim of protecting lung tissue and maintaining normal physiological function by preserving mitochondrial dynamic equilibrium *via* the hypoxia inducible factor-1α/heme oxygenase 1 signaling pathway[40]. However, different opinions on the lung protection of dexmedetomidine from Kim *et al* [41] have shown that, regardless of the advantage of anti-oxidative stress presented with the decreasing of malondialdehyde, the increase in urine output and less usage of vasoactive agents, for dexmedetomidine, it does not play an important role on lung protection in surgery.

Supportive intervention

Mechanical ventilation is a necessary support after surgery for Stanford type A aortic dissection. It maintains the stability of vital signs and promotes rehabilitation. Traditionally, supine position is widely accepted as the standard mode of mechanical ventilation, while recently, the prone position is considered the better alternative option. In a meta-analysis conducted by Cao *et al*[42], it has been indicated that, compared with traditional supine position, the mortality of patients undergoing prone position ventilation is lower, especially for the population < 60 years despite the findings of some



DOI: 10.12998/wjcc.v11.i14.3140

Figure 1 Risk factors of postoperative hypoxemia for patients with Stanford type A aortic dissection.

insignificant adverse events such as pressure ulcer, displacement of thoracotomy tube, and endotracheal tube obstruction. Based on the findings from another comparison study, under the support of prone position ventilation, compared with the supine position, the resting lung volume measured by functional residual capacity and end-expiratory lung volume increased while dynamic strain decreased, and all differences were significant[43]. As concluded, the lung protective and improved oxygenation mechanism of prone position ventilation is explained by the fact that first, lung volume is free from compression by heart; second, the improvement of ventilation/blood ratio, pulmonary shunts are eliminated; and third, the redistribution of edema fluid is influenced by gravity when the pressure changes gradually[44]. Furthermore, Fioretto *et al*[45] optimized the prone position ventilation strategy with high-frequency oscillatory and demonstrated that compared with conventional mechanical ventilation, the optimized strategy was more feasible and reliable in reducing oxidative damages and preventing lung injury. Also, positive end-expiratory pressure (PEEP) is an important mode for the improvement of hypoxemia. It has been suggested that PEEP has the potential to stabilize dependent lung regions at the end-expiration and inhibit inflammatory response during the stage of mechanical ventilation free from the influence of spontaneous breathing[46]. Wu *et al*[47] established a porcine model of ARDS exploring the practical feasibility of transpulmonary pressure guided PEEP. In accordance with this result, under transpulmonary pressure of 25 cm water, the positive effects of PEEP could be observed including compliance improvement, dead space ventilation reduction, and lung protection. In a clinical study for patients with moderate to severe ARDS, when PEEP was combined with prone position, relative lower titration of PEEP was more adaptive and recommended due to increased transpulmonary pressure caused by prone position[48]. However, obese patients with ARDS should be treated reversely and equipped with higher PEEP strategy to improve 60-d all-cause in-hospital mortality[49]. On the other hand, higher PEEP may involve the redistribution balance for both ventilation and perfusion within different lung units to avoid the excessive ineffective ventilation or perfusion, which adjusts the physiological ratio of ventilation/perfusion to optimize regional tidal volume and decrease the risk of lung injury[50]. Necessarily and possibly, even if mechanical ventilation is weaned, hypoxemic respiratory failure is also life threatening due to severe infection, edema, sepsis or ARDS; therefore, alternative high-flow nasal cannula is thought to be responsible for the persistent respiratory function improvement with comfortable acceptance, better airway clearance, and less abdominal distention[51].

CONCLUSION

Hypoxemia is one of the major complications after surgery for Stanford type A aortic dissection. Comprehensively, the pathogenesis and development of postoperative hypoxemia involve the interaction of many risk factors including organic disorder, obesity, transfusion, and CPB (Figure 1). For treatment, the combination between medicine and supportive intervention is considered the more sustainable model. Surgically, all perioperative points should be managed with caution and patience, starting with reasonable preoperative lung function assessment, experienced cooperation of surgical team, and flawless postoperative rehabilitation. The vision, therefore, seeks to have larger scale studies concentrating on the long-term outcome of postoperative hypoxemia and more effective and optimal management.

FOOTNOTES

Author contributions: Liu HY collected relevant data and drafted the manuscript; Zhang SP, Zhang CX, and Gao QY revised the manuscript; Ge SL and Liu YY supervised the audit process; All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: China

ORCID number: Hai-Yuan Liu 0000-0003-0345-9004.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Li X

REFERENCES

1 **Sayed A**, Munir M, Bahbah EI. Aortic Dissection: A Review of the Pathophysiology, Management and Prospective Advances. *Curr Cardiol Rev* 2021; **17**: e230421186875 [PMID: 33059568 DOI: 10.2174/1573403X16666201014142930]
2 **Gu J**, Chen Z. Clinical Efficacy of Hybrid Surgery for Stanford Type A Aortic Dissection. *Risk Manag Healthc Policy* 2021; **14**: 3013-3023 [PMID: 34285615 DOI: 10.2147/RMHP.S296165]
3 **Jormalainen M**, Kesävuori R, Raivio P, Vento A, Mustonen C, Honkanen HP, Rosato S, Simpanen J, Teittinen K, Biancari F, Juvonen T. Long-term outcomes after ascending aortic replacement and aortic root replacement for type A aortic dissection. *Interact Cardiovasc Thorac Surg* 2022; **34**: 453-461 [PMID: 35188959 DOI: 10.1093/icvts/ivab324]
4 **Zhang L**, Zhang L, Zhao Z, Liu Y, Wang J, Niu M, Sun X, Zhao X. Metabolic syndrome and its components are associated with hypoxemia after surgery for acute type A aortic dissection: an observational study. *J Cardiothorac Surg* 2022; **17**: 151 [PMID: 35698229 DOI: 10.1186/s13019-022-01901-y]
5 **Sheng W**, Le S, Song Y, Du Y, Wu J, Tang C, Wang H, Chen X, Wang S, Luo J, Li R, Xia J, Huang X, Ye P, Wu L, Du X, Wang D. Preoperative Nomogram and Risk Calculator for Postoperative Hypoxemia and Related Clinical Outcomes Following Stanford Type A Acute Aortic Dissection Surgery. *Front Cardiovasc Med* 2022; **9**: 851447 [PMID: 35548419 DOI: 10.3389/fcvm.2022.851447]
6 **Guo Z**, Yang Y, Zhao M, Zhang B, Lu J, Jin M, Cheng W. Preoperative hypoxemia in patients with type A acute aortic dissection: a retrospective study on incidence, related factors and clinical significance. *J Thorac Dis* 2019; **11**: 5390-5397 [PMID: 32030257 DOI: 10.21037/jtd.2019.11.68]
7 **Wang Y**, Xue S, Zhu H. Risk factors for postoperative hypoxemia in patients undergoing Stanford A aortic dissection surgery. *J Cardiothorac Surg* 2013; **8**: 118 [PMID: 23631417 DOI: 10.1186/1749-8090-8-118]
8 **Tsuruda T**, Yamashita A, Otsu M, Koide M, Nakamichi Y, Sekita-Hatakeyama Y, Hatakeyama K, Funamoto T, Chosa E, Asada Y, Udagawa N, Kato J, Kitamura K. Angiotensin II Induces Aortic Rupture and Dissection in Osteoprotegerin-Deficient Mice. *J Am Heart Assoc* 2022; **11**: e025336 [PMID: 35411794 DOI: 10.1161/JAHA.122.025336]
9 **Wu Z**, Dai F, Ren W, Liu H, Li B, Chang J. Angiotensin II induces apoptosis of human pulmonary microvascular endothelial cells in acute aortic dissection complicated with lung injury patients through modulating the expression of monocyte chemoattractant protein-1. *Am J Transl Res* 2016; **8**: 28-36 [PMID: 27069537]
10 **Gong M**, Wu Z, Xu S, Li L, Wang X, Guan X, Zhang H. Increased risk for the development of postoperative severe hypoxemia in obese women with acute type a aortic dissection. *J Cardiothorac Surg* 2019; **14**: 81 [PMID: 31023343 DOI: 10.1186/s13019-019-0888-9]
11 **Sheng W**, Yang HQ, Chi YF, Niu ZZ, Lin MS, Long S. Independent risk factors for hypoxemia after surgery for acute aortic dissection. *Saudi Med J* 2015; **36**: 940-946 [PMID: 26219444 DOI: 10.15537/smj.2015.8.11583]
12 **Shimizu T**, Kimura N, Mieno M, Hori D, Shiraishi M, Tashima Y, Yuri K, Itagaki R, Aizawa K, Kawahito K, Yamaguchi A. Effects of Obesity on Outcomes of Acute Type A Aortic Dissection Repair in Japan. *Circ Rep* 2020; **2**: 639-647 [PMID: 33693190 DOI: 10.1253/circrep.CR-20-0098]
13 **Shi S**, Gao Y, Wang L, Liu J, Yuan Z, Yu M. Elevated free fatty acid level is a risk factor for early postoperative hypoxemia after on-pump coronary artery bypass grafting: association with endothelial activation. *J Cardiothorac Surg* 2015; **10**: 122 [PMID: 26381483 DOI: 10.1186/s13019-015-0323-9]
14 **Wu Z**, Wang Z, Wu H, Hu R, Ren W, Hu Z, Chang J. Obesity is a risk factor for preoperative hypoxemia in Stanford A acute aortic dissection. *Medicine (Baltimore)* 2020; **99**: e19186 [PMID: 32176045 DOI: 10.1097/MD.0000000000019186]
15 **Wang D**, Xu JZ, Kang YY, Zhang W, Hu LX, Wang JG. Aortic Root Diameter in Hypertensive Patients With Various Stages of Obstructive Sleep Apnea. *Am J Hypertens* 2022; **35**: 142-148 [PMID: 34661652 DOI: 10.1093/ajh/hpab167]
16 **Maniaci A**, Iannella G, Cocuzza S, Vicini C, Magliulo G, Ferlito S, Cammaroto G, Meccariello G, De Vito A, Nicolai A, Pace A, Artico M, Taurone S. Oxidative Stress and Inflammation Biomarker Expression in Obstructive Sleep Apnea

Patients. *J Clin Med* 2021; **10** [PMID: 33451164 DOI: 10.3390/jcm10020277]

17 **Xi X**, Chen Y, Ma WG, Xie J, Liu YM, Zhu JM, Gong M, Zhu GF, Sun LZ. Is obstructive sleep apnoea associated with hypoxaemia and prolonged ICU stay after type A aortic dissection repair? *BMC Cardiovasc Disord* 2021; **21**: 421 [PMID: 34488643 DOI: 10.1186/s12872-021-02226-9]

18 **Klanderman RB**, van Mourik N, Eggermont D, Peters AL, Tuinman PR, Bosman R, Endeman H, Cremer OL, Arbous SM, Vlaar APJ. Incidence of transfusion-related acute lung injury temporally associated with solvent/detergent plasma use in the ICU: A retrospective before and after implementation study. *Transfusion* 2022; **62**: 1752-1762 [PMID: 35919958 DOI: 10.1111/trf.17049]

19 **Yu Y**, Jiang P, Sun P, Su N, Lin F. Pulmonary coagulation and fibrinolysis abnormalities that favor fibrin deposition in the lungs of mouse antibody-mediated transfusion-related acute lung injury. *Mol Med Rep* 2021; **24** [PMID: 34165170 DOI: 10.3892/mmr.2021.12239]

20 **Le A**, Wu Y, Liu W, Wu C, Hu P, Zou J, Kuang L. MiR-144-induced KLF2 inhibition and NF-kappaB/CXCR1 activation promote neutrophil extracellular trap-induced transfusion-related acute lung injury. *J Cell Mol Med* 2021; **25**: 6511-6523 [PMID: 34120407 DOI: 10.1111/jcmm.16650]

21 **Bayat B**, Nielsen KR, Bein G, Traum A, Burg-Roderfeld M, Sachs UJ. Transfusion of target antigens to preimmunized recipients: a new mechanism in transfusion-related acute lung injury. *Blood Adv* 2021; **5**: 3975-3985 [PMID: 34438443 DOI: 10.1182/bloodadvances.2020003843]

22 **Su IL**, Wu VC, Chou AH, Yang CH, Chu PH, Liu KS, Tsai FC, Lin PJ, Chang CH, Chen SW. Risk factor analysis of postoperative acute respiratory distress syndrome after type A aortic dissection repair surgery. *Medicine (Baltimore)* 2019; **98**: e16303 [PMID: 31335676 DOI: 10.1097/MD.0000000000016303]

23 **He Y**, Zhang HS, Zhang TZ, Feng Y, Zhu Y, Fan X. Analysis of the risk factors for severe lung injury after radical surgery for tetralogy of fallot. *Front Surg* 2022; **9**: 892562 [PMID: 36111236 DOI: 10.3389/fsurg.2022.892562]

24 **Deng Y**, Hou L, Xu Q, Liu Q, Pan S, Gao Y, Dixon RAF, He Z, Wang X. Cardiopulmonary Bypass Induces Acute Lung Injury *via* the High-Mobility Group Box 1/Toll-Like Receptor 4 Pathway. *Dis Markers* 2020; **2020**: 8854700 [PMID: 33062073 DOI: 10.1155/2020/8854700]

25 **Li J**, Gao PF, Xu YX, Gu H, Wang QX. Probiotic Saccharomyces boulardii attenuates cardiopulmonary bypass-induced acute lung injury by inhibiting ferroptosis. *Am J Transl Res* 2022; **14**: 5003-5013 [PMID: 35958495]

26 **Kong M**, Wei D, Li X, Zhu X, Hong Z, Ni M, Wang Y, Dong A. The dynamic changes in autophagy activity and its role in lung injury after deep hypothermic circulatory arrest. *J Cell Mol Med* 2022; **26**: 1113-1127 [PMID: 35014165 DOI: 10.1111/jcmm.17165]

27 **Cooney SJ**, Klawitter J, Khailova L, Robison J, Jaggers J, Ing RJ, Lawson S, Frank BS, Lujan SO, Davidson JA. Regional lung metabolic profile in a piglet model of cardiopulmonary bypass with circulatory arrest. *Metabolomics* 2021; **17**: 89 [PMID: 34553313 DOI: 10.1007/s11306-021-01842-y]

28 **Andualem AA**, Yesuf KA. Incidence and associated factors of postoperative hypoxemia among adult elective surgical patients at Dessie Comprehensive Specialized Hospital: An observational study. *Ann Med Surg (Lond)* 2022; **78**: 103747 [PMID: 35734654 DOI: 10.1016/j.amsu.2022.103747]

29 **Kaushal A**, Goyal P, Dhiraaj S, Agarwal A, Singh PK. Identification of Various Perioperative Risk Factors Responsible for Development of Postoperative Hypoxaemia. *Turk J Anaesthesiol Reanim* 2018; **46**: 416-423 [PMID: 30505603 DOI: 10.5152/TJAR.2018.82160]

30 **Wu CP**, Huang KL, Peng CK, Lan CC. Acute Hyperglycemia Aggravates Lung Injury *via* Activation of the SGK1-NKCC1 Pathway. *Int J Mol Sci* 2020; **21** [PMID: 32645929 DOI: 10.3390/ijms21134803]

31 **Morey M**, O'Gaora P, Pandit A, Hélary C. Hyperglycemia acts in synergy with hypoxia to maintain the pro-inflammatory phenotype of macrophages. *PLoS One* 2019; **14**: e0220577 [PMID: 31415598 DOI: 10.1371/journal.pone.0220577]

32 **Jiang YX**, Huang ZW. Ulinastatin alleviates pulmonary edema by reducing pulmonary permeability and stimulating alveolar fluid clearance in a rat model of acute lung injury. *Iran J Basic Med Sci* 2022; **25**: 1002-1008 [PMID: 36159332 DOI: 10.22038/IJBMS.2022.64655.14230]

33 **Zhang G**, Du Y, Sun N, Sun Y, Zhang L, Li X. Ulinastatin enhances autophagy against radiation-induced lung injury in mice. *Transl Cancer Res* 2020; **9**: 4162-4172 [PMID: 35117785 DOI: 10.21037/tcr-19-3018]

34 **Zheng F**, Wu X, Zhang J, Fu Z, Zhang Y. Sevoflurane reduces lipopolysaccharide-induced apoptosis and pulmonary fibrosis in the RAW264.7 cells and mice models to ameliorate acute lung injury by eliminating oxidative damages. *Redox Rep* 2022; **27**: 139-149 [PMID: 35801580 DOI: 10.1080/13510002.2022.2096339]

35 **Fu Z**, Wu X, Zheng F, Zhang Y. Sevoflurane anesthesia ameliorates LPS-induced acute lung injury (ALI) by modulating a novel LncRNA LINC00839/miR-223/NLRP3 axis. *BMC Pulm Med* 2022; **22**: 159 [PMID: 35473680 DOI: 10.1186/s12890-022-01957-5]

36 **Zhang H**, Liu Y, Meng X, Yang D, Shi S, Liu J, Yuan Z, Gu T, Han L, Lu F, Xu Z, Yu M. Effects of inhaled nitric oxide for postoperative hypoxemia in acute type A aortic dissection: a retrospective observational study. *J Cardiothorac Surg* 2020; **15**: 25 [PMID: 31969173 DOI: 10.1186/s13019-020-1069-6]

37 **Zheng P**, Jiang D, Liu C, Wei X, Li S. Nitric Oxide Inhalation Therapy Attenuates Postoperative Hypoxemia in Obese Patients with Acute Type A Aortic Dissection. *Comput Math Methods Med* 2022; **2022**: 9612548 [PMID: 35360551 DOI: 10.1155/2022/9612548]

38 **Ma GG**, Hao GW, Lai H, Yang XM, Liu L, Wang CS, Tu GW, Luo Z. Initial clinical impact of inhaled nitric oxide therapy for refractory hypoxemia following type A acute aortic dissection surgery. *J Thorac Dis* 2019; **11**: 495-504 [PMID: 30962993 DOI: 10.21037/jtd.2019.01.42]

39 **Lin X**, Ma X, Cui X, Zhang R, Pan H, Gao W. Effects of Erythropoietin on Lung Injury Induced by Cardiopulmonary Bypass After Cardiac Surgery. *Med Sci Monit* 2020; **26**: e920039 [PMID: 32310911 DOI: 10.12659/MSM.920039]

40 **Shi J**, Yu T, Song K, Du S, He S, Hu X, Li X, Li H, Dong S, Zhang Y, Xie Z, Li C, Yu J. Dexmedetomidine ameliorates endotoxin-induced acute lung injury *in vivo* and *in vitro* by preserving mitochondrial dynamic equilibrium through the HIF-1a/HO-1 signaling pathway. *Redox Biol* 2021; **41**: 101954 [PMID: 33774474 DOI: 10.1016/j.redox.2021.101954]

41 **Kim S**, Park SJ, Nam SB, Song SW, Han Y, Ko S, Song Y. Pulmonary effects of dexmedetomidine infusion in thoracic

aortic surgery under hypothermic circulatory arrest: a randomized placebo-controlled trial. *Sci Rep* 2021; **11**: 10975 [PMID: 34040043 DOI: 10.1038/s41598-021-90210-w]

42 **Cao Z**, Yang Z, Liang Z, Cen Q, Zhang Z, Liang H, Liu R, Zeng L, Xie Y, Wang Y. Prone *vs* Supine Position Ventilation in Adult Patients with Acute Respiratory Distress Syndrome: A Meta-Analysis of Randomized Controlled Trials. *Emerg Med Int* 2020; **2020**: 4973878 [PMID: 33343939 DOI: 10.1155/2020/4973878]

43 **Aguirre-Bermeo H**, Turella M, Bitondo M, Grandjean J, Italiano S, Festa O, Morán I, Mancebo J. Lung volumes and lung volume recruitment in ARDS: a comparison between supine and prone position. *Ann Intensive Care* 2018; **8**: 25 [PMID: 29445887 DOI: 10.1186/s13613-018-0371-0]

44 **Xia WH**, Yang CL, Chen Z, Ouyang CH, Ouyang GQ, Li QG. Clinical evaluation of prone position ventilation in the treatment of acute respiratory distress syndrome induced by sepsis. *World J Clin Cases* 2022; **10**: 5577-5585 [PMID: 35979108 DOI: 10.12998/wjcc.v10.i17.5577]

45 **Fioretto JR**, Klefens SO, Pires RF, Kurokawa CS, Carpi MF, Bonatto RC, Moraes MA, Ronchi CF. Comparison between conventional protective mechanical ventilation and high-frequency oscillatory ventilation associated with the prone position. *Rev Bras Ter Intensiva* 2017; **29**: 427-435 [PMID: 29236845 DOI: 10.5935/0103-507X.20170067]

46 **Kiss T**, Bluth T, Braune A, Huhle R, Denz A, Herzog M, Herold J, Vivona L, Millone M, Bergamaschi A, Andreeff M, Scharffenberg M, Wittenstein J, Vidal Melo MF, Koch T, Rocco PRM, Pelosi P, Kotzerke J, Gama de Abreu M. Effects of Positive End-Expiratory Pressure and Spontaneous Breathing Activity on Regional Lung Inflammation in Experimental Acute Respiratory Distress Syndrome. *Crit Care Med* 2019; **47**: e358-e365 [PMID: 30676338 DOI: 10.1097/CCM.0000000000003649]

47 **Wu X**, Zheng R, Zhuang Z. Effect of transpulmonary pressure-guided positive end-expiratory pressure titration on lung injury in pigs with acute respiratory distress syndrome. *J Clin Monit Comput* 2020; **34**: 151-159 [PMID: 30903412 DOI: 10.1007/s10877-019-00267-2]

48 **Boesing C**, Graf PT, Schmitt F, Thiel M, Pelosi P, Rocco PRM, Luecke T, Krebs J. Effects of different positive end-expiratory pressure titration strategies during prone positioning in patients with acute respiratory distress syndrome: a prospective interventional study. *Crit Care* 2022; **26**: 82 [PMID: 35346325 DOI: 10.1186/s13054-022-03956-8]

49 **Bime C**, Fiero M, Lu Z, Oren E, Berry CE, Parthasarathy S, Garcia JGN. High Positive End-Expiratory Pressure Is Associated with Improved Survival in Obese Patients with Acute Respiratory Distress Syndrome. *Am J Med* 2017; **130**: 207-213 [PMID: 27984004 DOI: 10.1016/j.amjmed.2016.09.029]

50 **Pavlovsky B**, Pesenti A, Spinelli E, Scaramuzzo G, Marongiu I, Tagliabue P, Spadaro S, Grasselli G, Mercat A, Mauri T. Effects of PEEP on regional ventilation-perfusion mismatch in the acute respiratory distress syndrome. *Crit Care* 2022; **26**: 211 [PMID: 35818077 DOI: 10.1186/s13054-022-04085-y]

51 **Shang X**, Wang Y. Comparison of outcomes of high-flow nasal cannula and noninvasive positive-pressure ventilation in patients with hypoxemia and various APACHE II scores after extubation. *Ther Adv Respir Dis* 2021; **15**: 17534666211004235 [PMID: 33781130 DOI: 10.1177/17534666211004235]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3148-3157

DOI: 10.12998/wjcc.v11.i14.3148

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Impact of extended nursing model after multi-disciplinary treatment on young patient with post-stroke

Xiao-Yan Xu, Zhi-Juan Pang, Mei-Hui Li, Kun Wang, Jie Song, Yue Cao, Mao Fang

Specialty type: Nursing

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dobrocky T, Switzerland; Karapanayiotides T, Greece

Received: January 10, 2023
Peer-review started: January 10, 2023
First decision: January 30, 2023
Revised: February 8, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Xiao-Yan Xu, Mei-Hui Li, Kun Wang, Jie Song, Yue Cao, Mao Fang, Second Ward, Department of Neurology, The Second Affiliated Hospital of Qiqihar Medical College, Qiqihar 161006, Heilongjiang Province, China

Zhi-Juan Pang, Department of Rehabilitation Medicine, The Second Affiliated Hospital of Qiqihar Medical College, Qiqihar 161006, Heilongjiang Province, China

Corresponding author: Mao Fang, Nurse, Second Ward, Department of Neurology, The Second Affiliated Hospital of Qiqihar Medical College, No. 64 Zhonghua West Road, Jianhua District, Qiqihar 161006, Heilongjiang Province, China. maof9929@qmu.edu.cn

Abstract

BACKGROUND

Stroke has become one of the most serious life-threatening diseases due to its high morbidity, disability, recurrence and mortality rates.

AIM

To explore the intervention effect of multi-disciplinary treatment (MDT) extended nursing model on negative emotions and quality of life of young patients with post-stroke.

METHODS

A total of 60 young stroke patients who were hospitalized in the neurology department of our hospital from January 2020 to December 2021 were selected and randomly divided into a control group and an experimental group, with 30 patients in each group. The control group used the conventional care model and the experimental group used the MDT extended nursing model. After the in-hospital and 3-mo post-discharge interventions, the differences in negative emotions and quality of life scores between the two groups were evaluated and analyzed at the time of admission, at the time of discharge and after discharge, respectively.

RESULTS

There are no statistically significant differences in the negative emotions scores between the two groups at admission, while there are statistically significant differences in the negative emotions scores within each group at admission and discharge, at discharge and post-discharge, and at discharge and post-discharge. In addition, the negative emotions scores were all statistically significant at

discharge and after discharge when compared between the two groups. There was no statistically significant difference in quality of life scores at the time of admission between the two groups, and the difference between quality of life scores at the time of admission and discharge, at the time of discharge and post-discharge, and at the time of admission and post-discharge for each group of patients was statistically significant.

CONCLUSION
The MDT extended nursing mode can improve the negative emotion of patients and improve their quality of life. Therefore, it can be applied in future clinical practice and is worthy of promotion.

Key Words: Multi-disciplinary treatment extended nursing model; Young people with post-stroke; Negative emotions; Quality of life

Core Tip: To explore the intervention effect of multi-disciplinary treatment (MDT) extended nursing model on negative emotions and quality of life of young patients with post-stroke. The control group used the conventional care model and the experimental group used the MDT extended nursing model. After the in-hospital and 3-mo post-discharge interventions, the differences in negative emotions and quality of life scores between the two groups were evaluated and analyzed at the time of admission. The MDT extended nursing mode can improve the negative emotion of patients and improve their quality of life. It can be applied in clinical practice and is worthy of promotion.

Citation: Xu XY, Pang ZJ, Li MH, Wang K, Song J, Cao Y, Fang M. Impact of extended nursing model after multi-disciplinary treatment on young patient with post-stroke. *World J Clin Cases* 2023; 11(14): 3148-3157
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3148.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3148

INTRODUCTION

Stroke has become one of the most serious life-threatening diseases due to its high morbidity, disability, recurrence and mortality rates[1]. It has been reported that there are about 2.5 million new cases of stroke in China every year, and the mortality rate can be up to 30%[2,3]. Nearly 70% of surviving patients have varying degrees of cognitive and physical impairment, which causes great suffering to the patients and places a heavy burden on their family[4]. As an important part of clinical treatment, nursing has a significant impact on the psychological and prognostic outcomes of stroke patients. Previous studies have demonstrated that different nursing models have different clinical effects on the improvement of negative mood and physical function recovery of stroke patients. For example, by applying nostalgia therapy to care for stroke patients, Mei *et al*[5] revealed that it not only relieves anxiety and depression of patients but also had a positive effect on the their careers, which could accelerate the recovery of patients. Brighton *et al*[6] applied supportive care coupled with psychological interventions to the care of patients with chronic diseases and found that this nursing model significantly reduced the dysphoria of patients and improved their life quality. Although the above-mentioned nursing model have had a positive effect on dysphoria and life quality of stroke patients, most of those studies were conducted in-hospital. The psychological changes and functional recovery of patients after discharge from hospital were not available until now. Due to lack of psychological intervention and rehabilitation guidance from professional medical personnel in home environment, patients are prone to training burnout and increased dysphoria[7,8]. Therefore, developing a more coordinated and continuous nursing model has become an urgent issue in clinical nursing practice. As one of the typical representatives of nursing models with greater coordination and continuity, the extended care model has been applied to the nursing work of various diseases and has achieved great effects[9,10]. However, this model also has certain drawbacks, such as the fact that the intervention personnel are mostly nursing staff and lack professional guidance on psychological intervention and physical functional rehabilitation[11,12]. To make up above deficiencies, the multi-disciplinary treatment (MDT) model was combined with the extended nursing mode to investigate the optimized care model for young stroke patients in this study.

MATERIALS AND METHODS

Basic characteristic of the samples

Sixty stroke patients who were hospitalized in the Department of Neurology of our hospital from January 2020 to December 2021 were selected and randomly divided into control group and experimental group, with 30 patients in each group. The control group were treated with conventional nursing while the experimental group were treated with MDT extended nursing mode. There are 16 males and 14 females in the control group aged 19-35 years (average age 28.27 ± 2.53 years). In the experimental group, there were 15 males and 15 females aged 20-38 years (average age 27.20 ± 2.23 years). There was no statistically significant difference in the basic characteristics of the patients in the two groups (Table 1). The inclusion criteria of stroke patients are as follows: (1) Patients with ischemic stroke who met the diagnostic criteria for ischemic stroke adopted by the 4th National Conference on Cerebrovascular Diseases of China and confirmed by cranial computerized tomography or magnetic resonance imaging; (2) Young patients aged 18-40 years; and (3) No history of psychiatry disorders. The exclusion criteria are as follows: (1) Patients > 40 aged years or < 18 aged years; and (2) Patients with severe underlying medical conditions or those who are unable to cooperate with the study due to their conditions. All patients volunteered to participate in the experiment and signed an informed consent form before the start of the trial. The study was approved by the Ethics Committee of our hospital.

The nursing mode of control group: Patients in the control group were given a routine nursing care, including safety briefing and disease briefing upon admission, dietary care, rehabilitation training instruction, complication care and preparation of medication and infusion for patients as prescribed by the doctor.

MDT extended nursing team organization: The MDT extended nursing team consisted of 21 members, including 2 associate chief neurologists, 1 rehabilitation physician, 1 dietician, 1 network engineer, 1 chief nurse, 2 associate chief nurses, 3 charge nurses and 10 nurse practitioners, all of whom are front-line staff. The team leader was the head nurse and 2 charge nurses were appointed as statisticians to be responsible for the collation and analysis of the trial data (Table 2).

Training of the MDT extended nursing team member: The lead nurse organized a unified lecture training for the team members, which mainly included: the significance of the MDT extended nursing, the objective, the progression of current research, the implementation process, the evaluation scale categories and their significance. The total training process is 3 h and was divided into 3 lectures. After the lecture, a training assessment is organized for the members, and the trial can only start after all members have passed the assessment.

Intervention strategies: After plenary discussion, the intervention content was developed by the group members through literature retrieval and books review. All members in the MDT extended nursing team were required to strictly follow the predetermined intervention content to ensure the trial was successfully completed. Before the intervention starting, a preliminary experiment was conducted in 10 patients who met the inclusion criteria, and any problems that arose during the implementation of the intervention were recorded in detail and modified after group discussion to arrive the final intervention content (Table 3).

Implementation of the MDT extended nursing: The clinical interventions were carried out by each group member in strict accordance with the intervention content form developed above. Patients in each group were assisted by the bedside nurses to fill in the questionnaires on admission and discharge respectively and the questionnaires were collected by the bedside nurses. The 2 charge nurses were responsible for the statistical scoring, database entry and statistical analysis of the collected forms, and 2 charge nurses were each responsible for the statistical and analytical calculations until the data of the 2 nurses were in complete agreement. The lead nurse is responsible for the arrangement, liaison and supervision of the whole experiment.

Quality control

To ensure the reliability of our results, the following quality control strategies were applied: (1) Nursing staff and patient allocation: The bedside nurses of the two groups of patients were only responsible for their own patients throughout the trial, and no staff transfer was made between the two groups. Patients in the two groups were arranged to different wards to prevent the accuracy of the final trial results from being affected by inter-patient communication; (2) In order to ensure homogeneity of evaluation, the group staff were given uniform training and assessment before the start of the trial to ensure the accuracy of the daily operation and assessment methods; and (3) The whole test was supervised and executed by the lead nurse, and the data collected was kept by a dedicated person. Data entry and statistical analysis were carried out by two people respectively to ensure that the data collected and the results calculated were accurate.

Table 1 The general information comparison between the two groups of patients

		Intervention group (*n* = 30)	Control group (*n* = 30)	*T* value	*P* value
Sex (*n*)	Men	15	16	0.067	0.796
	Women	15	14		
Age (yr)		27.20 ± 2.23	28.27 ± 2.53	-1.730	0.089
Occupation	Student	10	11	0.294	0.961
	Worker	7	6		
	Civil servant	5	4		
	Self-employed	8	9		
Education degree (*n*)	Primary school	7	6	0.269	0.874
	Middle school	8	7		
	College degree or above	15	13		
Expense category (*n*)	Health insurance	22	24	0.373	0.542
	Self-pay	8	6		
Inpatient days (d)		17.00 ± 2.29	16.33 ± 2.45	1.088	0.281

Table 2 Composition of the multi-disciplinary treatment extended nursing team and their responsibilities

Group members (*n*)	Group members responsibilities
Associate chief physician (2)	Responsible for the diagnosis and treatment of patients; the administration of medication and the follow-up of discharged
Rehabilitation physician (1)	Guidance of rehabilitation training for patients during convalescence
Dietician (1)	Evaluation of the nutritional status of patients and formulation personalized nutritional meals
Network engineer (1)	network maintenance
Chief nurse (1)	Experiment organization, personnel allocation, liaison and experiment supervision
Associate chief nurse (2)	Assisted in the implementation of the trial and the follow-up survey of discharged patients
Charge nurse (3)	Data collection and analysis
Nurse practitioners (10)	Clinical trial implementation, patient inpatient and discharge care, guide patients to fill in the scale

Evaluation indicators

In this study, two indicators, including negative emotions and quality of life were used to assess the intervention effect of MDT extended nursing mode. The negative emotions were evaluated by a series widely adopted anxiety and depression scale, including Self-rating Anxiety Scale (SAS), Self-rating Depression Scale (SDS), Hamilton Depression (HAMD) Scale, and Hamilton Anxiety (HAMA) Scale. SAS was developed by Zung[13] to assess the subjective feelings of anxiety of patients and their changes during treatment in 1971. It is consisting of 20 items, each with a score of 1-4. The minimum score is 20 and the maximum score is 80, with scores below 50 being normal, 50-59 being mild anxiety, 60-69 being moderate anxiety, and 70 or more being severe anxiety. Yue *et al*[14] reported that the SDS, a common scale for evaluating the depression of patients, was developed by Zung in 1965 and also contains 20 items, each with a score of 1-4. It is also divided into 4 grades, with scores below 50 being normal, 50-59 being mild depression, 60-69 being moderate depression, and 70 or more being major depression. HAMD scale was developed by Hamilton in 1960 and is a commonly used clinical scale to assess the depressive state of patients[15]. This scale has 7 dimensions and 24 entries, which evaluate somatic symptoms, loss of weight, retardation (slowness of thought and speech, impaired ability to concentrate, decreased motor activity), insomnia (early, middle and late), and depressed mood (sadness, hopeless, helpless, and worthless). Most items are scored 0-4 and a few are scored 0-2. A higher total score for the patient represents a more severe depression. The reliability coefficient of each individual item of the scale is 0.78-0.98 and the validity coefficient is 0.37. Lu *et al*[16] has reported that HAMA was developed by Hamilton in 1959 and is a commonly used scale to assess the severity of anxiety symptoms of adult patients. It has 14 items and can assess both somatic and psychic anxiety. Each item is assigned a score of 0-4 from "asymptomatic" to "severe," with a full score of 56, with higher scores indicating higher anxiety levels. The reliability coefficient of each item in this scale was 0.83-1.00, and the validity

Table 3 The details of the intervention strategy

Items		Content
Intervention timeline		Immediate admission to week 8 of discharge (1 time per week after discharge)
Intervention content		Psychological care to reduce psychological stress of patients and assist psychologists in psychological intervention
		Assisting the rehabilitation physician in guiding the rehabilitation training of patient
		Investigate the dietary habits of patients and assist dietitians in adjusting nutritional status of patients
		Assisting the bedside physician in daily care
Operators		MDT extended nursing team
Specific implementation steps	Psychological care to reduce psychological stress of patients and assist psychologists in psychological intervention	The bedside nurses assist the patients to fill in the anxiety self-assessment scale and the hospital anxiety and depression scale, the scores of which are analyzed by the psychiatrist and appropriate interventions are made. Talking and communicating with patients once a week through internet technology to understand their inner changes and provide timely feedback to the psychologist
	Assisting the rehabilitation physician in guiding the rehabilitation training of patients	The rehabilitation physician formulates the individualized rehabilitation training plan; the neurologist assists in optimizing the rehabilitation strategy; the rehabilitation physician implements the rehabilitation training plan; the bedside nurse assists the rehabilitation physician. After discharge, the completion of rehabilitation training of patients was investigated once a week through Internet technology such as WeChat video, and the degree of training was monitored
	Investigate the dietary habits of patients and assist dietitians in adjusting nutritional status of patients	The bedside nurse asks patients about their daily eating habits and assists the dietitian in formulating a nutrition improvement plan; follows up with the patient once a week after discharge and gives feedback to the dietitian, and guides the daily diet of patients according to the nutrition supplement plan adjusted by the dietitian
	Assisting the bedside physician in daily care	Implement orders of physician, record the disease progression of patients on the basis of basic care, and provide timely feedback to the bedside physician

MDT: Multi-disciplinary treatment.

coefficient was 0.36. The quality of life was evaluated by Barthel Index and the Short-Form (SF-36) Health Survey. Barthel Index was developed by Barthel in 1965, it is a commonly used index to measure the individual's ability to perform basic activities of daily life[17]. There is a total of 10 dimensions, with a score of 100, the higher the score, the higher the quality of life of the patient. The SF-36 Health Survey scale was first constructed to survey health status in the Medical Outcome Study, which was conducted by the RAND Corporation. In this study, we used a Chinese version of the scale translated by the Department of Social Medicine, School of Medicine, Zhejiang University in 1991, which was mentioned in the study of Kin *et al*[18]. The scale has 36 items grouped in 8 dimensions and the higher the total score represents the better the quality of life of patients. It has been showed that the 8 dimensions Cronbach's alpha of the scale are higher than 0.70, which has good reliability and validity.

Observation indicators

Patients in both groups were instructed by the bedside nurses and home care nurses to complete the above-mentioned scale at admission, at discharge and at the 3rd month of the discharge intervention to assess the patients' negative emotions and changes in quality of life respectively.

Statistical analysis

All the data collected in current study were entered into SPSS (version, 22.1) statistical software and analyzed. mean ± SD was used for description of quantitate data and independent samples *t*-test was used for comparison between groups. All statistical *P* values were bilateral, and $P < 0.05$ was considered statistically significant.

RESULTS

The general information comparison between the two groups of patients

The differences in general information between the two groups were not statistically significant and were comparable (Table 1).

Comparison of anxiety and depressio6 self-rating scale scores between the two groups of patients

Patients in the control group had SAS scores of 65.43 ± 2.08 on admission, 55.17 ± 3.00 on discharge and 71.13 ± 2.91 after discharge. The SDS scores of patients in control group were 68.13 ± 2.50 on admission,

57.27 ± 2.75 on discharge and 73.47 ± 2.97 after discharge. Patients in the intervention group had SAS scores of 65.57 ± 3.97 on admission, 21.13 ± 2.52 on discharge and 17.33 ± 3.06 after discharge. The SDS scores of patients in the intervention group were 69.27 ± 2.65 at admission, 25.13 ± 2.65 at discharge and 16.53 ± 2.27 after discharge. The differences in SAS scores and SDS scores on admission were not statistically significant between the two groups. The differences in SAS scores and SDS scores on admission and discharge, on discharge and after discharge, and on admission and after discharge were statistically significant within each group of patients, and the differences in SAS scores and SDS scores on discharge and after discharge were statistically significant between the two groups (Table 4).

Comparison of HAMD and HAMA scores between the two groups of patients

Patients in the control group had a HAMD score of 34.17 ± 1.49 on admission, 25.23 ± 1.74 on discharge and 31.10 ± 1.85 after discharge. The HAMA score of patients in control group were 26.27 ± 2.23 on admission, 21.53 ± 1.96 on discharge and 31.83 ± 2.00 after discharge. Patients in the intervention group had a HAMD score of 33.93 ± 1.23 on admission, 17.33 ± 2.54 on discharge and 11.13±1.59 after discharge. The HAMA score of patients in the intervention group were 25.20 ± 2.83 on admission, 15.23 ± 1.76 on discharge and 10.57 ± 2.39 after discharge. The differences in HAMD scores and HAMA scores at admission were not statistically significant between the two group. The differences in HAMD scores and HAMA scores at admission and discharge, at discharge and after discharge, and at admission and after discharge were statistically significant within each group, and the differences in HAMD scores and HAMA scores at discharge and after discharge were statistically significant between the two groups (Table 5).

Comparison of Barthel index between the two groups of patients

The Barthel Index for patients in the control group was 40.17 ± 2.23 at admission, 53.20 ± 1.86 at discharge and 41.23 ± 2.01 after discharge. The Barthel Index was 39.70 ± 1.60 at admission, 76.13 ± 2.00 at discharge and 83.77 ± 2.43 after discharge for patients in the intervention group. There was no statistically significant difference in Barthel index between the two groups of patients on admission. The difference between Barthel index on admission and discharge, on discharge and after discharge, and on admission and after discharge within each group of patients was statistically significant, and the difference between the two groups of patients was statistically significant when comparing Barthel index at discharge and post-discharge (Table 6).

Comparison of SF-36 scores for each dimension between the two groups of patients

There were no statistically significant differences in the SF-36 scores for each dimension between the two groups of patients at admission. The differences of SF-36 scores on each dimension within each group of patients on admission and on discharge, on discharge and post-discharge, and on admission and post-discharge were all statistically significant, and the differences between the two groups of patients on discharge and post-discharge were statistically significant (Table 7).

DISCUSSION

Young stroke patients have more severe negative emotions and poor quality of life

In this study, by comparing the negative emotions and quality of life scores on admission of both groups, we found that patients in both groups had more severe anxiety and depression and a lower quality of life, which is in line with the results of previous studies. For example, Schöttke *et al*[19] found that the prevalence of stroke patients suffering from one or more depressive symptoms within 5 years could be up to 39%-52%. Chen *et al*[20] conducted a retrospective study of stroke patients after treatment found that 24%-29% of patients had varying degrees of anxiety and depressive symptoms. Charidimou *et al*[21] performed a meta-analysis of the literatures on depression in stroke patients showed that the prevalence of depression in stroke patients was about 39%. In addition, studies focused on the reduction of quality of life in stroke patients have also been reported in recent years. A meta-analysis of nine papers on quality of life in stroke patients by Koivunen *et al*[22] showed a general reduction in quality of life in stroke patients. The underlying causes of this events are mostly related to the fact that the internal demands of stroke patients are not effectively met after discharge from the hospital and their repressed psychology is not effectively relieved. In addition, patients do not access to rehabilitation exercise guidance from health care professionals at home, making the symptoms of anxiety and depression progressively worse, slowing recovery from illness and drastically reducing the quality of life.

MDT extended nursing mode can improve the negative emotions of patients

According to previous studies that the psychological needs of stroke patients vary from inpatient treatment to post-discharge rehabilitation. However, due to the difference between the home environment and the hospital environment, although they are in a familiar living environment, their

Table 4 Comparison of anxiety and depression self-rating scale scores between the two groups of patients

Groups	SAS score			SDS score		
	At admission	At discharge	After discharge	At admission	At discharge	After discharge
Control group	65.43 ± 2.08	55.17 ± 3.00[a]	71.13 ± 2.91[c]	68.13 ± 2.50	57.27 ± 2.75[a]	73.47 ± 2.97[c]
Intervention group	65.57 ± 3.97	21.13 ± 2.52[a,c]	17.33 ± 3.06[c]	69.27 ± 2.65	25.13 ± 2.65[a,c]	16.53 ± 2.27[c]
T value	-0.163	47.660	69.849	-1.703	46.065	83.452
P value	0.871	< 0.000	< 0.000	0.094	< 0.000	< 0.000

[a]*P* value < 0.05, compared with at admission.
[c]*P* value < 0.05, compared with at discharge.
SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale.

Table 5 Comparison of Hamilton Depression and Hamilton Anxiety scores between the two groups of patients

Groups	HAMD score			HAMA score		
	At admission	At discharge	After discharge	At admission	At discharge	After discharge
Control group	34.17 ± 1.49	25.23 ± 1.74[a]	31.10 ± 1.85[c]	26.27 ± 2.23	21.53 ± 1.96[a]	31.83 ± 2.00[c]
Intervention group	33.93 ± 1.23	17.33 ± 2.54[a,c]	11.13 ± 1.59[a,c]	25.20 ± 2.83	15.23 ± 1.76[a,c]	10.57 ± 2.39[a,c]
T value	0.662	14.076	44.884	1.621	13.112	37.385
P value	0.510	0.000	0.000	0.110	0.000	0.000

[a]*P* value < 0.05, compared with at admission.
[c]*P* value < 0.05, compared with at discharge.
HAMD: Hamilton Depression; HAMA: Hamilton Anxiety.

Table 6 Comparison of Barthel Index between the two groups of patients

Group	At admission	At discharge	After discharge
Control group	40.17 ± 2.23	53.20 ± 1.86[a]	41.23 ± 2.01[c]
Intervention group	39.70 ± 1.60	76.13 ± 2.00[a,c]	83.77 ± 2.43[a,c]
T statistics	0.931	-45.997	-73.831
P value	0.356	0.000	0.000

[a]*P* value < 0.05, compared with at admission.
[c]*P* value < 0.05, compared with at discharge.

family members are usually lack of professional psychological training thus are less able to recognize their psychological changes and intervene with patients timely. The inner needs of patients cannot be met reasonably, and the anxiety, depression symptoms cannot get relieve. The patients have been immersed in the role of the disease which resulting in the negative emotions aggravated gradually[23]. In this study, the negative emotions of patients in both groups improved at the time of discharge compared with those at the time of admission, which may be related to the gradual increase of nursing staff in awareness of psychological interventions for patients. The degree of improvement in the negative emotions of patients in the experimental group was significantly better than that of the control group. This is probably due to the fact that the care model applied to the experimental group was multidisciplinary, with more targeted and specialized interventions for the negative emotions of patients, with each discipline providing specialist treatment and care for the patient. Among which each discipline works together with each other rather than independently. The increased attention given to the patients led to an effective reduction in their sense of inner isolation. When comparing the post-discharge anxiety and depression scores of the two groups, the results showed that the negative mood of the patients in the control group increased compared to the time of discharge, while the negative mood of the patients in the intervention group was further alleviated. The reason for this may be related to the continuity of care model used for patients in the experiment group, which compensates for the

Table 7 Comparison of Short-Form 36 scores for each dimension between the two groups of patients

Dimension	Control group			Intervention group		
	At admission	At discharge	After discharge	At admission	At discharge	After discharge
Physical functioning	44.17 ± 1.49	52.23 ± 1.72[a]	41.10 ± 2.06[a,c]	43.20 ± 2.06	67.13 ± 1.25[a,e]	78.83 ± 2.07[a,c,e]
Physical problems	43.93 ± 1.28	49.17 ± 1.72[a]	40.97 ± 1.71[a,c]	42.70 ± 2.52	71.03 ± 1.83[a,e]	88.97 ± 1.71[a,c,e]
Bodily pain	28.20 ± 2.31	41.87 ± 2.03[a]	23.60 ± 1.45[a,c]	29.00 ± 2.13	61.60 ± 2.06[a,e]	75.27 ± 1.95[a,c,e]
Generalhealth	24.37 ± 3.09	44.30 ± 2.48[a]	51.53 ± 1.28[a,c]	23.93 ± 3.13	74.47 ± 2.00[a,e]	80.07 ± 1.64[a,c,e]
Social vitality	33.17 ± 3.51	46.80 ± 1.97[a]	22.23 ± 1.45[a,c]	34.20 ± 2.78	64.70 ± 1.56[a,e]	74.43 ± 1.85[a,c,e]
Social functioning	34.67 ± 2.14	48.63 ± 2.03[a]	27.10 ± 2.28[a,c]	33.53 ± 2.74	72.13 ± 2.42[a,e]	86.47 ± 1.98[a,c,e]
Emotional problems	40.53 ± 2.15	50.17 ± 1.80[a]	26.93 ± 2.75[a,c]	41.80 ± 2.41	65.27 ± 1.31[a,e]	76.83 ± 2.38[a,c,e]
Mental health	35.27 ± 2.94	49.63 ± 2.58[a]	30.83 ± 1.62[a,c]	36.07 ± 2.38	69.37 ± 2.63[a,e]	77.37 ± 1.40[a,c,e]

[a]*P* value < 0.05, compared with at admission.
[c]*P* value < 0.05, compared with at discharge.
[e]*P* value < 0.05, compared with the control group.

lack of professional and effective psychological interventions available to patients at home as described above.

MDT extended nursing mode can improve the life quality of patients

It has been demonstrated that during home rehabilitation, the lack of training guidance from professional health care personnel makes the recovery of patients slower than expected and their motivation to rehabilitation exercise decreases, which in turn reduces their quality of daily life. In the two groups of patients included in this study, the life quality of the patients in the control group has been declining due to the absence of out-of-hospital rehabilitation training guidance and care, while the quality of life scores of the patients in the intervention group have been rising and differ significantly from those of the control group. In addition, the use of internet technology in the experiment group made it more convenient for patients to receive professional rehabilitation guidance and for the health care staff to provide rehabilitation guidance and care more quickly than in the conventional care mode.

CONCLUSION

In conclusion, the MDT extended nursing mode can improve the negative emotions and life quality of young stroke patients, so it can be used in future clinical practice and is worth of promoting. However, this study also has some limitations, the sample size of this study is small and may have been underpredictive. Therefore, further in-depth studies are still needed in the future.

ARTICLE HIGHLIGHTS

Research background

Stroke has become one of the most serious life-threatening diseases due to its high morbidity, disability, recurrence and mortality rates. As an important part of clinical treatment, nursing has a significant impact on the psychological and prognostic outcomes of stroke patients.

Research motivation

Previous studies have demonstrated that different nursing models have different clinical effects on the improvement of negative mood and physical function recovery of stroke patients. Although the nursing model have had a positive effect on dysphoria and life quality of stroke patients, most of those studies were conducted in-hospital. The psychological changes and functional recovery of patients after discharge from hospital were not available until now.

Research objectives

To make up deficiencies, the multi-disciplinary treatment (MDT) model was combined with the extended nursing mode to investigate the optimized care model for young stroke patients in this study.

Research methods

Sixty stroke patients who were hospitalized in the Department of Neurology of our hospital from January 2020 to December 2021 were selected and randomly divided into control group and experimental group, with 30 patients in each group. The control group were treated with conventional nursing while the experimental group were treated with MDT extended nursing mode. Self-rating Anxiety Scale, Self-rating Depression Scale, Hamilton Depression Scale, and Hamilton Anxiety Scale were used to evaluate the negative emotions of patients. The quality of life was evaluated by Barthel Index and the Short-Form Health Survey.

Research results

There are no statistically significant differences in the negative emotions scores between the two groups at admission, while there are statistically significant differences in the negative emotions scores within each group at admission and discharge, at discharge and post-discharge, and at discharge and post-discharge. In addition, the negative emotions scores were all statistically significant at discharge and after discharge when compared between the two groups. There was no statistically significant difference in quality of life scores at the time of admission between the two groups, and the difference between quality of life scores at the time of admission and discharge, at the time of discharge and post-discharge, and at the time of admission and post-discharge for each group of patients was statistically significant.

Research conclusions

In the two groups of patients included in this study, the life quality of the patients in the control group has been declining due to the absence of out-of-hospital rehabilitation training guidance and care, while the quality of life scores of the patients in the intervention group have been rising and differ significantly from those of the control group.

Research perspectives

The MDT extended nursing mode can improve the negative emotion of patients and improve their quality of life. Therefore, it can be applied in future clinical practice and is worthy of promotion.

FOOTNOTES

Author contributions: Fang M, Xu XY, Wang K, and Pang ZJ contributed to the conceptualization and study design; Fang M, Song J, and Xu XY contributed to the administrative support; Fang M, Xu XY, Wang K, Pang ZJ, and Song J contributed to resources; Xu XY, Pang ZJ, Li MH, Wang K, Song J, and Cao Y contributed to the data Collection; Xu XY, Pang ZJ, Li MH, Wang K, Song J, Cao Y, and Fang M contributed to the Data analysis; all the authors contributed to the manuscript writing, reviewing, revising, and editing.

Supported by the Joint Guidance Project of Qiqihar Science and Technology Plan in 2020, No. LHYD-202054.

Institutional review board statement: The study was approved by the Ethics Committee of the Second Affiliated Hospital of Qiqihar Medical College.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have stated that they have no conflict of interest.

Data sharing statement: The authors do not agree to share the data.

Country/Territory of origin: China

ORCID number: Mao Fang 0000-0002-1343-2625.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Thrift AG**, Cadilhac DA, Thayabaranathan T, Howard G, Howard VJ, Rothwell PM, Donnan GA. Global stroke statistics. *Int J Stroke* 2014; **9**: 6-18 [PMID: 24350870 DOI: 10.1111/ijs.12245]

2 **Li B**, Wang T, Lou Y, Guo X, Gu H, Zhu Y, Ning X, Wang J, Tu J. Sex Differences in Outcomes and Associated Risk Factors After Acute Ischemic Stroke in Elderly Patients: A Prospective Follow-up Study. *J Stroke Cerebrovasc Dis* 2015; **24**: 2277-2284 [PMID: 26169546 DOI: 10.1016/j.jstrokecerebrovasdis.2015.06.007]

3 **Sihvonen AJ**, Leo V, Ripollés P, Lehtovaara T, Ylönen A, Rajanaro P, Laitinen S, Forsblom A, Saunavaara J, Autti T, Laine M, Rodríguez-Fornells A, Tervaniemi M, Soinila S, Särkämö T. Vocal music enhances memory and language recovery after stroke: pooled results from two RCTs. *Ann Clin Transl Neurol* 2020; **7**: 2272-2287 [PMID: 33022148 DOI: 10.1002/acn3.51217]

4 **Joy MT**, Carmichael ST. Encouraging an excitable brain state: mechanisms of brain repair in stroke. *Nat Rev Neurosci* 2021; **22**: 38-53 [PMID: 33184469 DOI: 10.1038/s41583-020-00396-7]

5 **Mei Y**, Lin B, Li Y, Ding C, Zhang Z. Effects of modified 8-week reminiscence therapy on the older spouse caregivers of stroke survivors in Chinese communities: A randomized controlled trial. *Int J Geriatr Psychiatry* 2018; **33**: 633-641 [PMID: 29266450 DOI: 10.1002/gps.4833]

6 **Brighton LJ**, Bone AE, Maddocks M. Supportive and palliative care for people with chronic respiratory disease and frailty. *Curr Opin Support Palliat Care* 2020; **14**: 206-212 [PMID: 32740274 DOI: 10.1097/SPC.0000000000000523]

7 **Malhotra R**, Chei CL, Menon EB, Chow WL, Quah S, Chan A, Ajay S, Matchar DB. Trajectories of positive aspects of caregiving among family caregivers of stroke-survivors: the differential impact of stroke-survivor disability. *Top Stroke Rehabil* 2018; **25**: 261-268 [PMID: 29577825 DOI: 10.1080/10749357.2018.1455369]

8 **Wong AK**, Moran JA. Extended care unit: a feasible economic solution for longer-term palliative inpatients. *Intern Med J* 2018; **48**: 1389-1392 [PMID: 30387312 DOI: 10.1111/imj.14094]

9 **Daly RL**, Bunn F, Goodman C. Shared decision-making for people living with dementia in extended care settings: a systematic review. *BMJ Open* 2018; **8**: e018977 [PMID: 29886439 DOI: 10.1136/bmjopen-2017-018977]

10 **Shimada C**, Hirayama R, Wakui T, Nakazato K, Obuchi S, Ishizaki T, Takahashi R. Reconsidering long-term care in the end-of-life context in Japan. *Geriatr Gerontol Int* 2016; **16** Suppl 1: 132-139 [PMID: 27018291 DOI: 10.1111/ggi.12736]

11 **Choi J**, Kim DE, Yoon JY. Person-Centered Care Environment Associated With Care Staff Outcomes in Long-Term Care Facilities. *J Nurs Res* 2020; **29**: e133 [PMID: 33252502 DOI: 10.1097/JNR.0000000000000412]

12 **Gilster SD**, Boltz M, Dalessandro JL. Long-Term Care Workforce Issues: Practice Principles for Quality Dementia Care. *Gerontologist* 2018; **58**: S103-S113 [PMID: 29361072 DOI: 10.1093/geront/gnx174]

13 **Zung WW**, Gianturco JA. Personality dimension and the Self-Rating Depression Scale. *J Clin Psychol* 1971; **27**: 247-248 [PMID: 5100681 DOI: 10.1002/1097-4679(197104)27:2<247::aid-jclp2270270230>3.0.co;2-6]

14 **Yue T**, Li Q, Wang R, Liu Z, Guo M, Bai F, Zhang Z, Wang W, Cheng Y, Wang H. Comparison of Hospital Anxiety and Depression Scale (HADS) and Zung Self-Rating Anxiety/Depression Scale (SAS/SDS) in Evaluating Anxiety and Depression in Patients with Psoriatic Arthritis. *Dermatology* 2020; **236**: 170-178 [PMID: 31434087 DOI: 10.1159/000498848]

15 **Hamilton M**. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56-62 [PMID: 14399272 DOI: 10.1136/jnnp.23.1.56]

16 **Lu W**, Wang H, Lin Y, Li L. Psychological status of medical workforce during the COVID-19 pandemic: A cross-sectional study. *Psychiatry Res* 2020; **288**: 112936 [PMID: 32276196 DOI: 10.1016/j.psychres.2020.112936]

17 **Liu F**, Tsang RC, Zhou J, Zhou M, Zha F, Long J, Wang Y. Relationship of Barthel Index and its Short Form with the Modified Rankin Scale in acute stroke patients. *J Stroke Cerebrovasc Dis* 2020; **29**: 105033 [PMID: 32807445 DOI: 10.1016/j.jstrokecerebrovasdis.2020.105033]

18 **Kin K**, Yasuhara T, Tomita Y, Umakoshi M, Morimoto J, Date I. SF-36 scores predict postoperative delirium after surgery for cervical spondylotic myelopathy. *J Neurosurg Spine* 2019; 1-6 [PMID: 30835706 DOI: 10.3171/2018.11.SPINE181031]

19 **Schöttke H**, Giabbiconi CM. Post-stroke depression and post-stroke anxiety: prevalence and predictors. *Int Psychogeriatr* 2015; **27**: 1805-1812 [PMID: 26178418 DOI: 10.1017/S1041610215000988]

20 **Chen Q**, Wang H, Wang Y, Wang Z, Zhao D, Cai Y. Exploring effects of self-management on glycemic control using a modified information-motivation-behavioral skills model in type 2 diabetes mellitus patients in Shanghai, China: A cross-sectional study. *J Diabetes* 2018; **10**: 734-743 [PMID: 29457694 DOI: 10.1111/1753-0407.12655]

21 **Charidimou A**, Turc G, Oppenheim C, Yan S, Scheitz JF, Erdur H, Klinger-Gratz PP, El-Koussy M, Takahashi W, Moriya Y, Wilson D, Kidwell CS, Saver JL, Sallem A, Moulin S, Edjlali-Goujon M, Thijs V, Fox Z, Shoamanesh A, Albers GW, Mattle HP, Benavente OR, Jäger HR, Ambler G, Aoki J, Baron JC, Kimura K, Kakuda W, Takizawa S, Jung S, Nolte CH, Lou M, Cordonnier C, Werring DJ. Microbleeds, Cerebral Hemorrhage, and Functional Outcome After Stroke Thrombolysis. *Stroke* 2017; **48**: 2084-2090 [PMID: 28720659 DOI: 10.1161/STROKEAHA.116.012992]

22 **Koivunen RJ**, Harno H, Tatlisumak T, Putaala J. Depression, anxiety, and cognitive functioning after intracerebral hemorrhage. *Acta Neurol Scand* 2015; **132**: 179-184 [PMID: 25639837 DOI: 10.1111/ane.12367]

23 **Molaifard A**, Mohamadian H, Haghighi Zadeh MH. Predicting high school students' health-promoting lifestyle: a test of the information, motivation, behavioral skills model. *Int J Adolesc Med Health* 2018; **32** [PMID: 29397384 DOI: 10.1515/ijamh-2017-0194]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3158-3166

DOI: 10.12998/wjcc.v11.i14.3158

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Changes and significance of serum ubiquitin carboxyl-terminal hydrolase L1 and glial fibrillary acidic protein in patients with glioma

Qing-Hua Zhu, Jing-Kun Wu, Gao-Lei Hou

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Pierro A, Canada; Shah PS, Canada

Received: February 19, 2023
Peer-review started: February 19, 2023
First decision: February 28, 2023
Revised: March 17, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Qing-Hua Zhu, Jing-Kun Wu, Gao-Lei Hou, Department of Neurosurgery, Affiliated Hospital of Hebei Engineering University, Handan 056002, Hebei Province, China

Corresponding author: Jing-Kun Wu, MM, Associate Chief Physician, Department of Neurosurgery, Affiliated Hospital of Hebei Engineering University, No. 81 Congtai Street, Congtai District, Handan 056002, Hebei Province, China. wujingkunwjk@163.com

Abstract

BACKGROUND

Brain gliomas are malignant tumors with high postoperative recurrence rates. Early prediction of prognosis using specific indicators is of great significance.

AIM

To assess changes in ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) levels in patients with glioma pre-and postoperatively.

METHODS

Between June 2018 and June 2021, 91 patients with gliomas who underwent surgery at our hospital were enrolled in the glioma group. Sixty healthy volunteers were included in the control group. Serum UCH-L1 and GFAP levels were measured in peripheral blood collected from patients with glioma before and 3 d after surgery. UCH-L1 and GFAP levels in patients with glioma with different clinicopathological characteristics were compared before and after surgery. The patients were followed-up until February 2022. Postoperative glioma recurrence was recorded to determine the serum UCH-L1 and GFAP levels, which could assist in predicting postoperative glioma recurrence.

RESULTS

UCH-L1 and GFAP levels in patients with glioma decreased significantly 3 d after surgery compared to those before therapy ($P < 0.05$). However, UCH-L1 and GFAP levels in the glioma group were significantly higher than those in the control group before and after surgery ($P < 0.05$). There were no statistically significant differences in preoperative serum UCH-L1 and GFAP levels among patients with glioma according to sex, age, pathological type, tumor location, or number of lesions ($P > 0.05$). Serum UCH-L1 and GFAP levels were significantly lower in the patients with WHO grade I-II tumors than in those with grade III-IV tumors ($P < 0.05$). Serum UCH-L1 and GFAP levels were lower in the patients

with tumor diameter ≤ 5 cm than in those with diameter > 5 cm, in which the differences were statistically significant ($P < 0.05$). Glioma recurred in 22 patients. The preoperative and 3-d postoperative serum UCH-L1 and GFAP levels were significantly higher in the recurrence group than these in the non-recurrence group ($P < 0.05$). Receiver operating characteristic curves were plotted. The areas under the curves of preoperative serum UCH-L1 and GFAP levels for predicting postoperative glioma recurrence were 0.785 and 0.775, respectively. However, the efficacy of serum UCH-L1 and GFAP levels 3 d after surgery in predicting postoperative glioma recurrence was slightly lower compared with their preoperative levels.

CONCLUSION
UCH-L1 and GFAP efficiently reflected the development and recurrence of gliomas and could be used as potential indicators for the recurrence and prognosis of glioma.

Key Words: Glioma; Ubiquitin carboxy-terminal hydrolase L1; Glial fibrillary acidic protein; Surgery; Prognosis; Clinical significance

Core Tip: Since the recurrence rate of glioma is high, it is important to early predict its prognosis. Ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) are important markers for nervous system damages and lesions. Therefore, we evaluated the changes in UCH-L1 and GFAP levels in patients with glioma during the perioperative period and compared them with those in healthy volunteers to analyze their relationship with clinicopathological and postoperative recurrence. These results revealed that UCH-L1 and GFAP might reflect the development and recurrence of glioma and could be used as potential indicators to estimate prognosis of glioma.

Citation: Zhu QH, Wu JK, Hou GL. Changes and significance of serum ubiquitin carboxyl-terminal hydrolase L1 and glial fibrillary acidic protein in patients with glioma. *World J Clin Cases* 2023; 11(14): 3158-3166
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3158.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3158

INTRODUCTION

Brain glioma is an extremely common type of intracranial malignant tumor that deteriorates, grows rapidly and causes severe neurological impairment. Due to the poor sensitivity of brain gliomas to radiotherapy, they are mainly managed by surgical resection. However, some gliomas are large in size or close to important neural tissues and are difficult to completely remove intraoperatively. Therefore, the recurrence rate of brain gliomas after surgery is high[1,2]. Early prediction of postoperative prognosis in patients with gliomas is of great importance in clinical practice. Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) is a cysteine hydrolase that regulates the cell cycle, is involved in apoptosis and inflammatory responses, is present at high levels in the brain, and is regarded as a biomarker of brain injury[3]. Glial fibrillary acidic protein (GFAP) is a specific indicator of astrocytes and involved in neurological damage and lesions[4]. In this study, we evaluated changes in serum UCH-L1 and GFAP levels in patients with glioma before and after surgery. We also assessed the relationship between the two indicators and analyzed data of the patients' clinicopathological characteristics and postoperative recurrence. We also aimed to determine the values of UCH-L1 and GFAP for predicting glioma recurrence.

MATERIALS AND METHODS

Participants

A total of 91 patients with gliomas who underwent surgery in the hospital between June 2018 and June 2021 were enrolled in the glioma group. The control group included 60 healthy volunteers during the same period.

Patients with glioma

The inclusion criteria comprised patients: Who were treated surgically; with glioma that was clearly

detected by postoperative pathological examination; who underwent no radiotherapy before surgery; and with complete clinical case data. Patients with: acromegaly, hepatitis, and other diseases; severe defects in vital organ function; severe complications, and postoperative death; or other malignant tumors were excluded from the study.

The control group

The age and sex ratios in the control group were similar to those in the glioma group: Both groups underwent physical examination and had no previous history of tumors, intracranial lesions, or brain injury.

Methods

All patients with gliomas were surgically treated, and 5 mL of peripheral venous blood was collected from these patients with glioma before and 3 d after surgery. In the control group, venous blood was collected during fasting in the early morning on day two after enrollment.

Blood samples were immediately centrifuged at 3000 rpm for 15 min. The liquid supernatant was separated and stored at -80°C for later use. Serum GFAP and UCH-L1 Levels were detected by ABC-ELISA, and kits were purchased from Rapid Bio, USA. The experimental procedure was performed in strict accordance with the relevant kit standards.

Study aims

(1) To compare UCH-L1 and GFAP levels between the glioma and control groups; (2) To analyze data of preoperative serum UCH-L1 and GFAP levels in patients with gliomas with different clinicopathological features; and (3) The patients were followed up until February 2022 to record the preoperative recurrence of glioma and compare serum UCH-L1 and GFAP levels between the recurring and non-recurring patients. A receiver operating characteristic (ROC) curve was drawn. Furthermore, the values of preoperative and postoperative serum UCH-L1 and GFAP levels for predicting postoperative glioma recurrence were analyzed.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0. The measurement data was presented as mean ± SD. The independent samples t test was used for mean comparison between the two groups. The mean data before and after treatment were analyzed using the paired t test, and the count data were conveyed by case. The χ^2 test was used to compare the two groups. ROC curves were drawn (Figure 1). In addition, the best critical value was calculated by the Youden index formula to evaluate the efficacy of preoperative and postoperative serum UCH-L1 and GFAP levels in predicting postoperative glioma recurrence. P value < 0.05 was considered statistically significant.

RESULTS

Comparison of serum UCH-L1 and GFAP levels between the glioma and control groups

UCH-L1 and GFAP levels in the patients with glioma decreased significantly 3 d after surgery compared with their pre-therapy levels (P < 0.05). However, the UCH-L1 and GFAP levels in the glioma group were significantly higher than those in the control group before and after surgery (P < 0.05, Table 1).

Analysis of the relationship between preoperative serum UCH-L1 and GFAP levels and clinicopathological characteristics in patients with glioma

There were no significant differences in the preoperative serum UCH-L1 and GFAP levels in patients with brain glioma with respect to sex, age, pathological type, tumor location, or number of lesions (P > 0.05, Table 2). The UCH-L1 and GFAP levels in the patients with WHO grade I-II tumors were lower than those in the participants with grade III-IV tumors. Additionally, the UCH-L1 and GFAP levels in the patients with tumor diameters ≤ 5 cm were lower than those in the participants with tumor diameters > 5 cm.

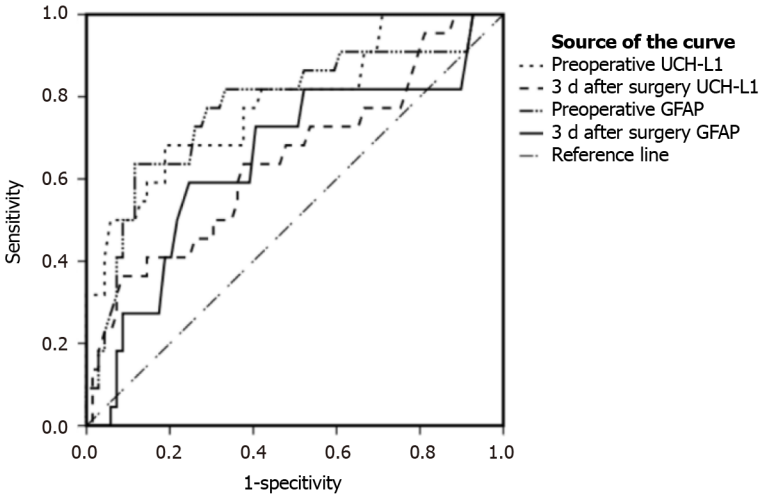
Comparison of UCH-L1 and GFAP levels in patients with glioma recurrence and those without recurrence before and after surgery

All patients were followed up until February 2022. A total of 22 patients with gliomas experienced recurrence. The preoperative and 3 d postoperative serum UCH-L1 and GFAP levels were significantly higher in the recurrence group compared with the non-recurrence group (P < 0.05, Table 3).

Table 1 Comparison of serum ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels between the glioma and control groups

Group	*n*	Time	UCH-L1 (pg/mL)	GFAP (ng/L)
Glioma group	91	Preoperative	96.89 ± 17.15[a]	16.69 ± 2.16[a]
		3 d after surgery	72.15 ± 12.33[a,d]	7.53 ± 1.74[a,d]
Control group	60		60.17 ± 10.78	1.16 ± 0.25

[a]$P < 0.05$ *vs* the control group.
[d]$P < 0.05$ *vs* the glioma group three days after surgery.
UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.



DOI: 10.12998/wjcc.v11.i14.3158

Figure 1 Receiver operating characteristic curve of serum ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels for predicting postoperative recurrence of glioma. UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

The value of UCH-L1 and GFAP levels for predicting postoperative recurrence of glioma

The AUC of the preoperative serum UCH-L1 and GFAP levels for predicting postoperative glioma recurrence were 0.785 and 0.775, respectively (Table 4). The efficacy of UCH-L1 and GFAP levels 3 d after surgery in predicting postoperative glioma recurrence was slightly lower than their preoperative levels.

DISCUSSION

Glioma is a tumor caused by glial cell lesions originating from the ectoderm of the nervous system with an incidence of approximately 5/100000. Owing to the lack of specific tumor markers related to gliomas, imaging examinations such as brain computed tomography or magnetic resonance imaging are the main methods for the clinical assessment of changes and treatment effects during the course of glioma. However, imaging examinations are particularly lagging behind clinical treatment and prognostic determination[5,6]. Therefore, finding more sensitive indicators that reflect treatment effect and prognosis in patients with glioma as soon as possible was one of the aims of the current study.

UCH-L1 is a member of the ubiquitin protease system family, which mainly consists of 223 amino acids, and is abundant in the brain. It is involved in cell proliferation, differentiation, apoptosis, and other physiological processes *via* the ubiquitin pathway. In addition, UCH-L1 has been shown to be relevant to brain nervous system development, brain tumors, and brain injury[7,8]. Studies have shown that[9] after acute cerebral infarction, a large amount of UCH-L1 could be released from damaged nerve cells and penetrate the blood-brain barrier into the blood circulation. Therefore, serum UCH-L1 levels were elevated in patients with cerebral infarction. Wang *et al*[10] found that serum UCH-L1 Levels had good clinical value for reflecting the degree of brain injury and prognosis in patients with severe cranio-cerebral injury. Elevated levels of UCH-L1 in the cerebrospinal fluid and peripheral blood have become effective indicators of the severity of central nervous cell damage.

Table 2 Analysis of the relationship between preoperative serum ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels and clinicopathological characteristics in the patients with glioma

Clinicopathological features	UCH-L1 (pg/mL)	GFAP (ng/L)
Gender		
Male (n = 49)	95.89 ± 16.79	16.58 ± 2.14
Female (n = 42)	98.05 ± 17.69	16.82 ± 2.20
t value	0.597	0.515
P value	0.552	0.608
Age (yr)		
< 40 (n = 44)	99.78 ± 18.42	17.03 ± 2.29
≥ 40 (n = 47)	94.19 ± 15.58	16.37 ± 2.01
t value	1.566	1.483
P value	0.121	0.141
Pathological type		
Glioblastoma (n = 76)	98.12 ± 17.14	16.84 ± 2.16
Medulloblastoma (n = 15)	90.65 ± 16.35	15.92 ± 2.04
t value	1.554	1.512
P value	0.124	0.134
Tumor location		
Frontal lobe (n = 41)	95.28 ± 16.24	16.50 ± 2.09
Temporal lobe (n = 39)	99.14 ± 17.59	16.97 ± 2.21
Other locations (n = 11)	94.93 ± 19.56	16.39 ± 2.29
F value	0.582	0.592
P value	0.561	0.555
Tumor grade		
WHO I-II grade (n = 33)	78.89 ± 5.05	14.39 ± 0.84
WHO III-IV grade (n = 58)	107.13 ± 12.48	18.01 ± 1.47
t value	12.402	12.900
P value	< 0.000	< 0.001
Tumor diameter		
≤ 5 cm (n = 19)	75.23 ± 3.04	13.80 ± 0.59
> 5 cm (n = 72)	102.61 ± 14.55	17.45 ± 1.73
t value	8.123	9.006
P value	< 0.001	< 0.001
Number of lesions		
Single (n = 70)	97.57 ± 17.70	16.77 ± 2.25
Multiple (n = 21)	94.63 ± 15.37	16.43 ± 1.84
t value	0.685	0.619
P value	0.495	0.537

WHO: World Health Organization; UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

This study revealed that the preoperative serum UCH-L1 levels in patients with glioma were notably higher than those in the control group. Furthermore, UCH-L1 Levels in patients with gliomas significantly decreased after surgical treatment. However, the postoperative UCH-L1 level was also

Table 3 Comparison of ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels in patients with glioma recurrence and those without recurrence before and after surgery

Time	UCH-L1 (pg/mL)	GFAP (ng/L)
Recurrence group (n = 22)		
Preoperative	120.44 ± 6.41	19.59 ± 0.57
3 d after surgery	88.01 ± 2.44	10.00 ± 0.46
t value	37.398	289.806
P value	< 0.001	< 0.001
Non-recurrence group (n = 69)		
Preoperative	89.38 ± 11.83	15.76 ± 1.58
3 d after surgery	67.09 ± 9.60	6.74 ± 1.16
t value	78.571	172.100
P value	< 0.001	< 0.001
Preoperative comparison of the two groups		
t value	11.749	11.118
P value	< 0.001	< 0.001
Comparison of the two groups at 3 d after surgery		
t value	10.086	12.791
P value	< 0.001	< 0.001

UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

Table 4 The value of ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein levels for predicting postoperative recurrence of glioma

Indicator	Critical value	AUC	95%CI	*P* value	Sensitivity (%)	Specificity (%)
Preoperative UCH-L1	103.85	0.785	0.670-0.901	< 0.001	68.2	81.2
3 d after surgery UCH-L1	85.61	0.646	0.507-0.785	0.040	63.6	62.3
Preoperative GFAP	18.70	0.775	0.651-0.898	< 0.001	63.6	88.4
3 d after surgery GFAP	8.58	0.648	0.508-0.787	0.038	59.1	75.4

AUC: Area under the curve; UCH-L1: Ubiquitin carboxy-terminal hydrolase L1; GFAP: Glial fibrillary acidic protein.

higher than that in healthy controls. This may be related to the fact that under compression by glioma, part of the brain nerve tissue could have been damaged, which in turn released a large amount of UCH-L1, leading to an increase in serum UCH-L1 Levels. Subsequently, the glioma was removed to relieve the compressed brain tissues and decrease the release of UCH-L1 from damaged nerve cells.

The WHO classifies gliomas into grades I–IV, with grades I–II as low-grade and those of III–IV as high-grade gliomas. This study demonstrated that UCH-L1 Levels in the patients with WHO grade III-IVI-II tumors were higher than those in those with grade I-II tumors. Additionally, the UCH-L1 Level was greater in the patients with a tumor diameter > 5 cm than in those with diameter ≤ 5 cm. It has been suggested that serum UCH-L1 Levels reflected development of glioma.

GFAP is a cytoskeletal protein that maintains the morphological and structural stability of astrocytes and determines the degree of astrocyte response to injury[11]. Some studies have shown that after central nervous system damage, astrocytes were abnormally active, manifesting as rapid synthesis and secretion of GFAP, and the addition of GFAP-positive astrocytes could further promote astrocyte mitosis. Some studies have found[12] that positive GFAP expression in astrocytes adjacent to the cerebral cortex significantly increased after brain injury. Feng *et al*[13] found that an increase in GFAP levels in patients with severe craniocerebral injury after surgery was a risk factor for poor prognosis, which had a certain value in promoting postoperative survival. Wang *et al*[14] found that serum GFAP levels were elevated in asphyxiated preterm infants with brain injury and serum GFAP had some value

in the diagnosis of brain injury and could be used as a marker for central nervous system injury and prognosis.

We found that the preoperative serum GFAP levels in the patients with glioma were higher than those in the control group. After surgery, the serum GFAP levels in these patients with gliomas decreased. However, this level was higher than that observed in healthy controls. In addition, the serum GFAP levels in the patients with WHO grade III-IVI-II tumors were dramatically higher than those in the participants with grade I-II tumors. The serum GFAP level in the patients with tumor diameter > 5 cm was higher than that in those with diameter ≤ 5 cm. It has been suggested that serum GFAP was valuable in predicting the occurrence and development of gliomas.

In the early stages of glioma, patients do not exhibit specific clinical manifestations. However, by the time the disease is diagnosed, glioma is mostly advanced, with a large tumor size involving important functional brain nerve areas[15-17]. In addition, distinguishing the boundary between the tumor and normal brain tissue becomes difficult, making complete removal of the tumor challenging and resulting in residual tumor tissue, which is considered the main reason for postoperative recurrence[18-20]. In this study, among the 91 patients with glioma, 22 experienced recurrence after surgery. In addition, the UCH-L1 and GFAP levels were higher in the recurrence group than that in the non-recurrence group before and 3 d after surgery. This indicated that serum UCH-L1 and GFAP levels had the potential to reflect postoperative glioma recurrence. By plotting ROC curves, we found that the efficacy of both preoperative UCH-L1 and GFAP levels in predicting postoperative glioma recurrence was slightly higher than that 3 d after surgery. However, limited by the study design, we did not discuss the optimal time points for serum UCH-L1 and GFAP levels to predict postoperative glioma recurrence. This study also did not consider the specific mechanisms of action of these two indicators of gliomas, which warrants further research.

CONCLUSION

The UCH-L1 and GFAP levels abnormally increased in patients with gliomas. Although the levels of these two indices decreased after the surgical treatment, they remained higher than those in the control group. Both serum UCH-L1 and GFAP levels may specifically reflect the development and postoperative recurrence of glioma. These two markers could be used as potential indicators of recurrence and prognosis in patients with postoperative glioma.

ARTICLE HIGHLIGHTS

Research background

Glioma is a very common intracranial malignant tumor with a high degree of malignancy, rapid growth, and high postoperative recurrence rate, which could cause severe damage to the nervous system. Early prediction of postoperative prognosis in patients with glioma is of great clinical significance.

Research motivation

Ubiquitin carboxyl terminal hydrolase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) reflect damage and lesions in the nervous system. Changes in serum UCH-L1 and GFAP levels in patients with glioma before and after surgery, and the relationship between them, have not been clarified.

Research objectives

This study aimed to assess the changes and correlation between pre-and postoperative serum UCH-L1 and GFAP levels in patients with glioma and predict the postoperative prognosis of patients with glioma after surgery.

Research methods

Total 91 patients with glioma were included in the experimental group and 60 healthy volunteers were selected as the control group. In the experimental group, 5 mL of peripheral venous blood was collected before and 3 d after surgery to detect UCH-L1 and GFAP levels in the peripheral blood serum. In the control group, venous blood was collected on an empty stomach morning on the second day after enrollment to monitor the levels of UCH-L1 and GFAP in the peripheral blood serum. At the same time, the postoperative recurrence of glioma was recorded to determine the value of serum UCH-L1 and GFAP for predicting glioma prognosis.

Research results

UCH-L1 and GFAP levels 3 d after surgery in the patients with gliomas were significantly lower than

those before surgery. Moreover, the UCH-L1 and GFAP levels in the glioma group were significantly higher than those in the control group before and after surgery. The levels of serum UCH-L1 and GFAP in 22 patients with glioma recurrence were higher compared with the non-recurrence group before and 3 d after surgery, and the difference was statistically significant.

Research conclusions

Although serum UCH-L1 and GFAP levels in the patients with glioma were abnormally increased, these levels decreased after surgery. Serum UCH-L1 and GFAP levels may be potential indicators for predicting the postoperative recurrence and prognosis of glioma.

Research perspectives

Future work and clinical research should be conducted to verify the accuracy of the experimental results through a more rigorous experimental design, expanded sample size, and multicenter studies and to provide favorable evidence for predicting the recurrence and prognosis of glioma.

FOOTNOTES

Author contributions: Zhu QH and Wu JK designed the study, and implemented and collected the data; Zhu QH analyzed the data, wrote and edited the manuscript; and Hou GL supervised and supported the research.

Supported by Hebei Medical Science Research Project, No. 20220648.

Institutional review board statement: This study was approved by the Ethics Committee of the Affiliated Hospital of Hebei Engineering University.

Informed consent statement: All study participants or their legal guardians provided written informed consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement checklist of items.

Country/Territory of origin: China

ORCID number: Qing-Hua Zhu 0000-0003-0740-5126; Jing-Kun Wu 0000-0001-7381-6180; Gao-Lei Hou 0000-0002-2556-0261.

S-Editor: Wang JL
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Ren CC**, Zhang LT, Kang JS, Kang L, Wang QX, Zhao J. Expressions and Diagnostic Efficacies of Serum NSE, CA15-3, S100B and IGF-1 in Patients with Brain Glioma. *Jiefangjun Yiyao Zazhi* 2022; **34**: 25-28 [DOI: 10.3969/j.issn.2095-140X.2022.01.005]

2 **He LJ**, Ren J, Zhao YB, Gao Q, Xu JC, Wang J. Scalp electroencephalogram characteristics of ganglioglioma and its correlation with post-operative prognosis. *Dianxian Yu Shenjingdianshenglixue Zazhi* 2022; **31**: 12-21 [DOI: 10.19984/j.cnki.1674-8972.2022.01.03]

3 **Amoo M**, Henry J, O'Halloran PJ, Brennan P, Husien MB, Campbell M, Caird J, Javadpour M, Curley GF. S100B, GFAP, UCH-L1 and NSE as predictors of abnormalities on CT imaging following mild traumatic brain injury: a systematic review and meta-analysis of diagnostic test accuracy. *Neurosurg Rev* 2022; **45**: 1171-1193 [PMID: 34709508 DOI: 10.1007/s10143-021-01678-z]

4 **Amalia L**. Glial Fibrillary Acidic Protein (GFAP): Neuroinflammation Biomarker in Acute Ischemic Stroke. *J Inflamm Res* 2021; **14**: 7501-7506 [PMID: 35002283 DOI: 10.2147/JIR.S342097]

5 **Leibetseder A**, Leitner J, Mair MJ, Meckel S, Hainfellner JA, Aichholzer M, Widhalm G, Dieckmann K, Weis S, Furtner J, von Oertzen T, Preusser M, Pichler J, Berghoff AS. Prognostic factors in adult brainstem glioma: a tertiary care center analysis and review of the literature. *J Neurol* 2022; **269**: 1574-1590 [PMID: 34342680 DOI: 10.1007/s00415-021-10725-0]

6 **Nicholson JG**, Fine HA. Diffuse Glioma Heterogeneity and Its Therapeutic Implications. *Cancer Discov* 2021; **11**: 575-590 [PMID: 33558264 DOI: 10.1158/2159-8290.CD-20-1474]

7 **Richard M**, Lagares A, Bondanese V, de la Cruz J, Mejan O, Pavlov V, Payen JF; BRAINI investigators. Study protocol for investigating the performance of an automated blood test measuring GFAP and UCH-L1 in a prospective observational cohort of patients with mild traumatic brain injury: European BRAINI study. *BMJ Open* 2021; **11**: e043635 [PMID: 33632753 DOI: 10.1136/bmjopen-2020-043635]

8 **Papa L**, Ladde JG, O'Brien JF, Thundiyil JG, Tesar J, Leech S, Cassidy DD, Roa J, Hunter C, Miller S, Baker S, Parrish GA, Davison J, Van Dillen C, Ralls GA, Briscoe J, Falk JL, Weber K, Giordano PA. Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury. *JAMA Netw Open* 2022; **5**: e221302 [PMID: 35285924 DOI: 10.1001/jamanetworkopen.2022.1302]

9 **Shan HL**, Jiao GM, Cheng X, Ma Z, Gao YJ, Yang N, Dou ZJ. Changes and significance of serum UCH-L1 and Fibulin-5 levels in patients with acute cerebral infarction. *Shandong Yiyao* 2021; **61**: 32-36 [DOI: 10.3969/j.issn.1002-266X.2021.07.008]

10 **Wang J**, Zhang HY, Du P, Wan J. The Predictive Value of the Serum Ubiquitin Carboxyl-terminal Hydrolase L1 and Neutrophil Gelatinase-associated Lipocalin to the Ill Condition and Prognosis in Patients with Severe Brain Injury. *Biaojimianyifenxi Yu Linchuang* 2020; **27**: 195-199, 205

11 **Yuan W**, Lu L, Rao M, Huang Y, Liu CE, Liu S, Zhao Y, Liu H, Zhu J, Chao T, Wu C, Ren J, Lv L, Li W, Qi S, Liang Y, Yue S, Gao J, Zhang Z, Kong E. GFAP hyperpalmitoylation exacerbates astrogliosis and neurodegenerative pathology in PPT1-deficient mice. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 33753498 DOI: 10.1073/pnas.2022261118]

12 **Hausmann R**, Riess R, Fieguth A, Betz P. Immunohistochemical investigations on the course of astroglial GFAP expression following human brain injury. *Int J Legal Med* 2000; **113**: 70-75 [PMID: 10741479 DOI: 10.1007/pl00007711]

13 **Feng AP**, Wang W, Du C. The relationship between the postoperative levels of serum copeptin and GFAP and the prognosis of patients with severe traumatic brain injury. *Shiyong Yiyuan Linchuang Zazhi* 2022; **19**: 132-135 [DOI: 10.3969/j.issn.1672-6170.2022.01.035]

14 **Wang T**, Li YF, Wang XS, Liu ZHJ. Diagnostic value of serum HMGB1, GFAP, and UCH-L1 for brain injury in asphyxia premature infants. *Guoji Jianyan Yixue Zazhi* 2021; **42**: 1549-1553 [DOI: 10.3969/j.issn.1673-4130.2021.13.004]

15 **Yang Y**. The factors related to postoperative recurrence in frontal low-grade gliomas after neurosurgeon determined gross-total resection. *Litidingxiang He Gongnengxing Shenjingwaike Zazhi* 2020; **33**: 280-284 [DOI: 10.19854/j.cnki.1008-2425.2020.05.0006]

16 **Zhang QH**, Duan WC, Liu XZ, Zhang ZHY. Clinical characteristics and postoperative survival of asymptomatic patients with WHO grade II gliomas. *Zhonghua Shenjingwaike Zazhi* 2020; **36**: 405-409 [DOI: 10.3760/cma.j.cn112050-20190822-00364]

17 **Ng S**, Lemaitre AL, Moritz-Gasser S, Herbet G, Duffau H. Recurrent Low-Grade Gliomas: Does Reoperation Affect Neurocognitive Functioning? *Neurosurgery* 2022; **90**: 221-232 [PMID: 34995251 DOI: 10.1227/NEU.0000000000001784]

18 **Rubin MC**, Sagberg LM, Jakola AS, Solheim O. Primary versus recurrent surgery for glioblastoma-a prospective cohort study. *Acta Neurochir (Wien)* 2022; **164**: 429-438 [PMID: 33052493 DOI: 10.1007/s00701-020-04605-1]

19 **Teyateeti A**, Geno CS, Stafford SS, Mahajan A, Yan ES, Merrell KW, Laack NN, Parney IF, Brown PD, Jethwa KR. Does the dural resection bed need to be irradiated? *Neurooncol Pract* 2021; **8**: 190-198 [PMID: 33898052 DOI: 10.1093/nop/npaa073]

20 **Strand PS**, Berntsen EM, Fyllingen EH, Sagberg LM, Reinertsen I, Gulati S, Bouget D, Solheim O. Brain infarctions after glioma surgery: prevalence, radiological characteristics and risk factors. *Acta Neurochir (Wien)* 2021; **163**: 3097-3108 [PMID: 34468884 DOI: 10.1007/s00701-021-04914-z]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3167-3175

DOI: 10.12998/wjcc.v11.i14.3167

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Multitrack and multianchor point screw technique combined with the Wiltse approach for lesion debridement for lumbar tuberculosis

Yu-Fei Yuan, Zhi-Xin Ren, Cun Zhang, Guan-Jun Li, Bing-Zhi Liu, Xiao-Dong Li, Jie Miao, Jian-Fei Li

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Elgafy H, United States; Keikha M, Iran; Vahedi P, Iran

Received: January 17, 2023
Peer-review started: January 17, 2023
First decision: March 24, 2023
Revised: April 1, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: May 16, 2023

Yu-Fei Yuan, Zhi-Xin Ren, Cun Zhang, Guan-Jun Li, Bing-Zhi Liu, Xiao-Dong Li, Department of Orthopadics, Handan Center Hospital, Handan 056001, Hebei Provence, China

Jie Miao, Department of Orthopedic Surgery, Handan Central Hospital, Handan 056001, Hebei Province, China

Jian-Fei Li, Department of CT, Handan Central Hospital, Handan 056001, Hebei Province, China

Corresponding author: Jie Miao, MD, Chief Doctor, Department of Orthopedic Surgery, Handan Central Hospital, No. 15 Zhonghua South Street, Handan 056001, Hebei Province, China. yangxue19851207@126.com

Abstract

BACKGROUND

The incidence of lumbar tuberculosis is high worldwide, and effective treatment is a continuing problem.

AIM

To study the safety and efficacy of the multitrack and multianchor point screw technique combined with the contralateral Wiltse approach for lesion debridement to treat lumbar tuberculosis.

METHODS

The C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), visual analogue scale (VAS) score, oswestry disability index (ODI) and American Spinal Injury Association (ASIA) grade were recorded and analysed pre- and postoperatively.

RESULTS

The CRP level and ESR returned to normal, and the VAS score and ODI were decreased at 3 mo postoperatively, with significant differences compared with the preoperative values ($P < 0.01$). Neurological dysfunction was relieved, and the ASIA grade increased, with no adverse events.

CONCLUSION

The multitrack, multianchor point screw fixation technique combined with the contralateral Wiltse approach for debridement is an effective and safe method for the treatment of lumbar tuberculosis.

Key Words: Lumbar spine; Tuberculosis; Debridement; Pedicle screw; Cortical bone trajectory screw; Wiltse approach

Core Tip: Pedicle screw combined with cortical bone trajectory screw+ contralateral Wiltse approach is safe and effective in the treatment of lumbar tuberculosis and suitable for the case of heavier lesion on one side and no large or flow abscesses in front of the lumbar spine.

Citation: Yuan YF, Ren ZX, Zhang C, Li GJ, Liu BZ, Li XD, Miao J, Li JF. Multitrack and multianchor point screw technique combined with the Wiltse approach for lesion debridement for lumbar tuberculosis. *World J Clin Cases* 2023; 11(14): 3167-3175
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3167.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3167

INTRODUCTION

2020 Global Tuberculosis Report stated that tuber-culosis remains the most common cause of death as a single infectious agent[1,2]. Spinal tuberculosis was first reported by Pott in 1782, and spinal tuber-culosis accounts for approximately 50% of cases of bone and joint tuberculosis[3], with lumbar tuberculosis accounting for 42.36% of spinal tuberculosis cases[4]. Spinal tuberculosis lesions often involve the vertebrae and intervertebral discs, leading to vertebral destruction and intervertebral space collapse, in turn resulting in intervertebral space abscesses, paravertebral abscesses[5], and angular kyphosis of the spine in severe cases[6]. Patients with lumbar spine tuberculosis may have clinical symptoms such as low back pain and neurological dysfunction, with or without symptoms of tuber-culosis toxicity[7]. In cases where medicine fails, surgery should be performed to relieve pain, correct deformity, and improve neurological function[8].

At present, the choice of surgical approach for lumbar tuberculosis remains controversial[9]. The surgical app-roaches can be divided into anterior, posterior, and combined anterior-posterior approaches, each with advantages and disadvantages. The anterior approach allows the removal of tuberculosis lesions and reconstruction of collapsed vertebrae under direct vision, but the risk of complications is high due to the complex anatomical structure of vessels and nerves in the anterior lumbar spine[9]. The combined anterior-posterior approach results in a long operation time and substantial intraoperative trauma. The conventional posterior approach requires the stripping of the paraspinal muscles, removal of normal posterior structures such as the lamina to expose and clear tuberculosis lesions, and use of screw-rod internal fixation to reconstruct lumbar lordosis[10,11].

Tuberculosis patients generally suffer from anaemia, hypoalbuminemia, and nutritional depletion [12], so surgical treatment should be as minimally invasive as possible to remove tuberculosis lesions while reducing damage to normal structures and reconstructing the spinal sequence[13]. Based on the above considerations, the author's team applied the posterior unilateral multitrack, multianchor screw technique combined with the contralateral Wiltse approach for lesion debridement in the treatment of lumbar tuberculosis.

An article in 2021 cited the pedicle screw as one of the top 10 inventions that shaped modern orthopaedics[14]. Pedicle screws were first used in vertebral fusion in 1959[15], and Roy-Camille first used pedicle screws for spinal fixation in 1963. Through the anterior column, pedicle screw placement can achieve three-column fixation of the spine, with excellent holding force and orthopaedic strength. In this study, the screw trajectory refers to the cortical bone trajectory (CBT) of the pedicle fixation technique, not the traditional technique. The CBT screw technique was first proposed by Santoni *et al* [16] in 2009; in this technique, the screw point is more inwards than the pedicle screw point, as it needs to be exposed to the isthmus of the lamina. The screw track runs from the medial-caudal to the lateral-cephalic direction. The screw is driven from the medial side of the lateral edge of the lamina into the posterior part of the superior endplate, and the screw path runs in the cortical bone. There are four cortical bone contact points to hold the screw, which results in a stronger screw holding force; thus, this technique is especially suitable for patients with osteoporosis and can be used for in revision surgery for adjacent segment disease[17] and in spinal orthopaedics[18].

MATERIALS AND METHODS

Patient population

Our research project was approved by the Ethics Committee of Handan Central Hospital. All patients signed informed consent forms. All methods were performed in accordance with the relevant guidelines and regulations.

The clinical data of patients with lumbar tuberculosis treated by unilateral pedicle screw combined with CBT screw fixation + the contralateral Wiltse approach for lumbar tuberculosis debridement from October 2014 to January 2021 were retrospectively analysed.

Inclusion criteria: X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and other imaging examinations of patients showed vertebral and intervertebral space destruction, sequestrum formation, intervertebral and paravertebral cold abscess formation, spinal instability/deformity, *etc.*, which were consistent with the characteristics of spinal tuberculosis; a caseous substance was present, consistent with the diagnosis of spinal tuberculosis by histopathology; the patient had symptoms such as night sweats, low fever in the afternoon, and fatigue; and the patient had intractable low back pain, progressive neurological impairment, and other symptoms. Exclusion criteria: huge abscess anterior to the lumbosacral spine; lumbar infusion abscess.

Preoperative preparation

All patients were absolutely bedridden; high-energy and high-protein diets were given to improve the nutritional status, and anaemia and hypoproteinaemia were corrected before surgery. Low-molecular-weight heparin (4100 units 1/d) was injected subcutaneously to prevent deep vein thrombosis. All patients received standard combinations of 4 drugs for 2–4 wk (H, isoniazid: 300 mg/d, R, rifampicin: 450 mg/d, E, ethambutol: 750 mg/d, Z, pyrazinamide: 750 mg/d).

Surgical strategy

Two advanced surgeons performed the operations. The patient underwent general anaesthesia and tracheal intubation in the prone position. The target segment was positioned, a midline incision was made in the posterior lumbar spine, and the paraspinal muscle on the opposite side of the lesion was stripped. The spinous process, lamina, and facet joints were exposed, and the pedicle screws and CBT screws were inserted according to the preoperative plan. A prebent titanium rod was fixed and locked, and then the incision was closed. A wound incision was made on the opposite side, the original muscle space was separated to reach the intervertebral space, the channel was expanded step by step, a quadrant dilator was placed, the facet joint was exposed, and electrocautery was used to stop bleeding and peel the surface soft tissue. Osteotomy was used to remove part of the inferior and superior articular processes, and limited cleavage of the lamina was used to expose the spinal canal. Exposure and protection were performed under direct vision, and the dural sac and nerve root were retracted. Then, the intervertebral space was exposed, suction was performed to remove pus, and curettage of the infected vertebral body and intervertebral space abscess, sequestrum and caseous necrosis was performed with different angled spatulas until the surface of the healthy bone showed slight bleeding. After the lesions were completely removed, the dural sac was carefully checked to ensure that there was no damage, and a large amount of iodophor hydrogen peroxide and normal saline were injected through a syringe to flush the intervertebral space. After irrigation, 1.0 g of streptomycin was sprinkled into the wound, an indwelling negative-pressure drainage tube was placed in the deep paraspinal muscle, and the incision was closed. The culture results of samples from the removed lesions were consistent with the diagnosis of tuberculosis.

Postoperative management

The motor and sensory functions of the legs of the patients were closely observed, and the patients were encouraged to perform straight leg raising exercises. When the drainage volume was less than 50 mL in 24 h, the drain was removed. Standard H/R/E/Z combinations were administered for at least 6 mo, and a lumbar brace was worn for at least 12-16 wk after surgery. It was recommended that the patients perform their daily activities without weight bearing. Routine blood examination results, liver and kidney function indicators, the C-reactive protein (CRP) level, and the erythrocyte sedimentation rate (ESR) were reviewed monthly according to the situation during the application of anti-tuberculosis drugs. X-rays were reviewed at 1, 3, 6, 9, and 12 mo after the operation and every year thereafter, and CT findings were reviewed every 3 mo. A trabecular bone connection between vertebrae as observed on CT reconstruction was considered to indicate bone fusion.

Data acquisition and factors of interest

The CRP level and ESR were recorded and evaluated preoperatively and at the last follow-up. The Oswestry disability index (ODI), American Spinal Injury Association (ASIA) classification, and visual analogue scale (VAS) score of low back pain were documented and analysed preoperatively, 3 mo after the operation, and at the last follow-up. All patients underwent follow-up for at least one year, and the time of osseous fusion was recorded.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 software (IBM, United States). The ESR and CRP level before surgery and at the last follow-up were continuous variables conforming to a normal distribution and were compared by paired *t* test. The ODI and VAS score before surgery, 3 mo after surgery, and at the last follow-up were analysed by one-way analysis of variance followed by the least significant difference test for comparisons between two groups. $P < 0.05$ was considered statistically significant.

RESULTS

General information

Among a total of 13 patients, the male/female ratio was 5:8, and the average age was 60.15 ± 10.31 years (Table 1). Four patients also had pulmonary tuberculosis; 9 patients had symptoms of tuberculosis toxicity, such as low fever, night sweats, weight loss, and fatigue; and all patients had persistent low back pain in the passive position and different degrees of lower extremity nerve dysfunction. All patients underwent laboratory tests (routine blood examination, CRP, ESR) and imaging examinations (X-ray, CT, MRI).

Surgical information

The mean operation time was 150.92 ± 37.32 min (110-210 min), the mean blood loss was 415.39 ± 151.91 mL (200-600 mL), and the mean follow-up time was 18.23 ± 4.69 mo (Table 1).

Follow-up data

At the last follow-up, the CRP level and ESR in all patients decreased to the normal physiological range, and the difference was statistically significant compared with the preoperative values (CRP: $t = 17.934$, $P < 0.001$; ESR: $t = 8.341$, $P < 0.001$, Table 1). The average preoperative ODI of 80.31% ± 3.35% (86% - 74%) decreased to 29.08% ± 1.94% (26% - 32%, $P < 0.05$ compared with preoperation) 3 mo after the operation. By the last follow-up, the ODI further decreased to 19.54% ± 2.18% (16% - 24%, $P < 0.05$ compared with preoperation and $P < 0.05$ compared with 3 mo postoperation) ($F = 2109.803$, $P < 0.001$). The preoperative VAS score of 7.54 ± 0.97 (6-9) decreased to 2.23 ± 0.73 (1-3; $P < 0.05$ compared with preoperation) 3 mo after the operation and decreased to 0.54 ± 0.66 (0-2) by the last follow-up ($P < 0.05$ compared with preoperation and $P < 0.05$ compared with 3 mo postoperation) ($F = 274.176$, $P < 0.001$) (Table 2). The ASIA grade improved from grade C to D in one patient and from grade C to E in another patient at the last follow-up, and the ASIA grade improved from grade D to E in all 8 remaining patients at the last follow-up. The mean time to osseous fusion after surgery was 8.85 ± 2.51 mo. A retrospective case is shown in Figure 1. Two patients suffered from pneumonia, which was cured by the application of sensitive antibiotics postoperatively. There were no cases of intraoperative vascular or nerve injury or implant-related complications. The incision healed well in all patients, with no cases of sinus tract formation or tuberculosis recurrence.

DISCUSSION

Benefits of the Wiltse approach in the treatment of lumbar tuberculosis

The Wiltse approach is more accurate for removing lumbar tuberculosis lesions, with less intraoperative trauma and faster postoperative recovery[19]. Biomechanical studies have shown that the posterior bone structures of the spine act as anchor points for posterior muscles and ligaments, which can share the stress of internal fixation and increase the stability of the spine. The Wiltse approach has the following advantages: (1) The target lesion is entered through the original muscle space, retaining the attachment of the paraspinal muscle to the spinous process and maintaining the integrity of the muscle structure, additionally, dead space is not easily formed, reducing the risk of infection; (2) The Quadrant channel is fixed to expose the surgical area, reducing repeated pulling on the soft tissue, which is beneficial for the recovery of the soft tissue; and (3) The operation under the channel allows a single-person operation and reduces the workload of the assistant; additionally, reducing the degree of injury to the dorsal branch of the spinal nerve root reduces the risk of paraspinal muscle neuropathic atrophy, which is conducive to enhancing the recovery of patients after surgery.

Reliability of the multitrack, multianchor screw technique

The combined use of pedicle screws and CBT screws was first performed in patients with degenerative scoliosis by Professor Ueno *et al*[20] in 2013. The purpose of surgery for lumbar tuberculosis is to remove the infection foci, protect nerve function, and stabilize the spine. For tuberculosis lesions invading the anterior column and part of the central column of the vertebral body, CBT screws can be placed to avoid lesions and fix the spine through the posterior and central columns. Biomechanical

Table 1 Baseline information and variables of patients

Case No.	Sex (M/F)	Age (year)	Bone fusion time (mo)	Operation		Follow-up (mo)	CRP (mg/L)		ESR (mm/h)	
				Time (min)	Blood loss (mL)		Preop	Final	Preop	Final
1	M	47	6	211	600	13	103.9	1.0	102	2
2	M	47	12	201	400	24	94.2	3.8	90	4
3	M	72	8	120	200	13	78.5	4.7	34	3.1
4	F	68	6	140	400	11	69	4.2	34.8	4
5	F	50	10	120	300	15	48.9	2.0	51	9
6	F	55	12	110	300	19	99	1.3	65	2.6
7	M	65	9	140	600	24	70	4.8	49	12
8	F	69	6	200	600	18	84	3.3	34	2
9	F	47	8	130	500	16	80	2.4	48	7
10	F	64	12	120	300	20	61	0.5	100	9
11	F	77	6	140	200	24	73	2.0	68	3
12	F	64	8	130	400	16	84	2.6	59	13
13	M	57	12	200	600	24	85	7	59	1.7
mean ± SD	-	60.15 ± 10.31	8.85 ± 2.51	150.92 ± 37.32	415.39 ± 151.91	18.23 ± 4.69	79.27 ± 15.23	3.05 ± 1.82[a]	61.06 ± 23.58	5.57 ± 3.70[a]

[a]$P < 0.001$. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

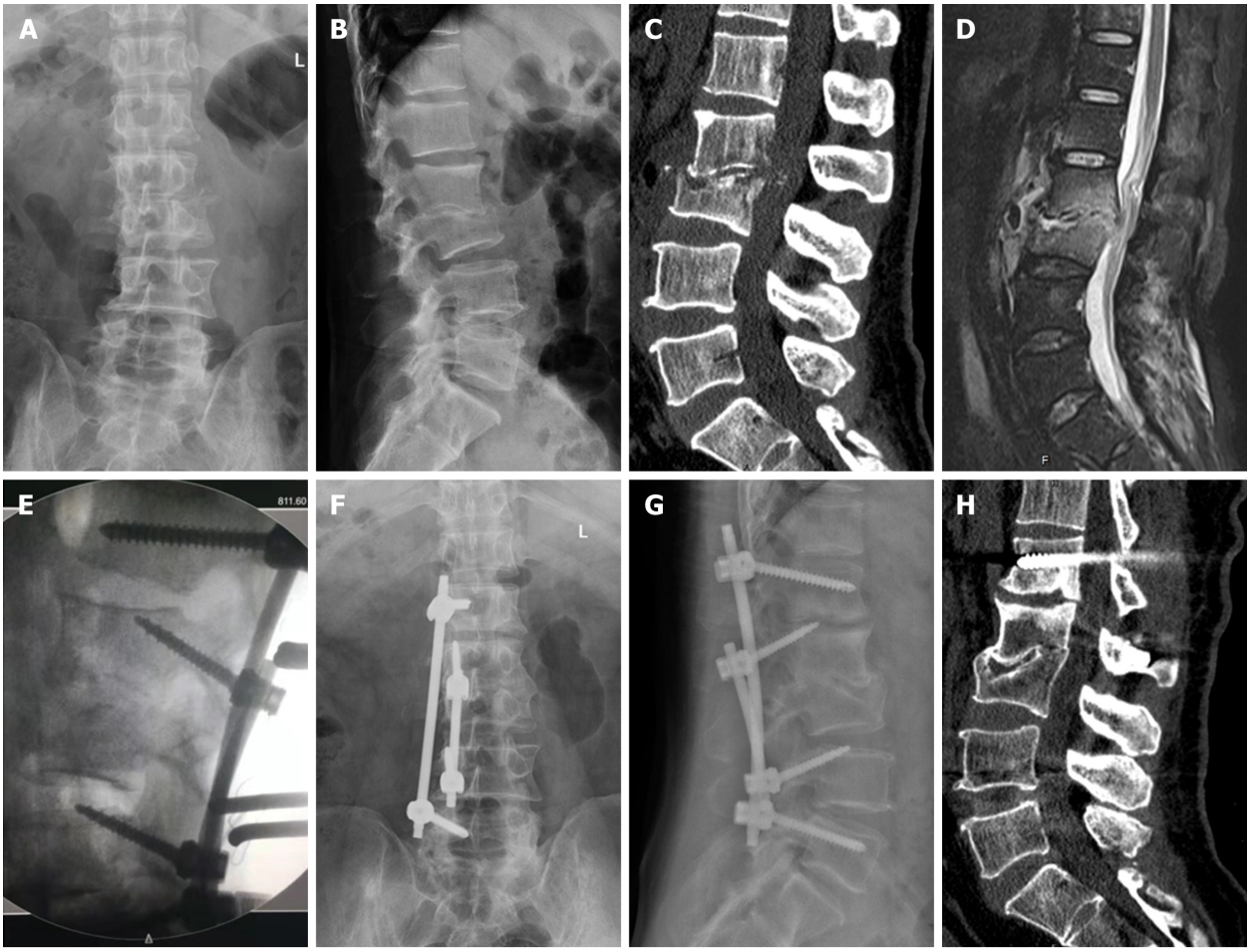
Table 2 Comparison between pre- and postoperative variables (mean ± SD)

Time	VAS	ODI (%)	ASIA				
			A	B	C	D	E
Preoperation	7.54 ± 0.97	80.31 ± 3.35	0	0	2	8	3
3 mo postoperation	2.23 ± 0.73[a]	29.08 ± 1.94[a]	0	0	1	1	11
Final follow-up	0.54 ± 0.66[a,d]	19.54 ± 2.18[a,d]	0	0	0	1	12

[a]$P < 0.05$ *vs* preoperation.
[d]$P < 0.05$ *vs* 3 mo after operation.
VAS: Visual analogue scale; ODI: Oswestry Disability Index; ASIA: American Spinal Injury Association Classification of Spine Injury.

studies have demonstrated that the insertion torque of CBT screws is 1.71 times that of pedicle screws [21], the uniaxial pullout resistance is increased by 30%[16]; additionally, the sagittal flexion and extension strength of CBT screws is better than that of pedicle screws. However, pedicle screws have strong resistance to axial rotation and coronal stress under lateral flexion[22], so we placed CBT screws in the middle and pedicle screws in the head and tail according to the characteristics of the lesion to achieve fixation with multiple tracks and anchors. In 2015, a study by Matsukawa *et al*[23] showed that the biomechanical strength of the same vertebral body after fixation with the cross-track technique was better than that after fixation with CBT and pedicle screws alone. Related studies have shown that short-term stabilization can be provided by an internal fixation system, while reconstruction with long-term stability requires bone fusion[24]. In this study, all patients were able to wear a brace to participate in daily activities. At the final follow-up, all patients showed bone fusion, with no cases of screw pullout or instrumentation failure. Thus, the authors speculate that multitrack, multianchor point screw technology provides outstanding fixation strength and a stable mechanical environment. However, the biomechanical strength of the fixed structure in this study needs to be further verified by biological models. Safety and efficacy of multitrack, multianchor point fixation combined with the Wiltse approach in the treatment of lumbar tuberculosis.

In this study, none of the patients experienced internal fixation-related neurological injury, and all achieved partial neurological recovery. At the last follow-up, the neurological function improved from



DOI: 10.12998/wjcc.v11.i14.3167

Figure 1 A typical case with bone fusion. A 47-year-old male patient presented with low back pain and left leg numbness and weakness. A and B: The pathological diagnosis was L2/3 lumbar tuberculosis, preoperative lumbar spinal X-ray showed L2/3 intervertebral space collapse; C: Lumbar spinal CT showed L2/3 intervertebral space stenosis and vertebral body destruction, and sequestrum could be seen invading the front of the intervertebral space and protruding backwards into the spinal canal; D: Fat-suppressed magnetic resonance imaging of the lumbar vertebrae showed destruction of the L2/3 intervertebral disc, narrowing of the intervertebral space, pus formation in the intervertebral space protruding towards the front and back of the intervertebral space, and compression of the dural sac; E: C-arm fluoroscopy during the operation confirmed good positioning of the pedicle screws and cortical bone trajectory screws; F and G: X-ray of the lumbar spine 1 year after the operation showed L2/3 intervertebral space fusion, normal positioning of the internal fixation device, and the absence of broken screws and rods; and H: CT scan of the lumbar spine 1 year after the operation showed that the L2/3 vertebral bodies had fused and that tuberculosis lesions had not developed. CT: Computed tomography.

ASIA grade D to grade E in 8 patients and ASIA grade C to grade E in 1 patient. The ODI and VAS score were also significantly improved at the last follow-up.

Safety and efficacy of pneumonectomy in the treatment of multidrug-resistant tuberculosis (MDR-TB)

For MDR-TB with cavitation, adjuvant pneumonectomy is safe and effective[25]. Adjuvant therapeutic surgery can improve the quality of life of pulmonary tuberculosis patients, with more obvious benefits in women, those aged < 40 years, those with a body mass index ≥ 20 kg·m^{-2}, and nonsmokers[26]. Pneumonectomy has been reported to have a 90% cure rate for MDR-TB, but the choice of surgical strategy requires the participation of both pulmonologists and cardiothoracic surgeons[27].

Research limitations

This was a retrospective study with a small sample size, no control group, and a short follow-up period, and a multicentre prospective randomized controlled trial with rich clinical data and a long follow-up period is needed. Due to the narrow operative field of the Wiltse approach under the channel, it is not suitable in cases where extensive debridement should be performed under direct anterior vision, such as in cases of large abscesses and infusion abscesses in front of the vertebra. Recurrence due to incomplete posterior debridement may occur in such cases. Due to the limitation of the surgical field, the surgeon needs to have sufficient patience to remove the lesion and repeatedly flush the intervertebral space.

CONCLUSION

Compared with other internal fixation techniques, fixation with pedicle screws combined with CBT screws and the contralateral Wiltse approach can be used to both effectively stabilize the spine and remove lesions with less trauma and is suitable in cases of larger lesions on one side and no large or only small abscesses in front of the lumbar spine.

ARTICLE HIGHLIGHTS

Research background

The incidence of lumbar tuberculosis is high worldwide, and effective treatment is a continuing problem.

Research motivation

There are different methods for internal fixation in the treatment of lumbar tuberculosis, but method with less trauma are more beneficial for patients.

Research objectives

The objective of this study was to examine the efficacy of multitrajectory, multianchor fixation techniques combined with the contralateral Wiltse approach in the treatment of lumbar tuberculosis.

Research methods

This retrospective analysis of patients diagnosed with lumbar tuberculosis compared the C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), visual analogue scale (VAS) score of low back pain, Oswestry disability index (ODI) and American Spinal Injury Association (ASIA) grade as well as neurological recovery before and after surgery.

Research results

The CRP level, ESR, VAS score and ODI were decreased after surgery. Neurological dysfunction was relieved, and the ASIA grade was increased.

Research conclusions

We propose that the multitrajectory, multianchor screw technique combined with the contralateral Wiltse approach for lesion removal is beneficial to improve the clinical symptoms and quality of life of patients with lumbar tuberculosis.

Research perspectives

The multitrajectory, multianchor screw technique combined with the contralateral Wiltse approach for lesion removal is safe and effective in the treatment of lumbar tuberculosis.

FOOTNOTES

Author contributions: Miao J contributed to the conception and design of this study; Yuan YF wrote the main manuscript text; Ren ZX and Li JF prepared Figure; Zhang C followed up the patients and collected the relevant data; Li GJ performed the statistical analysis; Li XD and Liu BZ prepared Tables; and all authors reviewed and approved the final manuscript.

Supported by 2023 Hebei Province Medical Science Research Project Plan, No. 20231958.

Institutional review board statement: Our research project was approved by the Ethics Committee of Handan Central Hospital.

Informed consent statement: All study participants or their legal guardian provided informed written consent for personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: China

ORCID number: Yu-Fei Yuan 0000-0002-0692-1519; Jie Miao 0000-0001-5629-0287.

S-Editor: Liu XF
L-Editor: A
P-Editor: Zhang YL

REFERENCES

1 **Sulis G**, Adam P, Nafade V, Gore G, Daniels B, Daftary A, Das J, Gandra S, Pai M. Antibiotic prescription practices in primary care in low- and middle-income countries: A systematic review and meta-analysis. *PLoS Med* 2020; **17**: e1003139 [PMID: 32544153 DOI: 10.1371/journal.pmed.1003139]

2 **Chakaya J**, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, Kapata N, Mfinanga S, Hasnain SE, Katoto PDMC, Bulabula ANH, Sam-Agudu NA, Nachega JB, Tiberi S, McHugh TD, Abubakar I, Zumla A. Global Tuberculosis Report 2020 - Reflections on the Global TB burden, treatment and prevention efforts. *Int J Infect Dis* 2021; **113** Suppl 1: S7-S12 [PMID: 33716195 DOI: 10.1016/j.ijid.2021.02.107]

3 **Millet JP**, Moreno A, Fina L, del Baño L, Orcau A, de Olalla PG, Caylà JA. Factors that influence current tuberculosis epidemiology. *Eur Spine J* 2013; **22** Suppl 4: 539-548 [PMID: 22565801 DOI: 10.1007/s00586-012-2334-8]

4 **Yang Z**, Liu C, Niu N, Tang J, Shi J, Wang Z, Ding H. Selection of the fusion and fixation range in the intervertebral surgery to correct thoracolumbar and lumbar tuberculosis: a retrospective clinical study. *BMC Musculoskelet Disord* 2021; **22**: 466 [PMID: 34020626 DOI: 10.1186/s12891-021-04335-0]

5 **Martinez V**, Rolland E, Bricaire F, Caumes E. Tuberculous paravertebral abscess. *Lancet* 2004; **363**: 615 [PMID: 14987886 DOI: 10.1016/S0140-6736(04)15593-1]

6 **Long W**, Gong L, Cui Y, Qi J, Duan D, Li W. Single posterior debridement, interbody fusion, and fixation on patients with continuous multivertebral lumbar spine tuberculosis (CMLSTB). *BMC Musculoskelet Disord* 2020; **21**: 606 [PMID: 32912166 DOI: 10.1186/s12891-020-03628-0]

7 **Varatharajah S**, Charles YP, Buy X, Walter A, Steib JP. Update on the surgical management of Pott's disease. *Orthop Traumatol Surg Res* 2014; **100**: 229-235 [PMID: 24613439 DOI: 10.1016/j.otsr.2013.09.013]

8 **Xu Z**, Wang X, Liu Z. One-stage posterior debridement and single-segment interbody fusion for treating mono-segmental lumbar and lumbosacral spinal tuberculosis in adults following minimum 5-year follow-up. *J Orthop Surg Res* 2020; **15**: 473 [PMID: 33054798 DOI: 10.1186/s13018-020-02005-w]

9 **Hassan K**, Elmorshidy E. Anterior *vs* posterior approach in surgical treatment of tuberculous spondylodiscitis of thoracic and lumbar spine. *Eur Spine J* 2016; **25**: 1056-1063 [PMID: 26922735 DOI: 10.1007/s00586-016-4451-2]

10 **Ukunda UNF**, Lukhele MM. The posterior-only surgical approach in the treatment of tuberculosis of the spine: outcomes using cortical bone allografts. *Bone Joint J* 2018; **100-B**: 1208-1213 [PMID: 30168757 DOI: 10.1302/0301-620X.100B9.BJJ-2017-1326.R2]

11 **Li M**, Huang J, Chen J, Liu S, Deng Z, Hu J, Cao Y, Wu T. Unilateral Limited Laminectomy for Debridement to Treat Localized Short-Segment Lumbosacral Spinal Tuberculosis: A Retrospective Case Series. *Orthop Surg* 2021; **13**: 1170-1180 [PMID: 33942987 DOI: 10.1111/os.12940]

12 **Shah K**, Kothari M, Nene A. Role of Frailty Scoring in the Assessment of Perioperative Mortality in Surgical Management of Tuberculous Spondylodiscitis in the Elderly. *Global Spine J* 2018; **8**: 698-702 [PMID: 30443479 DOI: 10.1177/2192568218764905]

13 **Yang X**, Luo C, Liu L, Song Y, Li T, Zhou Z, Hu B, Zhou Q, Xiu P. Minimally invasive lateral lumbar intervertebral fusion *vs* traditional anterior approach for localized lumbar tuberculosis: a matched-pair case control study. *Spine J* 2020; **20**: 426-434 [PMID: 31669614 DOI: 10.1016/j.spinee.2019.10.014]

14 **Baig MN**, Kearns SR, Shannon FJ, Devitt A. Ten Inventions That Shaped Modern Orthopedics. *Cureus* 2021; **13**: e12819 [PMID: 33628685 DOI: 10.7759/cureus.12819]

15 **Boucher HH**. A method of spinal fusion. *J Bone Joint Surg Br* 1959; **41-B**: 248-259 [PMID: 13641310 DOI: 10.1302/0301-620X.41B2.248]

16 **Santoni BG**, Hynes RA, McGilvray KC, Rodriguez-Canessa G, Lyons AS, Henson MA, Womack WJ, Puttlitz CM. Cortical bone trajectory for lumbar pedicle screws. *Spine J* 2009; **9**: 366-373 [PMID: 18790684 DOI: 10.1016/j.spinee.2008.07.008]

17 **Rodriguez A**, Neal MT, Liu A, Somasundaram A, Hsu W, Branch CL Jr. Novel placement of cortical bone trajectory screws in previously instrumented pedicles for adjacent-segment lumbar disease using CT image-guided navigation. *Neurosurg Focus* 2014; **36**: E9 [PMID: 24580010 DOI: 10.3171/2014.1.FOCUS13521]

18 **Ashayeri K**, Nasser R, Nakhla J, Yassari R. The use of a pedicle screw-cortical screw hybrid system for the surgical treatment of a patient with congenital multilevel spinal non-segmentation defect and spinal column deformity: a technical note. *Eur Spine J* 2016; **25**: 3760-3764 [PMID: 27137999 DOI: 10.1007/s00586-016-4561-x]

19 **Foley KT**, Holly LT, Schwender JD. Minimally invasive lumbar fusion. *Spine (Phila Pa 1976)* 2003; **28**: S26-S35 [PMID: 12897471 DOI: 10.1097/01.BRS.0000076895.52418.5E]

20 **Ueno M**, Imura T, Inoue G, Takaso M. Posterior corrective fusion using a double-trajectory technique (cortical bone trajectory combined with traditional trajectory) for degenerative lumbar scoliosis with osteoporosis: technical note. *J Neurosurg Spine* 2013; **19**: 600-607 [PMID: 24010899 DOI: 10.3171/2013.7.SPINE13191]

21 **Matsukawa K**, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. *Spine (Phila Pa 1976)* 2014; **39**: E240-E245 [PMID: 24253778

DOI: 10.1097/BRS.0000000000000116]

22 **Matsukawa K**, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite element study. *J Neurosurg Spine* 2015; **23**: 471-478 [PMID: 26161515 DOI: 10.3171/2015.1.SPINE141103]

23 **Matsukawa K**, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical Evaluation of Cross Trajectory Technique for Pedicle Screw Insertion: Combined Use of Traditional Trajectory and Cortical Bone Trajectory. *Orthop Surg* 2015; **7**: 317-323 [PMID: 26792576 DOI: 10.1111/os.12212]

24 **Zheng G**, Wang C, Wang T, Hu W, Ji Q, Hu F, Li J, Chaudhary SK, Song K, Song D, Zhang Z, Hao Y, Wang Y, Zheng Q, Zhang X. Relationship between postoperative lordosis distribution index and adjacent segment disease following L4-S1 posterior lumbar interbody fusion. *J Orthop Surg Res* 2020; **15**: 129 [PMID: 32245387 DOI: 10.1186/s13018-020-01630-9]

25 **Vashakidze SA**, Gogishvili SG, Nikolaishvili KG, Avaliani ZR, Chandrakumaran A, Gogishvili GS, Magee M, Blumberg HM, Kempker RR. Adjunctive surgery *vs* medical treatment among patients with cavitary multidrug-resistant tuberculosis. *Eur J Cardiothorac Surg* 2021; **60**: 1279-1285 [PMID: 34297819 DOI: 10.1093/ejcts/ezab337]

26 **Benito P**, Vashakidze S, Gogishvili S, Nikolaishvili K, Despuig A, Tukvadze N, Shubladze N, Avaliani Z, Vilaplana C. Impact of adjuvant therapeutic surgery on the health-related quality of life of pulmonary tuberculosis patients. *ERJ Open Res* 2020; **6** [PMID: 32904577 DOI: 10.1183/23120541.00083-2020]

27 **Alexander G**, Perumal R. Do specialist pulmonologists appropriately utilise thoracic surgery for drug-resistant pulmonary tuberculosis? *Afr J Thorac Crit Care Med* 2018; **24** [PMID: 34541507 DOI: 10.7196/SARJ.2018.v24i3.185]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3176-3186

DOI: 10.12998/wjcc.v11.i14.3176

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical features and prognostic factors in 49 patients with follicular lymphoma at a single center: A retrospective analysis

Hao Wu, Hui-Cong Sun, Gui-Fang Ouyang

Specialty type: Hematology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Klapper W, Germany; Shimokawa T, Japan

Received: February 27, 2023
Peer-review started: February 27, 2023
First decision: March 10, 2023
Revised: March 24, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Hao Wu, Gui-Fang Ouyang, Department of Hematology, Ningbo First Hospital, Ningbo 315010, Zhejiang Province, China

Hui-Cong Sun, Adult Internal Medicine, Ningbo Women and Children's Hospital, Ningbo 315012, Zhejiang Province, China

Corresponding author: Gui-Fang Ouyang, MD, Chief Physician, Department of Hematology, Ningbo First Hospital, No. 59 Liuting Street, Ningbo 315010, Zhejiang Province, China.
oyguifangoy@163.com

Abstract

BACKGROUND

Follicular lymphoma (FL) is a type of B-cell lymphoma that originates at the germinal center and has a low malignancy rate. FL has become the most common inert lymphoma in Europe and America but has a relatively low incidence in Asia.

AIM

To explore the clinical features, curative effects, and prognostic factors of FL.

METHODS

Completed medical records of 49 patients with FL who were admitted to the Ningbo First Hospital from June 2010 to June 2021 were examined. These patients were definitively diagnosed by pathological biopsy or immunohistochemical staining. The diagnostic criteria were based on the 2008 World Health Organization classification of lymphomas. Ann Arbor staging was performed according to the imaging and bone marrow examination results. Risk stratification of all patients was performed based on the International Prognostic Index (IPI), age-adjusted IPI, Follicular Lymphoma International Prognosis Index (FLIPI), and FLIPI2 to compare the efficacy of different treatment regimens and analyze the related prognostic factors.

RESULTS

The age of onset in patients ranged from 24 to 76 years, with a median age of 51 years. Most patients developed the disease at 40–59 years of age, and the male:female ratio was 1.6:1. No significant difference was noted in the curative effect between the non-chemotherapy, combined chemotherapy, and other chemotherapy regimens ($P > 0.05$). Hemoglobin (Hb) level < 120 g/L, Ki-67 value > 50%, bone marrow involvement, and clinical stages III–IV were associated with

a poor prognosis of FL ($P < 0.05$). However, the influence of other indicators was not statistically significant. Risk grouping was performed using the FLIPI, and the results showed that 24.5%, 40.8%, and 34.7% of patients were in the low-, moderate-, and high-risk groups, respectively. According to the survival analysis results, the survival rate of patients was lower in the high-risk group than in the other low-risk and moderate-risk groups ($P < 0.05$).

CONCLUSION
FL mainly occurs in middle-aged and elderly men, primarily affecting lymph nodes and bone marrow. Hb level, Ki-67 value, bone marrow involvement, and clinical staging were used to evaluate prognosis.

Key Words: Follicular lymphoma; Clinical feature; Curative effect; Prognosis; Survival analysis; Follicular Lymphoma International Prognosis Index

Core Tip: Follicular lymphoma (FL) is a B-cell lymphoma originating from the germinal center and has a low malignancy rate. Completed medical records of 49 patients with follicular lymphoma admitted from June 2010 to June 2021 were retrospectively reviewed. FL was more common in middle-aged and elderly men than in women, mainly involving the lymph nodes and bone marrow. However, an optimal treatment strategy remains unclear. Hemoglobin levels, Ki-67 values, bone marrow involvement, and clinical stage can be used to evaluate prognosis.

Citation: Wu H, Sun HC, Ouyang GF. Clinical features and prognostic factors in 49 patients with follicular lymphoma at a single center: A retrospective analysis. *World J Clin Cases* 2023; 11(14): 3176-3186
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3176.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3176

INTRODUCTION

Follicular lymphoma (FL) is a B-cell lymphoma derived from the germinal center of follicles with the genetic hallmark t (14; 18) (q32; q21). Characterized by a low malignancy rate, FL has become the most common inert lymphoma in Europe and America, accounting for approximately 22% of non-Hodgkin lymphomas (NHL)[1]. In contrast, the incidence of FL in Asia is relatively low[2]. For example, patients with FL in China accounted for approximately 6%–10% of all NHL patients in 2008-2010 period[3]. To provide deep insights into the clinical features, curative effects, and prognostic factors of FL in China and to provide guidance for clinical diagnosis and treatment, this retrospective analysis aimed to examine the clinical data, such as clinical features, curative effects, and prognostic survival factors, of patients with FL who were diagnosed and treated at our hospital in recent years. Through this study, we aim to improve the understanding of this disease among clinicians and assist with diagnosis and treatment in clinical practice.

MATERIALS AND METHODS

Clinical data

Completed medical records of 49 patients with FL who were admitted to the Ningbo First Hospital from June 2010 to June 2021 were collected. These patients were definitively diagnosed by pathological biopsy or immunohistochemical staining. The diagnostic criteria were based on the 2008 World Health Organization (WHO) classification of lymphomas[4]. Ann Arbor staging was performed according to the imaging and bone marrow examination results. Risk stratification was performed for all patients based on the International Prognostic Index (IPI), age-adjusted IPI, Follicular Lymphoma International Prognosis Index (FLIPI), and Follicular Lymphoma International Prognosis Index 2 (FLIPI2)[5,6]. Medical follow-up was conducted through hospitalization, outpatient services, or telephone calls from the date of diagnosis to June 2021. After completing all treatments, patients in the remission stage [Complete remission (CR) + Partial remission (PR)] were followed up once every 2–3 mo in the first 2 years and once every 6 mo thereafter. The extent of follow-up was mainly determined according to the treatment of the patient at the onset of FL and related abnormal laboratory examination findings.

Observation indicators

General indicators: The clinical data of 49 patients with FL were retrospectively analyzed. These included age, sex, initial site of FL, the presence or absence of B symptoms, number of extralymphatic involvement sites, hepatomegaly, and splenomegaly.

Laboratory indicators: These indicators included hemoglobin (Hb) level, platelet count (PLT), white blood cell (WBC) count, absolute lymphocyte (LYM) count, albumin (ALB) level, globulin (GLB) level, lactate dehydrogenase (LDH) level, hydroxybutyrate dehydrogenase (HBDH) level, β2-microglobulin (β 2-MG) level, immune phenotype, pathological grade, and Ki-67 value.

Clinical stage: All patients underwent computed tomography (CT) and bone marrow biopsy, and clinical staging was performed based on the Ann Arbor standards.

Survival and prognostic indicators: Survival time, overall survival (OS), progression-free survival (PFS), and related prognostic factors (such as age, pathological grade, clinical stage, LDH level, Hb level, and Ki-67 value) were analyzed.

Therapeutic scheme

The initial therapeutic schemes were classified as follows: Scheme I involved specifically targeted therapy without combined chemotherapy, including rituximab combined with lenalidomide in 10 patients and single-agent lenalidomide or rituximab in 4 patients (total: 14 patients); Scheme II involved rituximab combined with chemotherapy regimen, including rituximab or lenalidomide. Combined cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP) regimen was administered to 30 patients, and rituximab-combined cyclophosphamide + vincristine + prednisone (COP) regimen was administered to 2 patients (total: 32 patients); Scheme III involved other regimens, including rituximab plus bortezomib combined with CHOP regimen in 2 patients and an FC (fluorouracil + cyclophosphamide) regimen in 1 patient, and was not included in the comparison of curative effects. The drug doses in all schemes were calculated based on the standard dose and body surface area.

Curative effect evaluation

The short-term curative effect was evaluated according to the evaluation criteria for malignant lymphomas, including CR, PR, stable disease (SD), and progressive disease (PD), while CR + PR constituted the objective remission rate.

The patients were evaluated once every two regular chemotherapy sessions with respect to curative effects and then re-evaluated after every two courses of treatment. Patients were classified based on CR, unconfirmed complete remission (CRu), PR, SD, PD, and relapse (those who reached CR/CRu in the early stages). Patients who met the first three criteria were regarded to have effective samples, whereas those meeting the remaining criteria were regarded to have ineffective samples.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0. Data with normal distribution are presented as mean ± SD, and data with non-normal distribution are presented as median. Fisher's exact probability method was used to compare the curative effects of the different schemes. Survival data and prognosis were analyzed using the Kaplan–Meier method, and survival rates were compared using the log-rank test. Survival time, OS, PFS, and related prognostic factors (such as age, pathological grade, clinical stage, regular indicators, and Ki-67 value) were analyzed. $P < 0.05$ indicated statistically significant difference for all tests.

RESULTS

Basic data

The clinical data of 49 patients with FL were retrospectively analyzed, and the clinical characteristics, efficacy, prognosis, and survival factors were analyzed to improve the clinicians' understanding of this disease and provide guidance for clinical diagnosis and treatment.

Follow up results: Loss to follow-up (LTFU) was noted in three patients (LTFU rate: 6.1%), with a median follow-up time of 52 (2–85) mo.

Sex and age: Among the 49 patients, 30 (61.2%) were male and 19 (38.8%) were female patients, with male:female ratio of 1.6:1. The age at disease onset ranged from 24 to 76 years, with a median age of 51 years [17 (34.7%) patients aged > 60 years and 32 (65.3%) patients aged ≤ 60 years]. Overall, approximately 51% ($n = 25$) developed the disease between 40 and 59 years of age.

Pathological grade and clinical stage: The pathological grade and clinical stage of the 49 patients were determined according to the 2008 WHO classification of lymphomas and the Ann Arbor staging

standard. Eventually, 3 (6.1%) patients had Grade I FL, 16 (32.7%) had Grade II FL, and 30 (61.2%) had Grade III FL. In addition, 17 (34.7%) patients had Stage I FL, 32 (65.3%) had Stage II–III FL, and 31 (63.3%) had B symptoms. Among patients with Stage III–IV FL, 19 (59.4%) had B symptoms, 20 (40.9%) had anemia (Hb level < 120 g/L), 6 (18.8%) had PLT count ≤ 80 × 10^9/L, 24 (75.0%) had LYM count > 1 × 10^9/L, and 29 (90.6%) had increased LDH level.

Clinical features

Initial site and extra-lymphatic involvement: Overall, 35 patients (71.4%) initially presented with enlarged lymph nodes and 14 (28.6%) initially presented with extralymphatic involvement. Among those initially presenting with extralymphatic involvement, the symptoms included an enlarged abdominal mass, splenomegaly, enlarged leg mass, enlarged tonsils, gastrointestinal tract involvement, and bone marrow involvement. Overall, 19 patients (38.8%) had extralymphatic node tissue or organ involvement, including 10 (20.4%) patients with bone marrow involvement, which was confirmed by clinical imaging such as endoscopy and CT and pathological biopsy results.

Hepatosplenomegaly: Based on physical examination and imaging data of the whole cohort, 2 (4.1%) patients had hepatomegaly and 10 (31.3%) had splenomegaly, including 3 patients with megalosplenia.

Laboratory examination results

Blood routine examination: Overall, 20 (40.6%) patients had anemia (Hb level = 93 ± 4 g/L), 6 (18.8%) had PLT count ≤ 80 × 10^9/L (median, 65 × 10^9/L), 11 (22.4%) had leukopenia (median WBC count, 4.0 × 10^9/L), 7 (14.3%) had leukocytosis (median WBC count, 10.0 × 10^9/L), and 24 (75.0%) had LYM count > 1 × 10^9/L (median, 1.97 ± 0.67 × 10^9/L).

Biochemical indicators: There were 6 (12.4%) patients with decreased ALB level, 5 (10.2%) had increased GLB level, and 35 (71.4%) had increased LDH level (median, 317 IU/L).

Immune phenotypes: Among the 49 patients, B-cell-related common antigen CD20+ was expressed in 44 patients (89.8%), Bcl-2+ in 25 (51.0%) patients, Bcl-6+ in 32 (65.3%) patients, and CD10+ in 35 (71.4%) patients. The Ki-67 value was measured in the pathological specimens of 39 patients, with the results ranging from 5% to 90% (median, 30%). The Ki-67 value was ≤ 50% in 27 (55.1%) patients and > 50% in 22 (44.9%) patients.

Other indicators: Among the 49 patients, β2-MG was detected in 47 patients, including 22 patients (46.8%) with increased β2-MG level (median, 3.33 mg/L).

Curative effects and influencing factors

Curative effects: Among the 49 patients, the effective rate was 50.0% for patients with Scheme I (7/14), 75.0% for patients with Scheme II (24/32), and 100% for patients undergoing Scheme III (3/3). The results of the Fisher's exact test showed no significant differences in curative effects between the three schemes ($P > 0.05$) (Table 1).

The influence of different factors on the curative effect: The analysis results of the influence of various factors on the curative effect showed that anemia could affect the curative effect; hence, it was identified as an independent influencing factor. Among the 13 patients with anemia, 6 (46.2%) patients had CR+PR, while among 36 patients without anemia, 26 (72.2%) had CR + PR. Fisher's exact test results showed that the effective treatment rate was higher in patients without anemia than in patients with anemia ($P < 0.05$). Sex, age, B symptoms, involvement of more than four lymph nodes, pathological grade, clinical stage, bone marrow involvement, hepatomegaly, splenomegaly, increased LYM count, thrombocytopenia, leukopenia, increased LDH level, increased β2-MG level, and other indicators had no significant influence on the curative effect ($P > 0.05$).

Survival and prognosis analysis

Survival analysis: All patients were followed up *via* telephone (follow-up time was calculated from the end of the last hospitalization to October 2020), with a median follow-up period of 52 (2–85) mo. The overall median survival was 41 mo in the 49 patients, while the 3-year and 5-year OS was 81.6% and 62.3%, respectively. The 3-year and 5-year PFS was 71.4% and 40.8%, respectively. According to the risk stratification (low-, moderate-, and high-risk groups) and analysis results of the five FLIPI-based adverse prognostic factors (age > 60 years, stages III–IV, involvement of more than four lymph nodes, Hb level < 120 g/L, and increased LDH level) affecting the survival rate, the survival rate was significantly lower ($P < 0.05$) in the high-risk group than in the other two groups. However, no significant difference was noted in the survival rate between the low- and moderate-risk groups ($P > 0.05$) (Table 2). The survival and total survival curves for the three risk groups are shown in Figure 1.

Prognostic analysis: Univariate analysis showed that anemia, a Ki-67 value > 50%, bone marrow involvement, and clinical stages III–IV were the factors inducing a poor prognosis ($P < 0.05$). No

Table 1 Comparison of curative effects among different schemes, *n* (%)

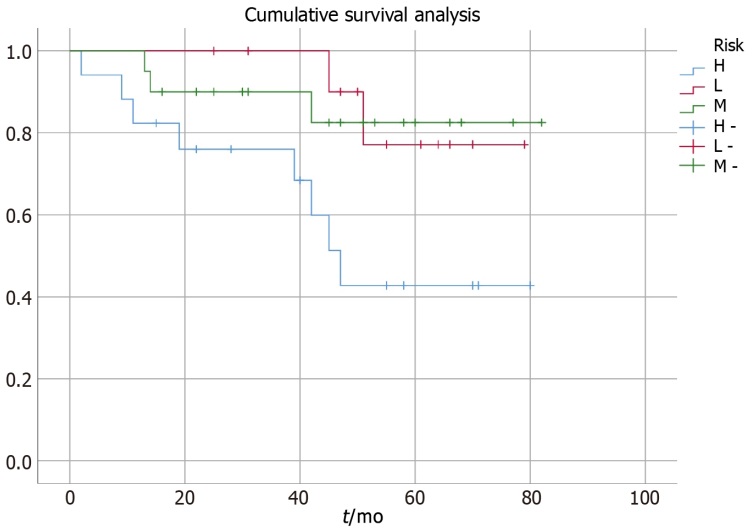
Scheme	Number of cases	CR	PR	SD	PD	ORR (%)
I	14	3 (21.4)	4 (28.6)	5 (35.7)	2 (14.3)	50.0
II	32	11 (34.4)	13 (40.6)	3 (9.4)	5 (15.6)	75.0
III	3	1 (33.3)	2 (66.7)	0	0	100.00

CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease; ORR: Objective remission rate.

Table 2 Correlation survival analysis of different risk groups, *n* (%)

Group	Risk factors	Cases, *n* (%)	3-year OS, % (SE)	3-year PFS, % (SE)	5-year OS, % (SE)	5-year PFS, % (SE)
Low risk	0–1	12 (24.5)	100	75.0 (0.18)	83.3 (0.12)	75.0 (0.18)
Medium risk	2	20 (40.8)	90.0 (0.08)	75.0 (0.08)	85.0 (0.11)	70.0 (0.16)
High risk	≥ 3	17 (34.7)	76.5 (0.10)	47.1 (0.13)	47.1 (0.13)	23.6 (0.20)

$P < 0.05$ compared with the other two groups. SE: Standard error; OS: Survival time; PFS:Progression-free survival.



DOI: 10.12998/wjcc.v11.i14.3176

Figure 1 Survival curve and total survival curve of different risk groups.

significant difference was noted in the prognosis between sex, age, B symptoms, pathological grade, number of involved lymph nodes, hepatosplenomegaly, decreased ALB level, leukopenia, increased GLB level, increased LDH level, leukocytosis, increased LYM count, increased β2-MG level, immune phenotype expression (CD10+, Bcl-2+, and Bcl-6+), and other factors ($P > 0.05$) (Table 3). The survival curves of the four adverse factors affecting prognosis are shown in Figure 2.

DISCUSSION

FL is an inert NHL originating from the germinal center of follicles in the lymph nodes. Although individuals of any age can develop this disease, it is more common in adults, particularly men[1]. In this study, the peak age at FL onset ranged from 40 to 59 years, with a median age of 51 years, and the male:female ratio was 1.6:1. Initial lymph node enlargement was the most common clinical feature. However, nearly half of the patients with FL had extralymphatic and organ involvement. The most commonly affected sites include the liver, spleen, bone marrow, and gastrointestinal tract[2-4]. In this study, 31.3% of the patients had splenomegaly, 20.4% had bone marrow involvement, 4.1% had hepatomegaly, and 4.1% had gastrointestinal tract involvement, similar to findings of other reports China and

Table 3 Clinical features and univariate prognosis of 49 patients with follicular lymphoma

Factors		3-year OS, % (SE)	5-year OS, % (SE)	Log-rank (*P* value)
Sex				
	M (30)	86.7 (0.05)	63.3 (0.09)	0.185
	F (19)	78.9 (0.09)	63.1 (0.13)	
Age (yr)				
	≤ 60 (32)	84.3 (0.05)	71.9 (0.08)	0.584
	> 60 (17)	82.4 (0.08)	70.6 (0.13)	
The presence or absence of B symptoms				
	Y (31)	77.4 (0.08)	58.1 (0.13)	0.237
	N (18)	88.9 (0.06)	72.2 (0.09)	
Stage				
	I-II (17)	94.1 (0.05)	94.1 (0.05)	0.043
	III-IV (32)	78.1 (0.06)	65.6 (0.10)	
Pathological grading				
	I (3)	100.0	100.0	0.321
	II (16)	87.5 (0.07)	68.7 (0.12)	
	III (30)	80.0 (0.05)	73.3 (0.11)	
BM infiltration				
	Y (10)	70.0 (0.13)	30.0 (0.15)	0.007
	N (39)	89.7 (0.04)	79.5 (0.08)	
Involved lymph node area				
	≤ 4 (36)	86.1 (0.05)	72.2 (0.08)	0.054
	> 4 (13)	76.9 (0.12)	53.8 (0.19)	
Hepatomegaly				
	Y (2)	100.0	100.0	0.835
	N (47)	85.1 (0.05)	74.4 (0.08)	
Splenomegaly				
	Y (10)	80.0 (0.10)	60.0 (0.14)	0.169
	N (39)	84.6 (0.05)	76.9 (0.09)	
LDH				
	Normal (14)	85.7 (0.10)	71.4 (0.10)	0.312
	High (35)	82.9 (0.05)	68.6 (0.09)	
Hb				
	< 120 g/L (20)	75.0 (0.09)	45.0 (0.12)	0.011
	≥ 120 g/L (29)	89.7 (0.04)	75.9 (0.09)	
WBC				
	≤ 4×10^9/L (11)	100	72.7 (0.18)	0.481
	> 4×10^9/L (38)	84.2 (0.05)	65.8 (0.08)	
WBC				
	≤ 10×10^9/L (42)	88.1 (0.05)	66.7 (0.08)	0.813
	> 10×10^9/L (7)	71.4 (0.21)	57.1 (0.21)	
LYM				

	≤ 1 × 10^9/L (25)	80.0 (0.09)	68.0 (0.15)	0.494
	> 1 × 10^9/L (24)	87.5 (0.05)	66.7 (0.09)	
PLT				
	≤ 80 × 10^9/L (9)	100	66.7 (0.19)	0.998
	> 80 × 10^9/L (40)	82.5 (0.06)	70.0 (0.08)	
ALB				
	≤ 35 g/L (6)	83.3 (0.15)	66.7 (0.19)	0.941
	> 35 g/L (43)	87.4 (0.05)	67.2 (0.08)	
GLB				
	≤ 34 g/L (44)	87.9 (0.05)	66.5 (0.08)	0.758
	> 34 g/L (5)	80.0 (0.18)	80.0 (0.18)	
Ki-67				
	≤ 50% (27)	96.2 (0.04)	91.3 (0.06)	0.004
	> 50% (22)	83.3 (0.15)	31.2 (0.25)	
Bcl-6+	32	83.9 (0.07)	74.6 (0.09)	0.926
Bcl-6-	17	100	68.6 (0.19)	
CD10+	35	85.7 (0.07)	64.6 (0.11)	0.293
CD10-	14	90.9 (0.09)	90.9 (0.09)	
Bcl-2+	25	91.4 (0.06)	76.4 (0.09)	0.493
Bcl-2-	24	80 (0.10)	66.7 (0.15)	

Statistical significance was set at $P < 0.05$. OS: Overall survival; Hb: Hemoglobin; PLT: Platelet; WBC: White blood cell; LYM: Lymphocyte; ALB: Albumin; GLB: Globulin; LDH: Lactate dehydrogenase; SE: Standard error.

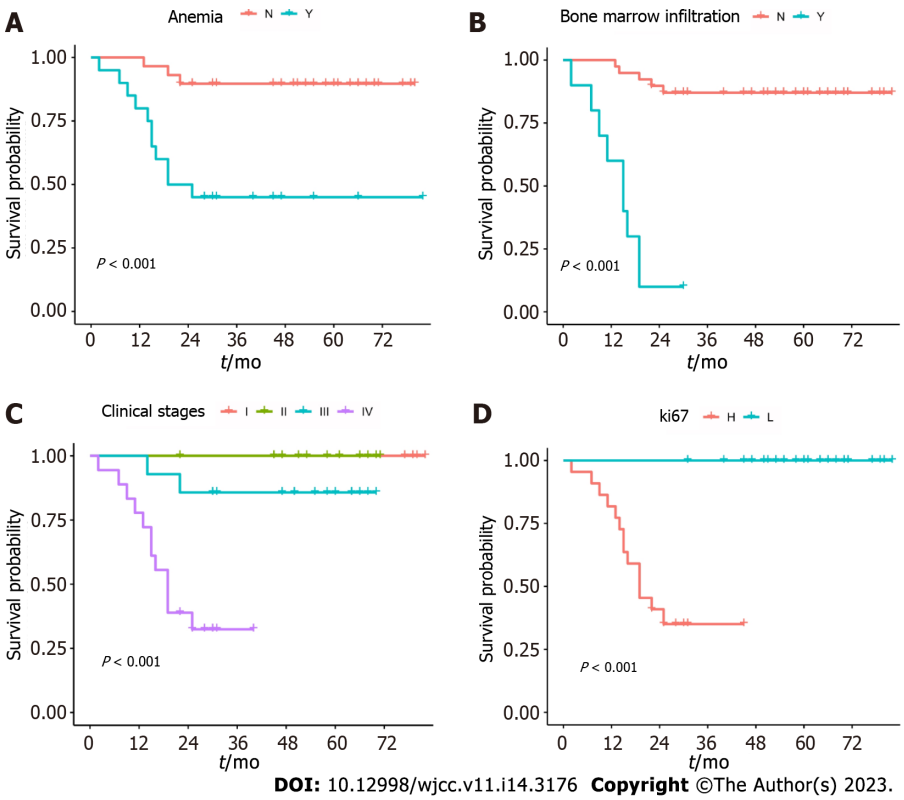
abroad, with the exception of low hepatomegaly incidence[5].

The immune phenotype of FL is vital for its diagnosis and treatment. Bcl-2, Bcl-6, and CD10 expression has been detected in most patients[6,7]. In terms of the immune phenotype detection results of 40 patients, 51.0% of patients expressed Bcl-2+, 65.3% expressed Bcl-6+, and 71.4% expressed CD10+, which is lower than the data reported abroad[8,9], which may be related to the small size of this sample.

The FLIPI is an important prognostic tool for patients with FL before treatment. As revealed in an international multicenter study involving 4,167 FL patients, age (≤ 60 years or > 60 years), Ann Arbor stage (Stage I–II or Stage III–IV), Hb level (< 120 g/L or > 120 g/L), LDH level (normal or increased), and number of lymph node area involved (≤ 4 or > 4) could affect the prognosis of patients[4]. According to the findings of the present study, clinical stage, bone marrow involvement, Ki67 value, and decreased Hb level can affect the prognosis of patients; however, age, LDH level, and number of involved lymph node areas were not associated with the prognosis of patients, which may be associated with the small sample size of the study. Analysis of the three different risk groups based on the FLIPI score demonstrated that the 5-year OS and PFS of patients were significantly lower in the high-risk group than in the low-risk and moderate-risk groups, which is consistent with the results reported abroad[10,11].

As reported in some articles abroad, the positive expression of molecular biological markers such as Bcl-2 and Bcl-6 could affect the curative effect and prognosis of patients with FL[7,12]. However, the positive expression of Bcl-2 and Bcl-6 was not significantly correlated with the prognosis of patients in this study[13]. The Southwest Oncology Group has selected Ki-67 value as an early indicator to predict the clinical progression of tumors and an important parameter for identifying NHL prognosis[14]. In this study, a Ki-67 value of 50% was selected as the cutoff point, and the analysis showed that the 5-year OS of patients > 50% was significantly lower than OS of patients ≤ 50%, which is in line with the results of a previous study[15]. Therefore, Ki-67 Levels must be measured during pathological examinations.

Currently, there is no consensus on the therapeutic schemes for FL. With continuous exploration of the pathogenesis, clinical features, and prognosis of FL, rituximab has been confirmed as an important drug for treating FL, as it can improve the total remission rate and prolong the remission duration in patients[16,17]. In this study, 32 newly treated patients with FL received rituximab therapy in conjunction with chemotherapy, and the overall response rate was 75%, which was slightly higher than that (67%) reported elsewhere[18].



DOI: 10.12998/wjcc.v11.i14.3176

Figure 2 Survival curve of poor prognostic factors. A: Anemia; B: Bone marrow infiltration; C: Clinical stages; D: ki67.

Because of the long course of the disease, high relapse rate after remission, and strong tendency to transform into diffuse large B-cell lymphoma, it is difficult to employ conventional therapies to improve the quality of life and disease-free survival rate of patients with FL. The key molecules, proteins, and pathways expressed in the development of FL are expected to become new treatment targets, including CD20 antibody, PI3K inhibitor, BTK pathway inhibitor, immunomodulator, and anti-PD1. Among these, obinutuzumab has received much attention, with many studies demonstrating that obinutuzumab can significantly prolong PFS and OS in patients with FL and can even become a candidate to replace rituximab because it has been launched in the market and is widely used. These drugs provide additional therapeutic options for patients with FL, further improving the remission rate and prolonging the survival time of patients, all of which can be attributed to the progress of individualized treatment based on further risk stratification of FL.

CONCLUSION

FL mainly occurs in men aged 50–69 years who specifically present with lymph node involvement. Currently, most FL patients are treated with chemotherapy, and there is a lack of a standard therapeutic scheme. Rituximab combined with chemotherapy can improve the remission rate and prolong the survival time of patients with FL, and therapy integrating fludarabine is expected to become the first-line therapeutic scheme. Advanced clinical stage, high Ki-67 value, anemia, and bone marrow involvement affect the prognosis of patients with FL.

ARTICLE HIGHLIGHTS

Research background

Follicular lymphoma (FL) is a B-cell lymphoma that originates at the germinal center and has a low malignancy rate.

Research motivation

To gain a deeper understanding of the clinical characteristics, efficacy, and prognostic factors of FL in China and to provide guidance for clinical diagnosis and treatment, we retrospectively analyzed the clinical data of 49 patients with FL who were diagnosed and treated at our hospital in recent years.

Research objectives

This study aimed to explore the clinical features, curative effects, and prognostic factors of FL.

Research methods

The medical records of 49 patients with FL admitted to the Ningbo First Hospital from June 2010 to June 2021 were retrospectively reviewed to compare the curative effects of different therapeutic schemes and analyze the related prognostic factors.

Research results

The age at onset in the 49 patients ranged from 24 to 76 years, with a median age of 51 years. The male:female ratio was 1.6:1. No significant difference was noted in the curative effect between the non-chemotherapy, combined chemotherapy, and other chemotherapy regimen groups. Hemoglobin (Hb) level < 120 g/L, Ki-67 value >50%, bone marrow involvement, and clinical stages III–IV were associated with a poor prognosis. However, the influence of the other indicators on prognosis was not statistically significant. Risk grouping was performed using the Follicular Lymphoma International Prognosis Index. The results showed that 24.5%, 40.8%, and 34.7% of patients were in the low-, moderate-, and high-risk groups, respectively. According to the survival analysis results, the survival rate of patients was lower in the high-risk group than in the other two groups.

Research conclusions

FL mainly occurs in middle-aged or older men who mainly present with lymph node and bone marrow involvement. Hb level, Ki-67 value, bone marrow involvement, and clinical stage can be used for prognostic estimation.

Research perspectives

To analyze the clinical characteristics, efficacy, prognosis, and survival factors of 49 patients in order to improve clinicians' understanding of the disease and provide guidance for clinical diagnosis and treatment.

FOOTNOTES

Author contributions: Ouyang GF provided the experimental idea; Wu H and Sun HC collected, sorted, and analyzed the data; Wu H completed the writing of this article; and all authors have read and approved the final draft.

Supported by Zhejiang TCM Science and Technology Project, No. 2023ZL653.

Institutional review board statement: This study was approved by the Institutional Ethics Committee of Ningbo First Hospital.

Informed consent statement: Informed consent was obtained from the patients and their parents/guardians.

Conflict-of-interest statement: We have no financial relationships or any other conflict of interest to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Hao Wu 0000-0001-6847-6898; Hui-Cong Sun 0000-0003-2985-6251; Gui-Fang Ouyang 0000-0002-6428-0000.

S-Editor: Wang JL
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Zelenetz AD**, Abramson JS, Advani RH, Andreadis CB, Bartlett N, Bellam N, Byrd JC, Czuczman MS, Fayad LE, Glenn MJ, Gockerman JP, Gordon LI, Harris NL, Hoppe RT, Horwitz SM, Kelsey CR, Kim YH, LaCasce AS, Nademanee A, Porcu P, Press O, Pro B, Reddy N, Sokol L, Swinnen LJ, Tsien C, Vose JM, Wierda WG, Yahalom J, Zafar N. Non-Hodgkin's lymphomas. *J Natl Compr Canc Netw* 2011; **9**: 484-560 [PMID: 21550968 DOI: 10.6004/jnccn.2011.0046]

2 **Gross SA**, Zhu X, Bao L, Ryder J, Le A, Chen Y, Wang XQ, Irons RD. A prospective study of 728 cases of non-Hodgkin lymphoma from a single laboratory in Shanghai, China. *Int J Hematol* 2008; **88**: 165-173 [PMID: 18648906 DOI: 10.1007/s12185-008-0132-1]

3 **Yang QP**, Zhang WY, Yu JB, Zhao S, Xu H, Wang WY, Bi CF, Zuo Z, Wang XQ, Huang J, Dai L, Liu WP. Subtype distribution of lymphomas in Southwest China: analysis of 6,382 cases using WHO classification in a single institution. *Diagn Pathol* 2011; **6**: 77 [PMID: 21854649 DOI: 10.1186/1746-1596-6-77]

4 **Campo E**, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011; **117**: 5019-5032 [PMID: 21300984 DOI: 10.1182/blood-2011-01-293050]

5 **Li Y**, Zhang Y, Wang W, Wei C, Zhao D, Zhang W. Follicular Lymphoma in China: Systematic Evaluation of Follicular Lymphoma Prognostic Models. *Cancer Manag Res* 2022; **14**: 1385-1393 [PMID: 35422658 DOI: 10.2147/CMAR.S349193]

6 **Federico M**, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, Pro B, Pileri S, Pulsoni A, Soubeyran P, Cortelazzo S, Martinelli G, Martelli M, Rigacci L, Arcaini L, Di Raimondo F, Merli F, Sabattini E, McLaughlin P, Solal-Céligny P. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol* 2009; **27**: 4555-4562 [PMID: 19652063 DOI: 10.1200/JCO.2008.21.3991]

7 **Khanlari M**, Chapman JR. Follicular lymphoma: updates for pathologists. *J Pathol Transl Med* 2022; **56**: 1-15 [PMID: 34942689 DOI: 10.4132/jptm.2021.09.29]

8 **Sakurai M**, Mori T, Kato K, Kanaya M, Mizuno S, Shiratori S, Wakayama T, Uchida N, Kobayashi H, Kubo K, Amano I, Ohta T, Miyazaki Y, Kanda J, Fukuda T, Atsuta Y, Kondo E; Adult Lymphoma Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Outcome of allogeneic hematopoietic stem cell transplantation for follicular lymphoma relapsing after autologous transplantation: analysis of the Japan Society for Hematopoietic Cell Transplantation. *Bone Marrow Transplant* 2021; **56**: 1462-1466 [PMID: 33514920 DOI: 10.1038/s41409-020-01192-8]

9 **Zinzani PL**, Flinn IW, Yuen SLS, Topp MS, Rusconi C, Fleury I, Le Dû K, Arthur C, Pro B, Gritti G, Crump M, Petrich A, Samineni D, Sinha A, Punnoose EA, Szafer-Glusman E, Spielewoy N, Mobasher M, Humphrey K, Kornacker M, Hiddemann W. Venetoclax-rituximab with or without bendamustine vs bendamustine-rituximab in relapsed/refractory follicular lymphoma. *Blood* 2020; **136**: 2628-2637 [PMID: 32785666 DOI: 10.1182/blood.2020005588]

10 **Gordon MJ**, Smith MR, Nastoupil LJ. Follicular lymphoma: The long and winding road leading to your cure? *Blood Rev* 2023; **57**: 100992 [PMID: 35908982 DOI: 10.1016/j.blre.2022.100992]

11 **Batlevi CL**, Sha F, Alperovich A, Ni A, Smith K, Ying Z, Soumerai JD, Caron PC, Falchi L, Hamilton A, Hamlin PA, Horwitz SM, Joffe E, Kumar A, Matasar MJ, Moskowitz AJ, Moskowitz CH, Noy A, Owens C, Palomba LM, Straus D, von Keudell G, Zelenetz AD, Seshan VE, Younes A. Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups. *Blood Cancer J* 2020; **10**: 74 [PMID: 32678074 DOI: 10.1038/s41408-020-00340-z]

12 **Dreyling M**, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M; ESMO Guidelines Committee. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27**: v83-v90 [PMID: 27664263 DOI: 10.1093/annonc/mdw400]

13 **Maurer MJ**, Bachy E, Ghesquières H, Ansell SM, Nowakowski GS, Thompson CA, Inwards DJ, Allmer C, Chassagne-Clément C, Nicolas-Virelizier E, Sebban C, Lebras L, Sarkozy C, Macon WR, Feldman AL, Syrbu SI, Traverse-Glehan A, Coiffier B, Slager SL, Weiner GJ, Witzig TE, Habermann TM, Salles G, Cerhan JR, Link BK. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. *Am J Hematol* 2016; **91**: 1096-1101 [PMID: 27465588 DOI: 10.1002/ajh.24492]

14 **Xu-Monette ZY**, Zhou J, Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. *Blood* 2018; **131**: 68-83 [PMID: 29118007 DOI: 10.1182/blood-2017-07-740993]

15 **Marcus R**, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *N Engl J Med* 2017; **377**: 1331-1344 [PMID: 28976863 DOI: 10.1056/NEJMoa1614598]

16 **Pastore A**, Jurinovic V, Kridel R, Hoster E, Staiger AM, Szczepanowski M, Pott C, Kopp N, Murakami M, Horn H, Leich E, Moccia AA, Mottok A, Sunkavalli A, Van Hummelen P, Ducar M, Ennishi D, Shulha HP, Hother C, Connors JM, Sehn LH, Dreyling M, Neuberg D, Möller P, Feller AC, Hansmann ML, Stein H, Rosenwald A, Ott G, Klapper W, Unterhalt M, Hiddemann W, Gascoyne RD, Weinstock DM, Weigert O. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol* 2015; **16**: 1111-1122 [PMID: 26256760 DOI: 10.1016/S1470-2045(15)00169-2]

17 **Casulo C**, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, Hainsworth JD, Maurer MJ, Cerhan JR, Link BK, Zelenetz AD, Friedberg JW. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *J Clin Oncol* 2015; **33**: 2516-2522 [PMID: 26124482 DOI: 10.1200/JCO.2014.59.7534]

18 **Lesokhin AM**, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, Millenson MM, Cohen AD, Schuster SJ, Lebovic D, Dhodapkar M, Avigan D, Chapuy B, Ligon AH, Freeman GJ, Rodig SJ, Cattry D, Zhu L, Grosso JF, Bradley Garelik MB, Shipp MA, Borrello I, Timmerman J. Nivolumab in Patients With Relapsed or Refractory Hematologic

Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol* 2016; **34**: 2698-2704 [PMID: 27269947 DOI: 10.1200/JCO.2015.65.9789]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3187-3194

DOI: 10.12998/wjcc.v11.i14.3187

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Value of optical coherence tomography measurement of macular thickness and optic disc parameters for glaucoma screening in patients with high myopia

Hua Mu, Rui-Shu Li, Zhen Yin, Zhuo-Lei Feng

Specialty type: Ophthalmology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Baird PN, Australia; Laude MC

Received: February 24, 2023
Peer-review started: February 24, 2023
First decision: March 10, 2023
Revised: March 12, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Hua Mu, Rui-Shu Li, Zhen Yin, Zhuo-Lei Feng, Department of Ophthalmology, The First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China

Corresponding author: Hua Mu, Doctor, Department of Ophthalmology, The First Affiliated Hospital of Harbin Medical University, No. 23 Youzheng Street, Nangang District, Harbin 150001, Heilongjiang Province, China. mh13836017782@163.com

Abstract

BACKGROUND

The basic method of glaucoma diagnosis is visual field examination, however, in patients with high myopia, the diagnosis of glaucoma is difficult.

AIM

To explore the value of optical coherence tomography (OCT) for measuring optic disc parameters and macular thickness as a screening tool for glaucoma in patients with high myopia.

METHODS

Visual values (contrast sensitivity, color vision, and best-corrected visual acuity) in three groups, patients with high myopia in Group A, patients with high myopia and glaucoma in Group B, and patients with high myopia suspicious for glaucoma in Group C, were compared. Optic disc parameters, retinal nerve fiber layer (RNFL) thickness, and ganglion cell layer (GCC) thickness were measured using OCT technology and used to compare the peri-optic disc vascular density of the patients and generate receiver operator characteristic (ROC) test performance curves of the RNFL and GCC for high myopia and glaucoma.

RESULTS

Of a total of 98 patients admitted to our hospital from May 2018 to March 2022, totaling 196 eyes in the study, 30 patients with 60 eyes were included in Group A, 33 patients with 66 eyes were included in Group B, and 35 patients with 70 eyes were included in Group C. Data were processed for Groups A and B to analyze the efficacy of RNFL and GCC measures in distinguishing high myopia from high myopia with glaucoma. The area under the ROC curve was greater than 0.7, indicating an acceptable diagnostic value.

CONCLUSION
The value of OCT measurement of RNFL and GCC thickness in diagnosing glaucoma in patients with high myopia and suspected glaucoma is worthy of development for clinical use.

Key Words: High myopia suspected glaucoma; Optical coherence tomography; Retinal nerve fiber layer thickness; Ganglion cell layer thickness; Diagnostic efficacy

Core Tip: Glaucoma is an irreversible, blinding eye disease with a high clinical incidence that is characterized by loss of visual acuity, optic disc atrophy, and visual field defects. The basic method of glaucoma diagnosis is visual field examination, however, in patients with high myopia, the diagnosis of glaucoma is difficult. optical coherence tomography (OCT) is a high-resolution technique that uses low-coherence light interference to reflect light from biological tissues, allowing visualization of internal structures of the living body *via* tomographic imaging. The value of OCT measurement of retinal nerve fiber layer and ganglion cell layer thickness in diagnosing glaucoma in patients with high myopia and suspected glaucoma is worthy of development for clinical use.

Citation: Mu H, Li RS, Yin Z, Feng ZL. Value of optical coherence tomography measurement of macular thickness and optic disc parameters for glaucoma screening in patients with high myopia. *World J Clin Cases* 2023; 11(14): 3187-3194
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3187.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3187

INTRODUCTION

Glaucoma is an irreversible, blinding eye disease with a high clinical incidence that is characterized by loss of visual acuity, optic disc atrophy, and visual field defects[1]. Studies have confirmed that glaucoma pathogenesis involved reduced blood supply to the optic nerve and pathologically elevated intraocular pressure[2,3].

Previously, a cup-to-disc ratio greater than 0.6 was considered to be a clinical characteristic of glaucoma and a marker for its development. However, it was found that this ratio was also seen in high myopia and was not specific to glaucoma[4]. Therefore, diagnosis of glaucoma in the setting of high myopia is more difficult.

Recent studies have confirmed a correlation between glaucoma and high myopia, which has been recognized as a risk factor for glaucoma[5]. In the early stages of glaucoma onset, abnormalities of the fundus are similar with those of highly myopic individuals. For example, enlarged cup-to-disc ratio is both a diagnostic clue for glaucoma and a clinical feature of high myopia[6,7]. Glaucoma can cause irreversible damage to visual function, and clinics are constantly searching for sensitive diagnostic indicators that can support the aim of early intervention[8].

Degenerative morphological changes in the fundus of highly myopic patients are the pathological basis for abnormal visual function. When glaucoma is comorbid with myopia, the retinal photoreceptor structure is significantly disturbed, and the patient's regulatory response during visualization is significantly worse than that of patients with pure myopia, resulting in a significant decrease in contrast sensitivity (CS). Previous studies have confirmed that color vision (CV) and best-corrected visual acuity (BCVA) are worse in patients with high myopia when it is combined with glaucoma[9]. It has been noted that in high myopia, thinning of the superior and inferior, as opposed to nasal, retinal nerve fiber layer (RNFL) thickness did not correlate well with myopic refraction; therefore, upon observation of this, RNFL damage due to glaucoma must be watched out for[10].

The basic method of glaucoma diagnosis is visual field examination; however, studies have shown that retinal ganglion cell damage may be present already before the development of visual field defects in glaucoma patients[11]. optical coherence tomography (OCT) is a high-resolution technique that uses low-coherence light interference to reflect light from biological tissues, allowing visualization of internal structures of the living body *via* tomographic imaging[12]. It is commonly used to measure parameters of the ocular RNFL and ganglion cell layer (GCC). The results of this method are in good agreement with histological testing and have been widely used in the diagnosis and follow-up of glaucoma. It has been clinically established[13] that the retinal plexiform layer, ganglion cell layer, and nerve fiber layer collectively constitute the macular ganglion cell complex, and the measurement of GCC thickness can assess ganglion cell loss. This technique accurately reflects retinal ganglion cell apoptosis and nerve fiber loss in glaucoma[14]. Many studies have confirmed the high sensitivity and validity of OCT for

glaucoma diagnosis[15,16].

This study applied OCT to the assessment of high myopia comorbid with glaucoma, evaluated its diagnostic value for glaucoma, and assessed the screening value of parameters such as optic disc parameters and macular thickness measured by OCT.

MATERIALS AND METHODS

Enrollment criteria

Patient who were enrolled into our hospital. Inclusion criteria were as follows: (1) All patients had myopia with refractive error greater than -6.00 D, and the patient's degree did not increase within 2 years, meeting the diagnostic criteria for high myopia; (2) Group B patients had elevated intraocular pressure on clinical examination, characteristic changes in the optic disc, open atrial angle, and a certain degree of visual field defect, meeting the diagnostic criteria for glaucoma in the *Expert Consensus on Glaucoma Diagnosis and Treatment* in China[17]; and (3) Group C patients had one or more of the following features in clinical examination: Open anterior chamber angle; persistent elevation of intraocular pressure; structural changes in the optic nerve suggesting glaucoma; suspicious early glaucomatous changes by visual field examination.

Exclusion criteria were as follows: (1) Optic nerve or retinal disease; (2) Family history of glaucoma; (3) Resistance of a patient to the study; (4) Ocular disease; and (5) Other diseases that may cause ocular pathology, such as intracranial pathology, hypertension, and diabetes.

All patients have given written informed consent.

Methods

OCT examination: The patient was instructed to sit with the lower jaw in the jaw frame and the pupil in its natural state without dialation. Spectralis OCT (Heidelberg, German was used for the examination. The scan was started with the central macular recess as the center, the scan diameter was set at 7 mm, and the depth was 5 μm. The thickness of the upper and lower macula and the average GCC and the general loss of volume (GLV) and focal loss of volume (FLV) were recorded. The thickness of the retinal nerve fiber layer (RNFL) of quadrant measurements (whole circumference, upper and lower quadrants, temporal side, and nasal side) in the Group A, B, and C was automatically measured and recorded by the instrument system, with the optic papilla as the center, and the scanning depth was set at 5 μm and the diameter was 3.45 mm.

Observation indicators

General ophthalmologic examination was performed on all patients, and their visual values, including CS, CV, and BCVA, were recorded. OCT was performed on all patients to record peripapillary parameters including optic cup area, optic disc area, cup/disc area ratio, and cup/disc diameter ratio.

Statistical methods

SPSS 23.0 (IBM, Amonk, New York, United States) was used to process the data. The *F*-test was performed for each patient measure (clinical examination data, RNFL thickness, optic disc parameters, mean GCC thickness, and peripapillary vascular density of patients), and the receiver operator characteristic (ROC) curve was used to determine the diagnostic value for high myopia accompanied by glaucoma at the level of $\alpha = 0.05$.

Patients in the three groups were compared for each retinal quadrant and the superior, inferior, and mean GCC thicknesses were compared to record the patients' GLV and FLV. The ROC curve for the diagnostic value of RNFL and mean GCC for high myopia comorbid with glaucoma was constructed after comparing the patients' peripapillary vascular density.

RESULTS

Ninety-eight patients (196 eyes) who were admitted to our hospital from May 2018 to March 2022 were included in the study, including 30 patients with 60 eyes with high myopia (Group A), 33 patients with 66 eyes with high myopia accompanied by glaucoma (Group B), and 35 patients with 70 eyes with high myopia suspected of glaucoma (Group C). There was no statistically significant difference in the baseline information of the three groups (Table 1), with high comparability ($P > 0.05$).

The visual value levels (of CS, CV, and BCVA) of the three groups were compared, and significant differences were observed ($P < 0.05$). Compared to Group A, the CS, CV, and BCVA levels of Groups B and C were lower, but the values in Group C were higher than those in Group B, and the differences were statistically significant ($P < 0.05$) (Table 2).

Table 1 Comparison of baseline data between the three patient groups (mean ± SD, *n*)

Group	Age (yr)	Gender (male/female)	Equivalent sphere diameter (D)	Mean refraction (D)
Group A (n = 60)	36.45 ± 3.78	22/38	-1.78 ± 2.21	-0.44 ± 1.56
Group B (n = 66)	35.48 ± 3.24	30/36	-2.16 ± 2.15	0.65 ± 2.45
Group C (n = 70)	36.15 ± 3.12	36/34	-2.57 ± 2.45	-1.05 ± 2.15
F/χ^2 value	1.384	2.858	1.949	1.430
P value	0.253	0.240	0.145	0.242

Table 2 Comparison of contrast sensitivity, color vision, and best-corrected visual acuity levels among three groups (mean ± SD, *n*)

Group	CS	CV	BCVA
Group A (n = 60)	96.45 ± 1.78	0.94 ± 0.08	0.97 ± 0.08
Group B (n = 66)	87.48 ± 1.24[a]	0.81 ± 0.05[a]	0.87 ± 0.15[a]
Group C (n = 70)	89.15 ± 1.12[a,b]	0.87 ± 0.02[a,b]	0.91 ± 0.11[a,b]
F value	32.163	90.314	11.430
P value	0.000	0.000	0.000

[a]P < 0.05 *vs* group A.
[b]P < 0.05 *vs* group B.
CS: Contrast sensitivity; CV: Color vision; BCVA: Best-corrected visual acuity.

There was no significant difference in the cup-to-disc area ratio among the three groups (P > 0.05); however, there were statistically significant differences in cup area, optic disc area, and cup/disc diameter ratio among all groups. The values of Groups B and C were significantly higher than those of Group A, and the area of the optic disc and cup/disc diameter ratio of Group C were significantly smaller than those of Group B (P < 0.05) (Table 3).

RNFL thicknesses in all quadrants (whole circumference, upper and lower quadrant, temporal side, and nasal side) were statistically different among the three groups. Compared with Group A, RNFL thickness in the whole circumference, upper and lower quadrants, and nasal side decreased in Groups B and C, and Group C was greater than that in Group B. The temporal RNFL thickness in Groups B and C was significantly higher than that in Group A, and the temporal RNFL thickness in Group C was significantly lower than that in Group B (P < 0.05) (Table 4).

The upper, lower, and mean GCC thickness and GLV and FLV values between the three groups decreased in Groups B and C, and each GCC thickness in Group C was greater than that in Group B; GLV and FLV in Groups B and C were higher than those in Group A, and Group C was lower than Group B, with statistical significance (P < 0.05). The comparison of capillary density around the optic disc among the three groups showed statistically significant differences in other regions but not in the comparison of capillary density in the optic disc (P < 0.05). The hologram, vascular density beside and within the optic disc, and capillary density beside the optic disc of Groups B and C were reduced to varying degrees, and the values of Group C were higher than those of Group B, and the difference was statistically significant (P < 0.05) (Table 5).

DISCUSSION

This study investigated the value of OCT measurement of peripapillary parameters and macular thickness as a screening test for patients with high myopia and suspected glaucoma.

There was no significant difference in the cup-to-disc area ratio between the groups when peripapillary parameters were compared. With the increase in the ocular axis of the eye that occur in high myopia, the myopic arcs gradually atrophied, some dimensions correlated with the those of disc defect, and the cup-disc area ratio also changed. Therefore, the change in cup-to-disc area ratio can only be used as an auxiliary indicator.

When combined with the measurements used in this study, the optic cup area, optic disc area, and cup/disc diameter ratio were significantly different among the three groups. Therefore, the above indicators can be applied in combination with a view to improve the effectiveness of screening for glaucoma suspected of high myopia. In this study, the CS, CV, and BCVA levels in the three groups

Table 3 Comparison of weekly parameters in the three groups (mean ± SD, *n*)

Group	Optic cup area (mm)	Optic disc area (mm)	Cup/disc area ratio	Cup/disc diameter ratio
Group A (*n* = 60)	1.02 ± 0.81	2.82 ± 0.88	0.34 ± 0.21	0.56 ± 0.05
Group B (*n* = 66)	1.31 ± 0.75[a]	3.87 ± 0.87[a]	0.37 ± 0.22	0.61 ± 0.06[a]
Group C (*n* = 70)	1.42 ± 0.65[a]	3.45 ± 0.75[a,b]	0.35 ± 0.18	0.59 ± 0.04[a,b]
F value	4.890	25.691	0.369	15.672
P value	0.009	0.000	0.692	0.000

[a]*P* < 0.05 *vs* group A.
[b]*P* < 0.05 *vs* group B.

Table 4 Retinal nerve fiber layer thickness in each of the three groups (mean ± SD, *n*)

Group	Complete cycle (μm)	Upper quadrant (μm)	Lower quadrant (μm)	Temporal side (μm)	nasal side (μm)
Group A (*n* = 60)	109.12 ± 10.54	133.23 ± 7.87	130.23 ±5.54	111.23 ± 5.36	60.45 ± 3.45
Group B (*n* = 66)	102.78 ± 9.23[a]	125.65 ± 7.54[a]	121.32 ± 5.45[a]	123.45 ± 5.21[a]	56.45 ± 2.98[a]
Group C (*n* = 70)	106.45 ± 10.21[a,b]	129.87 ± 8.56[a,b]	127.63 ± 5.78[a,b]	115.46 ± 5.14[a,b]	58.45 ± 2.12[a,b]
F value	4.212	14.177	42.888	89.611	30.552
P value	0.016	0	0	0	0

[a]*P* < 0.05 *vs* group A.
[b]*P* < 0.05 *vs* group B.

Table 5 Comparison of mean ganglion cell layer thickness and general loss of volume and focal loss of volume in the three groups (mean ± SD, *n*)

Group	Upper GCC (μm)	Bottom GCC (μm)	Mean GCC (μm)	GLV (%)	FLV (%)
Group A (*n* = 60)	94.15 ± 6.78	92.45 ± 7.45	92.56 ± 7.45	5.16 ± 4.12	1.36 ± 1.12
Group B (*n* = 66)	71.45 ± 6.56[a]	78.26 ± 11.65[a]	73.66 ± 8.12[a]	23.15 ± 8.97[a]	7.54 ± 4.85[a]
Group C (*n* = 70)	83.54 ± 5.54[a,b]	82.64 ± 8.78[a,b]	82.43 ± 8.26[a,b]	15.05 ± 8.78[a,b]	3.88 ± 2.56[a,b]
F value	205.836	36.474	88.326	85.061	57.448
P value	0	0	0	0	0

[a]*P* < 0.05 *vs* group A.
[b]*P* < 0.05 *vs* group B.
GCC: Ganglion cell layer; GLV: General loss of volume; FLV: Focal loss of volume.

were also compared, and statistically significant differences were found between the groups. We also found that these values decreased sequentially in Groups A, C, and B. These facts suggest that the above indices are more likely to be affected in patients with high myopia and glaucoma. Therefore, an effective method for the early assessment of retinal ganglion cell abnormalities is more meaningful when screening for glaucoma in the setting of high myopia. When RNFL thickness in the outer macular ring region was measured in the three groups in this study, the temporal side was found to be the thinnest and the other quadrants to be thicker, which were consistent with clinically-recognized anatomical features.

In this study, we further compared the differences between the three groups and found statistical differences in RNFL thickness in each orbital quadrant (whole circumference, upper and lower quadrants, temporal side, and nasal side), with thicker RNFL in the upper and lower quadrants next to the optic disc in each group, followed by the temporal and nasal side. The full circumferential, upper and lower quadrant, and nasal RNFL thickness in patients with high myopia accompanied by glaucoma were the smallest among the three groups, while the temporal side was the largest. Previous studies have confirmed that CV and BCVA were worse in patients with high myopia combined with glaucoma

[14], and the present study yielded consistent results.

It is suggested that the above index characteristics can be used to screen for glaucoma with suspected high myopia. The analysis was as follows: The high myopia-suspect glaucoma population may already have nerve fiber layer loss and ganglion cell damage, with the phenomenon more pronounced in patients with comorbid glaucoma. In high myopia with glaucoma, the temporal optic disc undergoes significant tilting and anticlockwise transposition, resulting in an overlap of retinal temporal fiber bundles and a significant increase in temporal RNFL thickness[18].

The efficacy of the GCC thickness parameter has been found to be better than that of the RNFL thickness parameter for the diagnosis of glaucoma[19]. In this study, GCC thickness was found to be minimal in Group B—significantly lower than those in the other two groups—and significantly lower in that in Group C than that in Group A. It has been suggested that the GCC can be used to screen people with high myopia and glaucoma. Structural changes in the macular optic ganglion cell complex can affect the function of this layer of the retina, which may account for the different sensitivities of the GCC and RNFL. Retinal ganglion cell apoptosis and axonal damage are among the pathological changes in glaucoma; therefore, GCC thickness testing is more commonly used and more effective.

Indicators, such as GLV and FLV, can assess optic nerve atrophy and changes in visual function, such as visual acuity and visual field. In the present study, the highest values of these indices were found in patients with high myopia comorbid with glaucoma, and GLV and FLV measured the average amount of loss in the whole and local GCC. The results confirmed that the GCC was significantly thinner in patients with high myopia accompanied by glaucoma. The altered GLV and FLV values are consistent with the pathological basis of glaucoma.

The results of this study showed that whole-image vascular density, intra- and near-optic disc density, and peri-optic capillary density were significantly lower in Groups A, C, and B, with statistical significance between the groups. It has been clinically established that the above indices were reduced to a greater extent in high myopia accompanied by glaucoma than in high myopia alone[20], and the AUC values for pars plana vascular density analyzed in that study were higher than those for the intra-optic disc. The results of the present study are similar to those of the previous studies.

Numerous studies have used OCT as the primary method for examining glaucoma. The present study showed that changes in RNFL thickness and each GCC parameter were more obvious in the population with high myopia comorbid with glaucoma, and the efficacy of diagnosing high myopia with glaucoma was higher. In highly myopic eyes with significant tilted degeneration of the optic disc, segmentation of the optic nerve fiber stratification measured by OCT occurs with a large error, and the combined analysis of OCT parameters was a meaningful method. The sample size of each group in this study was small and did not consider the effect of other relevant factors on the results. Further studies are required to improve the screening of high myopia with glaucoma.

CONCLUSION

In conclusion, OCT measurement of RNFL and GCC thickness is of diagnostic value for glaucoma with suspected high myopia and is worthy of clinical promotion.

ARTICLE HIGHLIGHTS

Research background

Glaucoma is an irreversible, blinding eye disease with a high clinical incidence that is characterized by loss of visual acuity, optic disc atrophy, and visual field defects. The basic method of glaucoma diagnosis is visual field examination, however, in patients with high myopia, the diagnosis of glaucoma is difficult.

Research motivation

Optical coherence tomography (OCT) is a high-resolution technique that uses low-coherence light interference to reflect light from biological tissues, allowing visualization of internal structures of the living body *via* tomographic imaging. It is commonly used to measure parameters of the ocular retinal nerve fiber layer and ganglion cell layer.

Research objectives

This study was to explore the value of OCT for measuring optic disc parameters and macular thickness as a screening tool for glaucoma in patients with high myopia. The results could promote the improvement of the diagnosis of glaucoma in patients with high myopia and suspected glaucoma.

Research methods

Visual values in patients with high myopia in, patients with high myopia and glaucoma, and patients with high myopia suspicious for glaucoma were compared. Optic disc parameters, retinal nerve fiber layer thickness (RNFL), and ganglion cell layer (GCC) thickness were measured using OCT technology and used to compare the peri-optic disc vascular density of the patients and generate receiver operator characteristic test performance curves of the RNFL and GCC for high myopia and glaucoma.

Research results

The visual value levels of the three groups were significantly different. There were statistically significant differences in cup area, optic disc area, and cup/disc diameter ratio among all groups. RNFL thicknesses in all quadrants were statistically different among the three groups. The area under the ROC curve was greater than 0.7, indicating an acceptable diagnostic value.

Research conclusions

The value of OCT measurement of RNFL and GCC thickness in diagnosing glaucoma in patients with high myopia and suspected glaucoma is worthy of development for clinical use.

Research perspectives

Further studies with large sample and other relevant factors are required to improve the screening of high myopia with glaucoma.

FOOTNOTES

Author contributions: Mu H designed the research study; Li RS performed the research; Mu H and Yin Z analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the [The First Affiliated Hospital of Harbin Medical University] Institutional Review Board.

Informed consent statement: The informed consent was obtained from every patient.

Conflict-of-interest statement: There is no conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Mh13836017782@163.com.

Country/Territory of origin: China

ORCID number: Hua Mu 0000-0002-5224-3405; Rui-Shu Li 0000-0003-0463-672X; Zhen Yin 0000-0002-9095-518X; Zhuo-Lei Feng 0000-0001-9383-5661.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Shin JW**, Song MK, Sung KR. Longitudinal Macular Ganglion Cell-Inner Plexiform Layer Measurements to Detect Glaucoma Progression in High Myopia. *Am J Ophthalmol* 2021; **223**: 9-20 [PMID: 33007275 DOI: 10.1016/j.ajo.2020.09.039]

2 **Chen YH**, Wei RH, Hui YN. Commentary review on peripapillary morphological characteristics in high myopia eyes with glaucoma: diagnostic challenges and strategies. *Int J Ophthalmol* 2021; **14**: 600-605 [PMID: 33875954 DOI: 10.18240/ijo.2021.04.18]

3 **Zhang XD**, Wang CX, Jiang HH, Jing SL, Zhao JY, Yu ZY. Trends in research related to high myopia from 2010 to 2019: a bibliometric and knowledge mapping analysis. *Int J Ophthalmol* 2021; **14**: 589-599 [PMID: 33875953 DOI: 10.18240/ijo.2021.04.17]

4 **Berenguer-Vidal R**, Verdú-Monedero R, Morales-Sánchez J, Sellés-Navarro I, Kovalyk O, Sancho-Gómez JL. Decision

Trees for Glaucoma Screening Based on the Asymmetry of the Retinal Nerve Fiber Layer in Optical Coherence Tomography. *Sensors (Basel)* 2022; **22** [PMID: 35808338 DOI: 10.3390/s22134842]

5 **Miller GD**, Abu-Qamar O, Salim S. Evaluation of Retinal Nerve Fiber Layer, Ganglion Cell-Inner Plexiform Layer, and Optic Nerve Head in Glaucoma Suspects With Varying Myopia. *J Glaucoma* 2021; **30**: e213-e221 [PMID: 33731645 DOI: 10.1097/IJG.0000000000001834]

6 **Rezapour J**, Bowd C, Dohleman J, Belghith A, Proudfoot JA, Christopher M, Hyman L, Jonas JB, Penteado RC, Moghimi S, Hou H, El-Nimri NW, Micheletti E, Fazio MA, Weinreb RN, Zangwill LM. Macula structural and vascular differences in glaucoma eyes with and without high axial myopia. *Br J Ophthalmol* 2022 [PMID: 35725293 DOI: 10.1136/bjophthalmol-2021-320430]

7 **Ha A**, Kim CY, Shim SR, Chang IB, Kim YK. Degree of Myopia and Glaucoma Risk: A Dose-Response Meta-analysis. *Am J Ophthalmol* 2022; **236**: 107-119 [PMID: 34648776 DOI: 10.1016/j.ajo.2021.10.007]

8 **Wang X**, Li RS, Wei YH, Fang Y, Tian T, Li M, Pan YZ. Applications of the isolated-check visual evoked potential in primary open angle glaucoma with or without high myopia. *Int J Ophthalmol* 2021; **14**: 704-713 [PMID: 34012885 DOI: 10.18240/ijo.2021.05.10]

9 **Jyothi GD**, Sivaswamy J. Glaucoma Assessment from Fundus Images with Fundus to OCT Feature Space Mapping. *ACM Trans Comput Healthc* 2022; **3**: 1-15 [DOI: 10.1145/3470979]

10 **El-Dabae AM**, Rashed MO, El-Hakim Zaky MA, Ahmed Ebeid WM. Retinal Nerve Fibre Layer Assessment in Glaucoma and Glaucoma Suspect by Optical Coherence Tomography (OCT). *QJM* 2021; **114** Suppl 1: 256-268 [DOI: 10.1093/qjmed/hcab109]

11 **Wen Y**, Chen Z, Zuo C, Yang Y, Xu J, Kong Y, Cheng H, Yu M. High-Pass Visual Acuity Loss and Macular Structure-Function Relationship in Patients With Primary Open-Angle Glaucoma. *Transl Vis Sci Technol* 2021; **10**: 26 [PMID: 34004003 DOI: 10.1167/tvst.10.4.26]

12 **Juneja M**, Minhas J S, Singla N, Thakur S, Thakur N, Jindal P. Fused framework for glaucoma diagnosis using Optical Coherence Tomography (OCT) images. *Expert Syst Appl* 2022; **201** (9): 117202 [DOI: 10.1016/j.eswa.2022.117202]

13 **Berenguer-Vidal R**, Verdú-Monedero R, Morales-Sánchez J, Sellés-Navarro I, Kovalyk O. Analysis of the Asymmetry in RNFL Thickness Using Spectralis OCT Measurements in Healthy and Glaucoma Patients. In: Ferrández Vicente. Artificial Intelligence in Neuroscience: Affective Analysis and Health Applications. IWINAC 2022. Lecture Notes in Computer Science, vol 13258. Springer, Cham 507-515 [DOI: 10.1007/978-3-031-06242-1_50]

14 **García G**, Del Amor R, Colomer A, Verdú-Monedero R, Morales-Sánchez J, Naranjo V. Circumpapillary OCT-focused hybrid learning for glaucoma grading using tailored prototypical neural networks. *Artif Intell Med* 2021; **118**: 102132 [PMID: 34412848 DOI: 10.1016/j.artmed.2021.102132]

15 **Naderi Beni A**, Entezari D, Koosha N, Kianersi F, Naderan M. Ganglion cell complex and macular thickness layers in primary open-angle glaucoma, pseudoexfoliation glaucoma and healthy eyes: A comparative study. *Photodiagnosis Photodyn Ther* 2021; **36**: 102563 [PMID: 34614425 DOI: 10.1016/j.pdpdt.2021.102563]

16 **Lee MY**, Park HL, Kim SA, Jung Y, Park CK. Predicting Visual Field Progression by Optical Coherence Tomography Angiography and Pattern Electroretinography in Glaucoma. *J Glaucoma* 2022; **31**: 881-890 [PMID: 35882039 DOI: 10.1097/IJG.0000000000002088]

17 **Chinese Society of Hepatology**, Chinese Society of Infectious Diseases; Chinese Medical Association. Consensus on the diagnosis and treatment of hepatic fibrosis (2019). *J Dig Dis* 2020; **21**: 127-138 [PMID: 32108989 DOI: 10.1111/1751-2980.12854]

18 **Polat YD**, Kocatürk T, Abdullayev ÖK, Abdullayev O, Bilgen M. Correlation of Measurements From Doppler Ultrasound and Optical Coherence Tomography in Glaucoma. *J Ultrasound Med* 2022; **41**: 1405-1413 [PMID: 34491596 DOI: 10.1002/jum.15823]

19 **Dikmetas O**, Deliktas O, Toprak H, Karahan S, Kocabeyoglu S, Cankaya AB. Correlation of Ocular Biometric Parameters and Macular Ganglion Cell Layer in Normal Eyes. *Semin Ophthalmol* 2021; **36**: 812-817 [PMID: 33952048 DOI: 10.1080/08820538.2021.1922711]

20 **Vahedian Z**, Fakhraie G, Ghasemi M, Azimi A, Tabatabaei SM. The thickness of the outer retina in the macula and circumpapillary area in patients with unilateral advanced glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2022; **260**: 3935-3944 [PMID: 35838807 DOI: 10.1007/s00417-022-05756-w]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3195-3203

DOI: 10.12998/wjcc.v11.i14.3195

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Comparative study of the clinical efficacy of all-inside and traditional techniques in anterior cruciate ligament reconstruction

Bai-Jing An, Yao-Ting Wang, Zhe Zhao, Ming-Xin Wang, Geng-Yan Xing

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bernardes A, Portugal; Velázquez-Saornil J, Spain

Received: November 20, 2022
Peer-review started: November 20, 2022
First decision: February 14, 2023
Revised: March 5, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 16, 2023

Bai-Jing An, Yao-Ting Wang, Zhe Zhao, Ming-Xin Wang, Geng-Yan Xing, Department of Sports Medicine, The Fourth Medical Center of PLA General Hospital, Beijing 100000, China

Corresponding author: Geng-Yan Xing, FCCP, Dean, Director, Doctor, Professor, Surgeon, Department of Sports Medicine, The Fourth Medical Center of PLA General Hospital, No. 51 Fucheng Road, Haidian District, Beijing 100000, China. xinggengyan123@163.com

Abstract

BACKGROUND

Many studies have focused on the femoral tunnel technique and fixation method, but few studies have involved the tibial tunnel technique and fixation method. The all-inside technique is one of the new techniques that has been described in recent years. All-inside anterior cruciate ligament (ACL) reconstruction is based on a tibial socket instead of a full tunnel. This method has many potential advantages.

AIM

To compare clinical outcomes of knee ACL autograft reconstruction using all-inside quadrupled semitendinosus (AIST) and traditional hamstring tendon (TBT) techniques.

METHODS

From January 2017 to October 2019, the clinical data of 80 patients with ACL reconstruction were retrospectively analyzed, including 67 males and 13 females. The patients had an average age of 24.3 ± 3.1 years (age range: 18-33 years). The AIST technique was used in 42 patients and the TBT technique was used in 38 patients. The time between operation and injury, operative duration, post-operative visual analogue scale (VAS) score and knee functional recovery were recorded and compared between the two groups. The International Knee Documentation Committee (IKDC) and Lysholm scoring system were used to comprehensively evaluate clinical efficacy.

RESULTS

Eighty patients were followed for 24-36 mo, with an average follow-up duration of 27.5 ± 1.8 mo. There were no significant differences in the time between surgery and injury, operative duration, IKDC and Lysholm scores of the affected knee at the last follow-up evaluation between the two groups. There were significant differences in VAS scores 1 d, 3 d, 7 d, 2 wk and 1 mo after surgery ($P < 0.05$).

There was no significant difference in VAS score at 3 mo, 6 mo and 1 year after operation.

CONCLUSION
The efficacy of the AIST ACL reconstruction technique was comparable to the TBT technique, but the postoperative pain was less with the AIST technique. Thus, the AIST technique is an ideal treatment choice for ACL reconstruction.

Key Words: Anterior cruciate ligament reconstruction; All-inside quadrupled semitendinosus; Clinical curative effect; Traditional hamstring tendon; Visual analogue scale

Core Tip: This study retrospectively analyzed 80 patients with anterior cruciate ligament (ACL) injuries who underwent all-inside quadrupled semitendinosus (AIST) or traditional hamstring tendon (TBT). We demonstrated that there were no significant differences in the time between surgery and injury, operative duration, International Knee Documentation Committee and Lysholm scores of the affected knee. However, there were significant differences in visual analogue scale scores 1 d, 3 d, 7 d, 2 wk and 1 mo after surgery ($P < 0.05$). These results indicated the efficacy of the AIST ACL reconstruction technique was comparable to the TBT technique, but the postoperative pain was less with the AIST technique. Thus, the AIST technique is a better choice for ACL reconstruction.

Citation: An BJ, Wang YT, Zhao Z, Wang MX, Xing GY. Comparative study of the clinical efficacy of all-inside and traditional techniques in anterior cruciate ligament reconstruction. *World J Clin Cases* 2023; 11(14): 3195-3203
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3195.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3195

INTRODUCTION

Anterior cruciate ligament (ACL) injuries are common sports injuries that often lead to knee instability and secondary traumatic osteoarthritis, meniscus injuries, and contralateral ACL injuries[1,2]. Arthroscopic reconstruction of the ACL is the main method of repair. The optimal ACL reconstruction technique has not been determined, with reported graft retear rates ranging from 10%-25%[3-5]. This is a significant clinical problem due to the increasing frequency of ACL injuries occurring in this group[6-9] and to the high rate of secondary injuries following ACL reconstruction in this particular cohort[10-15]. Many studies have focused on the femoral tunnel technique and fixation method, but few studies have involved the tibial tunnel technique and fixation method. The all-inside technique is one of the new techniques that has been descried in recent years. All-inside ACL reconstruction is based on a tibial socket instead of a full tunnel[16]. This method has many potential advantages. Specifically, Lubowitz *et al*[17] reported less pain with all-inside allograft ACL reconstruction compared with a full tibial tunnel in a randomized controlled trial. Therefore, this all-inside approach improved graft integration and stability of a hamstring construct[18], in contrast to other described hamstring reconstruction techniques that have been compared with a bone-patellar-tendon-bone graft, along with the added benefit of less anterior knee pain. The purpose of this investigation was to compare knee ACL autograft reconstruction using all-inside quadrupled semitendinosus (AIST) and traditional hamstring tendon (TBT) techniques. In this study 80 patients with ACL injuries admitted to our hospital from January 2017 to October 2019 were retrospectively analyzed.

MATERIALS AND METHODS

Clinical data

This study retrospectively analyzed the data of 80 patients with ACL injuries admitted to the Department of Orthopedics at the Third Medical Center of PLA General Hospital from January 2017 to October 2019. There were 67 males and 13 females, 18-33 years of age, with an average age of 24.3 ± 3.1 years. There were 42 patients in the AIST group and 38 patients in the TBT group. There were no significant differences in sex, age, injured side, and time between operation and injury between the two groups ($P > 0.05$). This study was conducted with the informed consent of the patients and according to the guidelines of the Declaration of Helsinki.

Eligibility criteria

Eligibility for the study was assessed before consent and conducted by a research coordinator at the study site. The inclusion criteria were patients with an ACL-deficient knee who agreed to ACL reconstructive surgery using autograft tissue. Patients with associated meniscal and chondral pathologic changes (except those meeting exclusion criteria) were included in the study; the pathologic changes treated at the time of ACL reconstruction were at the discretion of the study surgeon. All pathologic changes and treatments were recorded. Patients who had previous ACL reconstructive surgery or underwent multi-ligament, medial collateral ligament, posterior cruciate ligament, lateral collateral ligament, posteromedial corner, or posterolateral corner repair or reconstruction surgery were excluded.

Surgical technique

AIST technique group: The ipsilateral semitendinosus muscle was passed through the respective TightRope loops, quadrupled, and the two free ends on the tibial side were sutured together with #0 FiberLoop (Arthrex,) in a SpeedWhip-type pattern leaving the suture ends intact (Figure 1). Using the remaining native ACL fibers as a reference and the over-the-top position with a guide (Arthrex), a pin was placed and the lateral femur was drilled out. In this way, the femoral socket was created as close as possible to the anatomic ACL center *via* anteromedial portal drilling using a low-profile reamer (Arthrex) matching the graft diameter. The minimal graft in socket depth was 25 mm. The pin was used to place a #2 FiberWire (Arthrex) shuttle suture. The intra-articular ACL graft distance was measured with an intra-articular ruler (Arthrex), and this distance was added to the length of the graft in the femoral socket to determine the depth of graft in the tibial socket based on the total graft length. The tibial socket was created at the anatomic tibial site indexing off the anterior horn of the lateral meniscus using a FlipCutter aiming guide (Arthrex). A straight FlipCutter pin matching the graft diameter was then drilled into the joint and "unflipped" to become a reamer to retro-cut the tibial socket, which was also reamed 5 mm deeper than needed to allow for optimal graft tensioning with the all-inside technique. The FlipCutter pin was drilled back into the joint, "unflipped," removed, and a #2 TigerStick suture (Arthrex) was passed through this FlipCutter pin hole up into the joint and retrieved as a tibial shuttle suture. The #2 FiberWire shuttle suture from the femoral socket was used to pull the graft through the anteromedial portal across the joint up into the femur, flipping the suspensory TightRope RT button on the lateral femoral cortex. The graft was then hoisted up into the socket to the appropriate depth with the TightRope shortening strands (Figure 2).

TBT technique group: A #2 FiberWire was used to suture 2 cm at each end of the ipsilateral semitendinosus and gracilis tendons. The tibial insertion was located by point-to-point sight (Smith and Nephew), and the medial side of the femoral lateral condyle was located *via* the tibia, and the femoral side was fixed by an Endobutton (Smith and Nephew). The graft was tightened at 30° flexion of the knee and tibial fixation was achieved using an interference screw (Smith and Nephew).

Rehabilitation protocol

The rehabilitation protocol for the AIST and TBT technique cohorts were the same. The affected limbs of the two groups were fixed with braces after surgery. Quadriceps isometric exercises were started on the 2nd d after surgery, straight leg raising exercises were started on the 3rd d after surgery with gradual weight-bearing under brace protection, and complete weight-bearing was achieved 4 wk after surgery. Passive knee flexion and extension exercise were started the 2nd wk after surgery, increasing by 30° every week, and reaching > 120° (close to normal) 6 wk after surgery. Activities of daily living were resumed the 4th mo after surgery and physical exercises were gradually resumed 6 mo after surgery.

Outcome measures

All patients underwent an extensive clinical, subjective, and objective evaluation preoperatively. Visual analogue scale (VAS) scores were evaluated and recorded 1, 3, and 7 d, 2 wk, 1 and 6 mo, and 1 and 2 years postoperatively for each patient. The operative duration, and International Knee Documentation Committee (IKDC) and Lysholm scores of the affected knee at the last follow-up evaluation were recorded.

Statistical methods

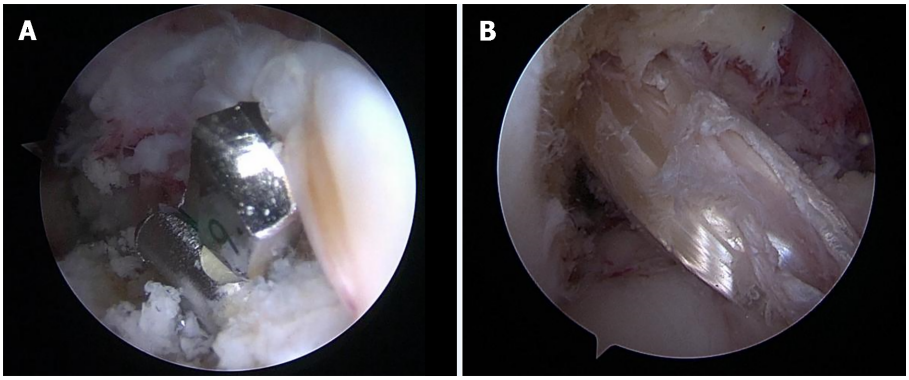
To determine the difference between the two-sample means, normal distribution measurement data are expressed as the mean ± standard deviation. *T*-test and repeated measurement data analysis of variance were used. The Fisher test was used for enumeration data, and the Kruskal-Wallis test was used for multi-valued ordinal data. Statistical analyses were performed with commercially-available software (SPSS version 18.0). A $P < 0.05$ was considered statistically significant.

RESULTS

All patients had follow-up evaluations for 24-36 mo (mean, 27.5 ± 1.8 mo). There was no significant

DOI: 10.12998/wjcc.v11.i14.3195

Figure 1 The quadrupled semitendinosus GraftLink construct was secured by #2 FiberWire cerclage sutures on each side of the suspensory fixation loops.



DOI: 10.12998/wjcc.v11.i14.3195

Figure 2 Arthroscopic image. A: The tibial socket was created at the anatomic tibial site indexing off the anterior horn of the lateral meniscus using a FlipCutter aiming guide (Arthrex); B: Arthroscopic view from the anterolateral portal in the right knee shows that the graft was hoisted up into the socket to the appropriate depth with TightRope shortening strands.

difference in the operative duration between the two groups. One patient in each group had grade C knee function postoperatively. Two patients in the traditional group had numbness at the graft site postoperatively; the numbness was significantly relieved 1 year postoperatively. There was no significant difference in the IKDC score between the two groups (Table 1). The Lysholm scores of all patients were > 90°. There was no significant difference in the mean scores between the two groups (Table 2). The VAS score of the internal group was lower than the traditional group ($P < 0.05$). All patients were pain-free 6 mo, and 1 year and 2 years postoperatively (Table 3). No complications, such as ligament re-injuries and infections, occurred in the two groups during the follow-up period.

DISCUSSION

An ACL injury is one of the most common sports-related knee injuries. With the advances in arthroscopic technology, arthroscopic ACL reconstruction is a widely performed surgical procedure. Some studies[17,19]; however, have shown that the absence of the hamstring tendon of the knee will lead to a reduction in the flexion internal rotation force of the knee by 5%-10%. Yosmaoglu *et al*[20] have shown that preserving the gracilis muscle is crucial for postoperative rehabilitation training, especially for patients who participate in knee flexion exercises > 70°. Preservation of the gracilis muscle significantly accelerates recovery of knee function after ACL reconstruction. Volpi *et al*[21] believed that to restore joint motion and function, the clinical effect of the all-inside technique is similar to traditional single-beam reconstruction surgery. The bone tunnel of the tibia in the AIST group was drilled from outside-in, and the tunnel was thin outside and thick inside, which is conducive to reducing the leakage of joint fluid and thereby reducing the risk of infection. Based on a retrospective analysis, Connaughton *et al*[22] concluded that the operative time, Lysholm score, and IKDC score were not significantly different between the AIST and TBT groups, but the postoperative VAS score of the AIST group was significantly lower than the TBT group ($P < 0.05$). Connaughton *et al*[22] believed that the efficacy of all-inside reconstruction was similar to the traditional group, but the postoperative pain of the all-inside group

Table 1 Comparison of knee International Knee Documentation Committee scores between the two groups

IKDC score	AIST group	TBT group	χ^2 value	*P* value
Grade A	30	24	1.657	0.233
Grade B	11	13		
Grade C	1	1		

AIST: All-inside quadrupled semitendinosus; IKDC: International Knee Documentation Committee; TBT: Traditional hamstring tendon.

Table 2 Comparison of knee Lysholm scores between the two groups (mean ± SD)

Group	Patient	Preoperative	6 wk postoperatively	12 wk postoperatively
AIST group	42	63.3 ± 5.6	75.3 ± 6.5	86.7 ± 5.8
Group	38	64.6 ± 4.8	74.6 ± 7.1	85.5 ± 6.6
t value		0.765	0.799	0.631
P value		0.365	0.434	0.523

Comparison of the preoperative and 6-wk postoperative scores (t =4.889, P = 0.005); Comparison of the preoperative and 12-wk postoperative scores (t = 11.568, P = 0.005). In the control group, the preoperative and 6-wk postoperative scores were compared [t = 3.121, P = 0.004 (corrected t-test)]. In the control group, the preoperative and 12-wk postoperative scores were compared (t = 9.281, P = 0.005). AIST: All-inside quadrupled semitendinosus.

Table 3 Visual analog scale pain scale results

Time	TBT	95%CI	AIST	95%CI	*P* value
Day 1	9.4 ± 0.6	1.0	7.5 ± 0.5	0.9	0.032
Day 3	7.5 ± 0.5	0.9	4.8 ± 0.8	0.8	0.028
Day 7	4.1 ± 0.6	0.8	2.5 ± 0.7	0.7	0.004
2 wk	2.6 ± 0.5	0.8	0.6 ± 0.5	0.5	0.011
1 mo	1.2 ± 0.5	0.6	0.5 ± 0.5	0.5	0.023
6 mo	0.8 ± 0.6	0.4	0.6 ± 0.5	0.4	0.815
1 yr	0.4 ± 0.5	0.2	0.3 ± 0.6	0.3	0.782
2 yr	0.3 ± 0.3	0.1	0.1 ± 0.5	0.2	0.769

Bolded values represent statistical significance (P < 0.05). AIST: All-inside quadrupled semitendinosus; CI: Confidence interval; TBT: Traditional hamstring tendon.

was less severe. Benea *et al*[23] also reported that the pain at the graft removal site was apparent in the short term after surgery, and only one tendon could be removed to alleviate postoperative pain. Within 1 mo after surgery, the pain among patients in the all-inside group was significantly lower than the traditional group. This study also confirmed that the VAS score of the all-inside group was significantly lower than the traditional reconstruction group, and the patients felt well. In our study, the VAS score for postoperative pain in the all-inside group was lower than the traditional group. The reasons for this finding were as follows: The diameter of the cortical tibial tunnel in the all-inside group was 3.5 mm and 7 or 8 mm in the traditional group; and only semitendinosus muscle was taken as the graft in the all-inside group, which caused less injury to the surrounding soft tissues.

Kouloumentas *et al*[24] showed that fixed and adjustable loop buttons of the femoral end fixation greatly exceed the mechanical strength required for early knee exercises in the maximum load biomechanical test, which met the needs of patients for early functional exercises. In a randomized controlled study involving 188 patients, Boyle *et al*[25] showed that there was no statistical difference in the test results of KT-1000, the graft failure rate, and the graft failure time between adjustable and fixed loops at the femoral end. The tibial lateral fixation method was changed from the traditional inter-facial screw extrusion fixation to suspension fixation. Biomechanical tests confirmed that extrusion screw fixation had a lower relaxation rate of graft elongation and ideal anti-pull-out performance, while suspension

fixation had a higher load limit and did not show increased graft displacement compared with screw fixation[26]. A meta-analysis concluded that there was no significant difference between suspension fixation and tunnel extrusion screw fixation in terms of normal knee relaxation, the graft failure rate, patient satisfaction, and recovery to the pre-injury activity rate. Therefore, it can be concluded that both the all-inside suspension fixation technique and the traditional total tibial tunnel interface extrusion screw fixation technique achieved excellent results in ACL reconstruction[27,28]. Our study also showed that the tension of the all-inside reconstruction graft and the stability of the knee postoperatively were ideal, and there was no graft relaxation or failure. There was no significant difference in the treatment effect and postoperative knee function recovery between the two groups. The two groups achieved satisfactory treatment effects in pain improvement and recovery of knee motor function.

In our study the all-inside technique was used to reconstruct the ACL. Only the semitendinosus tendon was used as a graft, which reduced loss of the internal rotation force in flexion of the affected knee after surgery and was beneficial to postoperative rehabilitation. One patient in the traditional group had numbness at the graft site after surgery, which may have been caused by injury of the inferior patellar branch of the saphenous nerve during tendon extraction, leading to numbness on the medial aspect of the proximal knee. In the all-inside group, one patient had a postoperative knee extension limitation of 8°. This patient underwent ACL reconstruction on the 19th d after the injury. The reason for this finding may be that the operation was too close to the injury time, thus resulting in knee stiffness. Andernord *et al*[29] showed that ACL reconstruction in the early stage after injury increased the incidence of knee stiffness, and the mechanism may be related to the influence of operation timing on postoperative joint fibrosis.

In addition, the femoral tunnel is independently drilled through the foot location area of the anterolateral entrance of the positioning hook, which does not require excessive flexion of the affected knee and is in agreement with the concept of anatomic reconstruction[30,31], which effectively avoids pain caused by the impact of the non-anatomic reconstruction graft on the intercondylar fossa or posterior cruciate ligament during knee activity[23]. Lubowitz *et al*[17] also reached the same conclusion in a prospective randomized controlled study. The bone tunnel of the whole inner group of the tibia was drilled from inside-to-outside, which effectively preserved the cortical bone of the proximal tibia and avoided a burst fracture. In addition, the tunnel is thin outside and thick inside, and the tunnel communicating with the outside world is very small, so the joint fluid will not leak, thus reducing the risk of infection[21]. The tibia and femur sides of the all-inside group were suspended and fixed by a TightRope locking loop bone plate, which not only makes full use of the tendon-bone interface and promotes tendon-bone healing, but also effectively avoids the cutting effect of squeeze nails on the graft [32]. Compared with an Endobutton, the TightRope has an adjustable locking wire loop[31], so there is no need to reserve the loop turning distance when making the bone tunnel, which reduces bone loss and keeps the graft close to the bottom of the bone tunnel, thus effectively avoiding the "bungee effect" of suspensory fixation[33,34].

CONCLUSION

In conclusion, the all-inside technique has the same efficacy as the traditional technique with respect to knee function and exercise level, but has less postoperative pain, higher tendon utilization, and less injury. In addition, the all-inside technique has little damage to the proximal tibial cortex and only uses one hamstring muscle, which is of great value in simultaneous ACL reconstruction with high tibial osteotomy, multiple knee ligament reconstruction, and revision surgery for ACL re-tears.

ARTICLE HIGHLIGHTS

Research background

We compare clinical outcomes of knee anterior cruciate ligament (ACL) autograft reconstruction using all-inside quadruple semitendinosus (AIST) and traditional hamstring tendon (TBT) techniques.

Research motivation

To seek a good fixation method to reconstruct the ACL and reduce the failure rate.

Research objectives

To compare clinical outcomes of knee ACL autograft reconstruction using AIST and TBT techniques.

Research methods

From January 2017 to October 2019, the clinical data of 80 patients with ACL reconstruction were retrospectively analyzed, including 67 males and 13 females. The patients had an average age of 24.3 ±

3.1 years (age range: 18-33 years). The AIST technique was used in 42 patients and the TBT technique was used in 38 patients. The time between operation and injury, operative duration, postoperative visual analogue scale (VAS) score and knee functional recovery were recorded and compared between the two groups. The International Knee Documentation Committee (IKDC) and Lysholm scoring system were used to comprehensively evaluate clinical efficacy.

Research results

Eighty patients were followed for 24-36 mo, with an average of follow-up duration of 27.5 ± 1.8 mo. There were no significant differences in the time between surgery and injury, operative duration, IKDC and Lysholm scores of the affected knee at the last follow-up evaluation between the two groups. There were significant differences in VAS scores 1 d, 3 d, 7 d, 2 wk and 1 mo after surgery ($P < 0.05$). There was no significant difference in VAS score at 3 mo, 6 mo and 1 year after operation.

Research conclusions

The efficacy of the AIST ACL reconstruction technique was comparable to the TBT technique, but the postoperative pain was less with the AIST technique. Thus, the AIST technique is an ideal treatment choice for ACL reconstruction.

Research perspectives

Arthroscopic reconstruction of the ACL is the main method of repair, the optimal ACL reconstruction technique has not been determined.

FOOTNOTES

Author contributions: Xing GY designed the research study; Wang YT, Zhao Z and Wang MX performed the research; An BJ analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Third Medical Center of PLA General Hospital Institutional Review Board, No. KY2021-040.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrollment.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at xinggengyan123@163.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: China

ORCID number: Bai-Jing An 0000-0002-3434-2813; Yao-Ting Wang 0000-0002-1512-6285; Zhe Zhao 0000-0003-3300-4756; Ming-Xin Wang 0000-0002-3269-6482; Geng-Yan Xing 0000-0003-3997-4964.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Li X

REFERENCES

1 **Hettrich CM**, Dunn WR, Reinke EK; MOON Group, Spindler KP. The rate of subsequent surgery and predictors after anterior cruciate ligament reconstruction: two- and 6-year follow-up results from a multicenter cohort. *Am J Sports Med* 2013; **41**: 1534-1540 [PMID: 23722056 DOI: 10.1177/0363546513490277]

2 **Poulsen E**, Goncalves GH, Bricca A, Roos EM, Thorlund JB, Juhl CB. Knee osteoarthritis risk is increased 4-6 fold after

knee injury - a systematic review and meta-analysis. *Br J Sports Med* 2019; **53**: 1454-1463 [PMID: 31072840 DOI: 10.1136/bjsports-2018-100022]

3 **Ho B**, Edmonds EW, Chambers HG, Bastrom TP, Pennock AT. Risk Factors for Early ACL Reconstruction Failure in Pediatric and Adolescent Patients: A Review of 561 Cases. *J Pediatr Orthop* 2018; **38**: 388-392 [PMID: 27379789 DOI: 10.1097/BPO.0000000000000831]

4 **Dekker TJ**, Godin JA, Dale KM, Garrett WE, Taylor DC, Riboh JC. Return to Sport After Pediatric Anterior Cruciate Ligament Reconstruction and Its Effect on Subsequent Anterior Cruciate Ligament Injury. *J Bone Joint Surg Am* 2017; **99**: 897-904 [PMID: 28590374 DOI: 10.2106/JBJS.16.00758]

5 **Kay J**, Memon M, Marx RG, Peterson D, Simunovic N, Ayeni OR. Over 90 % of children and adolescents return to sport after anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 2018; **26**: 1019-1036 [PMID: 29332225 DOI: 10.1007/s00167-018-4830-9]

6 **Herzog MM**, Marshall SW, Lund JL, Pate V, Mack CD, Spang JT. Trends in Incidence of ACL Reconstruction and Concomitant Procedures Among Commercially Insured Individuals in the United States, 2002-2014. *Sports Health* 2018; **10**: 523-531 [PMID: 30355175 DOI: 10.1177/1941738118803616]

7 **Werner BC**, Yang S, Looney AM, Gwathmey FW Jr. Trends in Pediatric and Adolescent Anterior Cruciate Ligament Injury and Reconstruction. *J Pediatr Orthop* 2016; **36**: 447-452 [PMID: 25985368 DOI: 10.1097/BPO.0000000000000482]

8 **Dodwell ER**, Lamont LE, Green DW, Pan TJ, Marx RG, Lyman S. 20 years of pediatric anterior cruciate ligament reconstruction in New York State. *Am J Sports Med* 2014; **42**: 675-680 [PMID: 24477820 DOI: 10.1177/0363546513518412]

9 **Johnsen MB**, Guddal MH, Småstuen MC, Moksnes H, Engebretsen L, Storheim K, Zwart JA. Sport Participation and the Risk of Anterior Cruciate Ligament Reconstruction in Adolescents: A Population-based Prospective Cohort Study (The Young-HUNT Study). *Am J Sports Med* 2016; **44**: 2917-2924 [PMID: 27159313 DOI: 10.1177/0363546516643807]

10 **Allen MM**, Pareek A, Krych AJ, Hewett TE, Levy BA, Stuart MJ, Dahm DL. Are Female Soccer Players at an Increased Risk of Second Anterior Cruciate Ligament Injury Compared With Their Athletic Peers? *Am J Sports Med* 2016; **44**: 2492-2498 [PMID: 27261476 DOI: 10.1177/0363546516648439]

11 **Webster KE**, Feller JA, Leigh WB, Richmond AK. Younger patients are at increased risk for graft rupture and contralateral injury after anterior cruciate ligament reconstruction. *Am J Sports Med* 2014; **42**: 641-647 [PMID: 24451111 DOI: 10.1177/0363546513517540]

12 **Paterno MV**, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of Second ACL Injuries 2 Years After Primary ACL Reconstruction and Return to Sport. *Am J Sports Med* 2014; **42**: 1567-1573 [PMID: 24753238 DOI: 10.1177/0363546514530088]

13 **Salmon LJ**, Heath E, Akrawi H, Roe JP, Linklater J, Pinczewski LA. 20-Year Outcomes of Anterior Cruciate Ligament Reconstruction With Hamstring Tendon Autograft: The Catastrophic Effect of Age and Posterior Tibial Slope. *Am J Sports Med* 2018; **46**: 531-543 [PMID: 29244525 DOI: 10.1177/0363546517741497]

14 **Shelbourne KD**, Gray T, Haro M. Incidence of subsequent injury to either knee within 5 years after anterior cruciate ligament reconstruction with patellar tendon autograft. *Am J Sports Med* 2009; **37**: 246-251 [PMID: 19109531 DOI: 10.1177/0363546508325665]

15 **Wiggins AJ**, Grandhi RK, Schneider DK, Stanfield D, Webster KE, Myer GD. Risk of Secondary Injury in Younger Athletes After Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-analysis. *Am J Sports Med* 2016; **44**: 1861-1876 [PMID: 26772611 DOI: 10.1177/0363546515621554]

16 **Lubowitz JH**. No-tunnel anterior cruciate ligament reconstruction: the transtibial all-inside technique. *Arthroscopy* 2006; **22**: 900.e1-900.11 [PMID: 16904591 DOI: 10.1016/j.arthro.2006.06.003]

17 **Lubowitz JH**, Schwartzberg R, Smith P. Randomized controlled trial comparing all-inside anterior cruciate ligament reconstruction technique with anterior cruciate ligament reconstruction with a full tibial tunnel. *Arthroscopy* 2013; **29**: 1195-1200 [PMID: 23809454 DOI: 10.1016/j.arthro.2013.04.009]

18 **Browning WM 3rd**, Kluczynski MA, Curatolo C, Marzo JM. Suspensory Versus Aperture Fixation of a Quadrupled Hamstring Tendon Autograft in Anterior Cruciate Ligament Reconstruction: A Meta-analysis. *Am J Sports Med* 2017; **45**: 2418-2427 [PMID: 28068159 DOI: 10.1177/0363546516680995]

19 **Segawa H**, Omori G, Koga Y, Kameo T, Iida S, Tanaka M. Rotational muscle strength of the limb after anterior cruciate ligament reconstruction using semitendinosus and gracilis tendon. *Arthroscopy* 2002; **18**: 177-182 [PMID: 11830812 DOI: 10.1053/jars.2002.29894]

20 **Yosmaoglu HB**, Baltaci G, Ozer H, Atay A. Effects of additional gracilis tendon harvest on muscle torque, motor coordination, and knee laxity in ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1287-1292 [PMID: 21298255 DOI: 10.1007/s00167-011-1412-5]

21 **Volpi P**, Bait C, Cervellin M, Denti M, Prospero E, Morenghi E, Quaglia A. No difference at two years between all inside transtibial technique and traditional transtibial technique in anterior cruciate ligament reconstruction. *Muscles Ligaments Tendons J* 2014; **4**: 95-99 [PMID: 24932456]

22 **Connaughton AJ**, Geeslin AG, Uggen CW. All-inside ACL reconstruction: How does it compare to standard ACL reconstruction techniques? *J Orthop* 2017; **14**: 241-246 [PMID: 28360487 DOI: 10.1016/j.jor.2017.03.002]

23 **Benea H**, d'Astorg H, Klouche S, Bauer T, Tomoaia G, Hardy P. Pain evaluation after all-inside anterior cruciate ligament reconstruction and short term functional results of a prospective randomized study. *Knee* 2014; **21**: 102-106 [PMID: 24269603 DOI: 10.1016/j.knee.2013.09.006]

24 **Kouloumentas P**, Kavroudakis E, Charalampidis E, Kavroudakis D, Triantafyllopoulos GK. Superior knee flexor strength at 2 years with all-inside short-graft anterior cruciate ligament reconstruction *vs* a conventional hamstring technique. *Knee Surg Sports Traumatol Arthrosc* 2019; **27**: 3592-3598 [PMID: 30888448 DOI: 10.1007/s00167-019-05456-9]

25 **Boyle MJ**, Vovos TJ, Walker CG, Stabile KJ, Roth JM, Garrett WE Jr. Does adjustable-loop femoral cortical suspension loosen after anterior cruciate ligament reconstruction? *Knee* 2015; **22**: 304-308 [PMID: 25999126 DOI: 10.1016/j.knee.2015.04.016]

26 **Mayr R**, Heinrichs CH, Eichinger M, Coppola C, Schmoelz W, Attal R. Biomechanical comparison of 2 anterior cruciate ligament graft preparation techniques for tibial fixation: adjustable-length loop cortical button or interference screw. *Am J Sports Med* 2015; **43**: 1380-1385 [PMID: 25767269 DOI: 10.1177/0363546515574062]

27 **Desai VS**, Anderson GR, Wu IT, Levy BA, Dahm DL, Camp CL, Krych AJ, Stuart MJ. Anterior Cruciate Ligament Reconstruction With Hamstring Autograft: A Matched Cohort Comparison of the All-Inside and Complete Tibial Tunnel Techniques. *Orthop J Sports Med* 2019; **7**: 2325967118820297 [PMID: 30671490 DOI: 10.1177/2325967118820297]

28 **Zanchi N**, Posner M, Herickhoff P. All-Inside Tibial Tunnel Drilling: How to Calculate a Safe Drilling Length to Avoid Anterior Cortex Violation. *Arthrosc Tech* 2022; **11**: e2371-e2381 [PMID: 36632400 DOI: 10.1016/j.eats.2022.08.044]

29 **Andernord D**, Desai N, Björnsson H, Ylander M, Karlsson J, Samuelsson K. Patient predictors of early revision surgery after anterior cruciate ligament reconstruction: a cohort study of 16,930 patients with 2-year follow-up. *Am J Sports Med* 2015; **43**: 121-127 [PMID: 25325560 DOI: 10.1177/0363546514552788]

30 **Jones PE**, Schuett DJ. All-Inside Anterior Cruciate Ligament Reconstruction as a Salvage for Small or Attenuated Hamstring Grafts. *Arthrosc Tech* 2018; **7**: e453-e457 [PMID: 29868418 DOI: 10.1016/j.eats.2017.11.007]

31 **Papaloucas N**. All-Inside Technique for ACL-Reconstruction using a FlipCutter® and the TightRope® System. *Surg Technol Int* 2018; **32**: 337-345 [PMID: 29791702]

32 **Nuelle CW**, Balldin BC, Slone HS. All-Inside Anterior Cruciate Ligament Reconstruction. *Arthroscopy* 2022; **38**: 2368-2369 [PMID: 35940736 DOI: 10.1016/j.arthro.2022.06.001]

33 **Monaco E**, Fabbri M, Redler A, Gaj E, De Carli A, Argento G, Saithna A, Ferretti A. Anterior cruciate ligament reconstruction is associated with greater tibial tunnel widening when using a bioabsorbable screw compared to an all-inside technique with suspensory fixation. *Knee Surg Sports Traumatol Arthrosc* 2019; **27**: 2577-2584 [PMID: 30406408 DOI: 10.1007/s00167-018-5275-x]

34 **Zeman P**, Kautzner J, Havel O, Matějka J, Pavelka T, Havlas V. [Anatomical All-Inside Anterior Cruciate Ligament Reconstruction Using Quadrupled Semitendinosus Tendon Graft with Posteromedial Harvest - Clinical Results of Prospective Study at a Minimum 12-Months Follow-up]. *Acta Chir Orthop Traumatol Cech* 2018; **85**: 94-101 [PMID: 30295594]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3204-3210

DOI: 10.12998/wjcc.v11.i14.3204

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Positioning and design by computed tomography imaging in neuroendoscopic surgery of patients with chronic subdural hematoma

Xue-Jian Wang, Yu-Hua Yin, Long-Yao Zhang, Zhi-Feng Wang, Cheng Sun, Zhi-Ming Cui

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Shariati MBH, Iran; Velnar T, Slovenia

Received: December 9, 2022
Peer-review started: December 9, 2022
First decision: March 10, 2023
Revised: March 22, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Xue-Jian Wang, Long-Yao Zhang, Zhi-Feng Wang, Department of Neurosurgery, Affiliated Hospital 2 to Nantong University, Nantong 226001, Jiangsu Province, China

Yu-Hua Yin, Department of Neurosurgery, Renji Hospital, Shanghai Jiao Tong University, Shanghai 200000, China

Cheng Sun, Jiangsu Provincial Key Laboratory of Nerve Regeneration, Nantong University, Nantong 226001, Jiangsu Province, China

Zhi-Ming Cui, Department of Orthopedic, Affiliate Hospital 2 to Nantong University, Nantong 226001, Jiangsu Province, China

Corresponding author: Xue-Jian Wang, MD, PhD, Professor, Surgeon, Department of Neurosurgery, Affiliated Hospital 2 to Nantong University, No. 666 Shengli Road, Chongchuan District, Nantong 226001, Jiangsu Province, China. 6841441@163.com

Abstract

BACKGROUND

Neuroendoscopy is a very useful technique to Chronic Subdural Hematoma (CSH). But how to achieve the goal of treatment more minimally invasive?

AIM

To develop a simple, fast and accurate preoperative planning method in our way for endoscopic surgery of patients with CSH.

METHODS

From June 2018 to May 2020, forty-two patients with CSH, admitted to our hospital, were performed endoscopic minimally invasive surgery; computed tomography (CT) imaging was employed to locate the intracerebral hematoma and select the appropriate endoscopic approach before the endoscopic surgery. The clinical data and treatment efficacy were analyzed.

RESULTS

According to the learning of CT scanning images, the surgeon can accurately design the best minimally invasive neuroendoscopic surgical approach and realize the precise positioning and design of the drilling site of the skull and the

size of the bone window, so as to provide the most effective operation space with the smallest bone window. In this group, the average operation time was only about 1 h, and the clearance rate of hematoma was about 95%.

CONCLUSION

Patients with CSH can achieve good therapeutic effect by using our way to positioning and design to assist the operation of CSH according to CT scan and image, and our way is very useful and necessary.

Key Words: Chronic subdural hematoma; Neurosurgery neuroendoscopy; Positioning and design; Bone window design

Core Tip: Via minimally invasive neuroendoscopic surgery, one can use smaller surgical incisions and bone windows to achieve effective removal of intracranial hematoma, minimal trauma to brain tissue, and effective reduction of recurrence rate. However, due to variations in hematoma site, shape, size and degree of clots, the location of bone hole and approaches for minimally invasive endoscopy are also different for each patient. How to accurately locate the intracerebral hematoma in chronic subdural hematoma (cSDH) patients before surgery and design an individualized approach for minimally invasive endoscopy is one of the keys to success. To better treat cSDH patients using minimally invasive neuroendoscopy, we use computed tomography scanning to locate cSDH and select the best endoscopic micro-mirror approach before performing minimally invasive neuroendoscopic surgery and analyzed the clinical data and treatment efficacy.

Citation: Wang XJ, Yin YH, Zhang LY, Wang ZF, Sun C, Cui ZM. Positioning and design by computed tomography imaging in neuroendoscopic surgery of patients with chronic subdural hematoma. *World J Clin Cases* 2023; 11(14): 3204-3210

URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3204.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3204

INTRODUCTION

Chronic subdural hematoma (cSDH) is one of the common diseases in neurosurgery, but its pathogenesis is still not fully understood[1-3]. cSDH can be caused by many convenient factors and presented with different manifestations and symptoms. Although many methods including drilling drainage, burr hole surgery and craniotomy have been used to treat cSDH[4-6], for patients with muscularized and separated hematoma, their treatment efficacy is poor, and the operation risk and recurrence rate are high[6-8]. With the development of microinvasive neurosurgical techniques and neuroendoscopy, cSDH evacuation with minimally invasive neuroendoscopy has become an important means of surgical treatment. Via minimally invasive neuroendoscopic surgery, one can use smaller surgical incisions and bone windows to achieve effective removal of intracranial hematoma, minimal trauma to brain tissue, and effective reduction of recurrence rate[1,2]. However, due to variations in hematoma site, shape, size and degree of clots, the location of bone hole and approaches for minimally invasive endoscopy are also different for each patient. How to accurately locate the intracerebral hematoma in cSDH patients before surgery and design an individualized approach for minimally invasive endoscopy is one of the keys to success. In clinical work, we need to find a simple and reliable way to design surgical incision and bone window, so as to more easily achieve minimally invasive surgery, which is very necessary[1]. To better treat cSDH patients using minimally invasive neuroendoscopy, surgeons in our Department, treated 42 cSDH patients from June 2018 to May 2020 using computed tomography (CT) scanning to locate cSDH and select the best endoscopic micro-mirror approach before performing minimally invasive neuroendoscopic surgery and analyzed the clinical data and treatment efficacy. The summary is as follows.

MATERIALS AND METHODS

Clinical information

A total of 42 cSDH patients (26 males and 16 females) at age of 34–76 years old with average of 55.3 years old were enrolled in the study. The amount of hematoma in these patients was calculated according to the Tada formula. The average amount of blood loss was 64.3 ± 15.2 mL. The Glasgow Coma score at admission was 13–15 points for 29 patients and 9–12 points for 13 patients.

CT scan and image reconstruction methods for cSDH patients

Based on the emergency CT results of cSDH patients at admission, the location, shape and the thickest part of the intracranial hematoma were estimated to initially design the possible approach of minimally invasive endoscopic surgery. The approach was used as the alternative bone window site for the minimally invasive surgery. Before operation, a 64-slice spiral CT scanner was used to perform the conventional head CT scan with the scan line parallel to the orbitomeatal line and the scan range from the base to the top of the skull.

Minimally invasive neuroendoscopic surgery positioning and techniques

After the preoperative CT scan (Figure 1A and B), the thickest point of the hematoma was selected as the approximate location of the skull bone window for minimally invasive endoscopic surgery. (Figure 1A) On the thickest layer of the hematoma cavity in the CT image, make a straight line perpendicular to brain surface, which cross the skull at point A' at the inner side and point B' at the outer side. At the edge of the hematoma at the layer, find points C' and D' with distance to A' and B' equal to the thickness of the hematoma, respectively. Connect and extend C'A' and D'A', which intersect at points E' and F' with the surface of the skull, respectively (Figure 1A and C). The length and distance of E'F' were the optimal size and range of the bone window (Figure 1C and D). Similarly, the range of bone windows could also be found in the coronal position, so that a complete bone window can be formed.

The operation was performed using a rigid Storz neuroendoscope with zero viewing angle along with special TV monitoring and video recording system, conventional endoscopic special surgical instruments and deep microsurgery instruments. In detail, (1) Place special locating marker on the surface of the scalp according to the range of bone window obtained previously; (2) Determine the position of the scalp incision; (3) Cut the scalp skin as needed and keep it open using an opener; (4) Drill a hole on the skull, and mill out the bone window using a milling cutter; (5) Radially cut the dura mater with a sharp knife; (6) Remove the hematoma and mechanized tissues using a attractor under the guide of the endoscope; (7) Coagulate the separating tissue using a bipolar electrocoagulation followed by suction, and if necessary, cut apart the separating tissue using scissors; (8) Once confirmed the surrounding area was cleaned under the direct vision of the endoscope, coagulate the local active bleeding points using a bipolar electrocoagulation method or special endoscopic bipolar coagulation; (9) Rinse the hematoma cavity repeatedly to make sure no further bleeding; and (10) At the end of the operation, place the drainage tube in the hematoma cavity under the direct view of the neuroendoscope, suture the dura mater, return the bone flap and suture the skin.

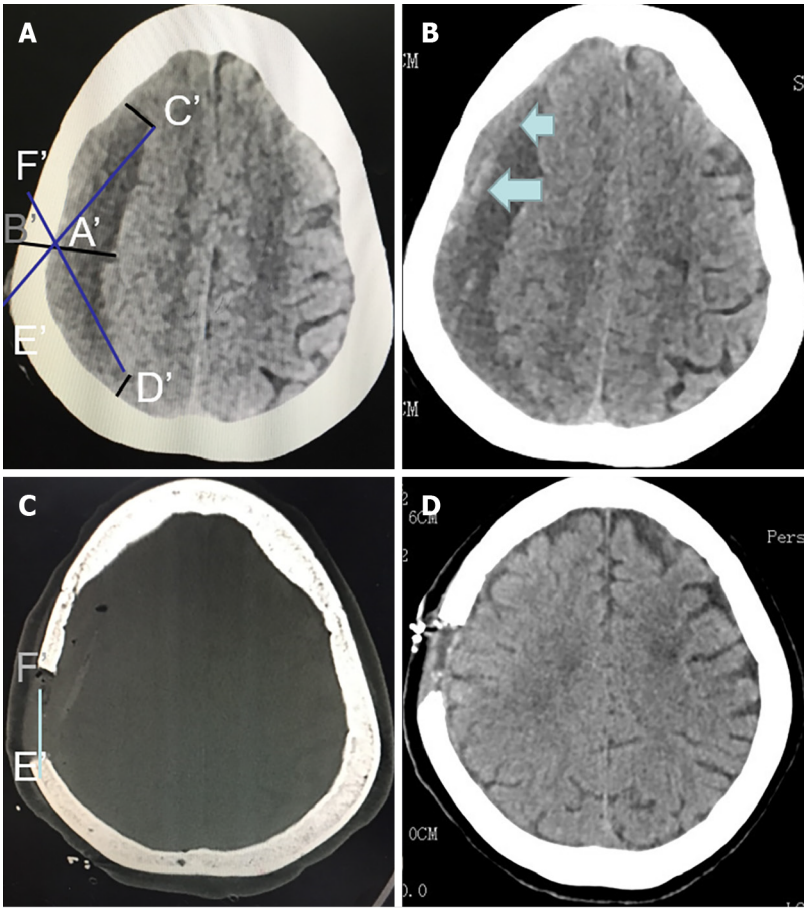
RESULTS

CT positioning and surgical planning methods can quickly and effectively determine the scope of surgical incisions and bone windows, effectively providing a surgical operation window for neuroendoscopic surgery. Figure 1 shows the design of bone window before head CT surgery for a female with cSDH. Figure 2 shows the results of surgical incision and intraoperative findings before and after minimally invasive surgery for this patient.

According to the surgical approach design, the surgeon can accurately design the optimal approach for minimally invasive endoscopic surgery, therefore achieving accurate positioning of the skull drilling site and accurate determination of the bone window size, and reducing the time for surgical preparation, anesthesia and operation. In this study, the average operation time was only about 1 h and the hematoma clearance rate was about 95%.

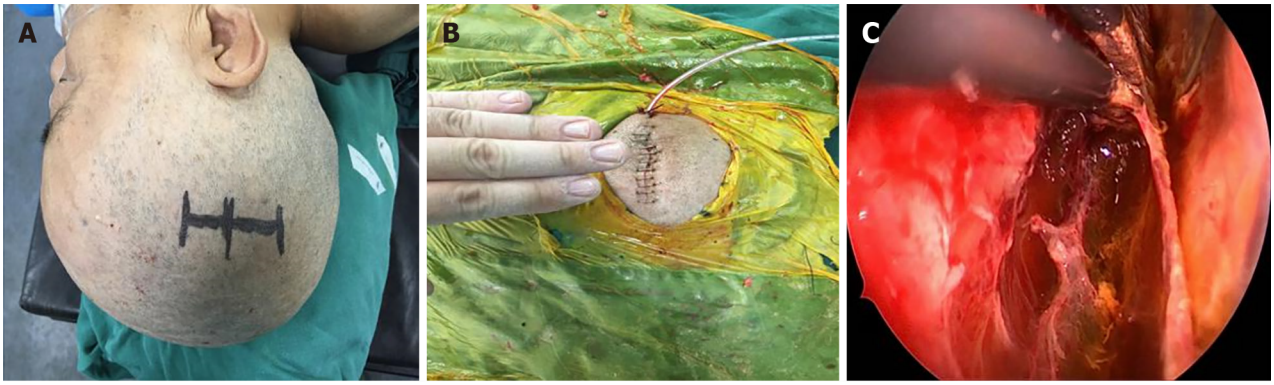
DISCUSSION

cSDH is one of the most common diseases in neurosurgery, with a prevalence rate of 8.2–13.1/100,000[9,10], accounting for about 10% of various intracranial hematomas. The disease is caused by many factors and can be treated using multiple methods including drilling drainage, cone craniotomy, and craniotomy hematoma removal. Among all cSDH patients, 25% have subdural hematoma and 14% bilateral hematoma. Studies have shown that head trauma is the main reason for the formation of cSDH, and is related to brain atrophy, low intracranial pressure and increased venous tension[6,11].



DOI: 10.12998/wjcc.v11.i14.3204

Figure 1 Head computed tomography imaging and surgical design. A: On the thickest layer of the hematoma cavity in the computed tomography (CT) image, make a straight line perpendicular to brain surface, which cross the skull at point A' at the inner side and point B' at the outer side. At the edge of the hematoma at the layer, find points C' and D' with distance to A' and B' equal to the thickness of the hematoma, respectively. Connect and extend C'A' and D'A', which intersect at points E' and F' with the surface of the skull, respectively; B: Axial CT scan showing septated right chronic subdural hematoma with two clear compartments. Small blue arrows indicate the membrane to be opened; C: Axial CT scan showing the range of bone window; and D: Axial CT scan showing the postoperative intracranial conditions. CT: Computed tomography.



DOI: 10.12998/wjcc.v11.i14.3204

Figure 2 Surgical incision and intraoperative image. A: Preoperative planning of incisions; B: Postoperative planning of incisions; and C: Endoscopic view of the subdural space identifying the membrane with its rich microvascularization and organized blood clot.

With the development of minimally invasive neuroendoscopic techniques and surgical instruments, cSDH can be visually and rapidly cleared *via* small bone hole and scalp incision through minimally invasive neuroendoscopic surgery[2]. As a minimally invasive, visual and rapid surgical treatment for direct removal of hematoma and capsule for cSDH patients, minimally invasive neuroendoscopic surgery has become an important alternative for surgical treatment of cSDH. Especially for those with muscularized and separated hematoma, it has advantage to avoid craniotomy of large bone flap[6].

Because the location, shape and size of intracranial hematoma in cSDH patients are different, it is necessary to design a personalized minimally invasive surgery for each cSDH patient. Designing a personalized minimally invasive surgical procedure is one of the key factors affecting the success of minimally invasive neuroendoscopic treatment of cSDH. At present, very few studies have investigated the design of minimally invasive neuroendoscopy for cSDH[1,7]. In traditional neurosurgery for cSDH, surgeons mainly determine the approximate location of cSDH and its surrounding structures based on the results of conventional CT scans, as well as physicians' anatomic knowledge and experiences, thus selecting the point of drilling drainage or the incision of the craniotomy[3]. However, the position of the drilling drainage is required to be lower, and the traumatic lesions of craniotomy are large, while neuroendoscopy is required to be performed under the smallest minimally invasive incision to achieve the purpose of adequate surgical operation. Under the minimally invasive incision, sufficient surgical operation is achieved[8]. Therefore, in actual surgery, in order to avoid deviations in positioning, it is often necessary to make a relatively large scalp incision and bone window. Due to its large error, the traditional method often fails to meet the practical needs of precise positioning cSDH under a minimally invasive neuroendoscope[8]. With the development of imaging technology, stereotactic technology and neuron navigation system have become important means of neurosurgical positioning. However, stereotactic hematoma positioning needs a long time for surgery preparation. Although the neuron navigation system is a commonly used surgical positioning method in neurosurgery, it also needs many steps such as installing navigation and positioning frames, navigation registration and other steps before the operation, which also needs longer time for preparation[12,13]. In addition, stereotactic and neuron navigation techniques are only used to guide specific locations. For any incision and operational positioning, there is still need to design an adequate approach. Therefore, finding an accurate, reliable, intuitive, simple, fast, and inexpensive positioning method has become an important topic for minimally invasive neuroendoscopy for cSDH.

In order to explore a surgical positioning method for applying minimally invasive neuroendoscopy for cSDH, we firstly estimated the location and shape and its thickest part to the inner plate of the skull of cSDH based on the results of emergency CT. We then selected the CT at the thickest layer of the hematoma cavity to make a straight line perpendicular to the brain surface at the thickest part, which cross the skull at point A at the inner side and point B at the outer side. At the edge of the hematoma at the layer, the points C and D with distance to A and B equal to the thickness of the hematoma can be found, respectively. We then connected and extended CA and DA, which intersected at points E and F with the surface of the skull, respectively. The length and distance of EF were the optimal size and range of the bone window. In this study, we applied this technique for 42 cSDH patients and successfully completed the operation. The average operation time was only about 1 h, and the hematoma clearance rate was about 95%. Therefore, the positioning technology used in this study is simple and requires no stereotactic system, navigation system, no need to install a positioning head frame or a positioning frame before surgery. Over all, the technique needs shorter time for surgical preparation and anesthesia, and is less expensive, more flexible and more efficient, which not only saves the cost of hospitals and departments, but also reduces the medical expenses and economic burden of the patients.

Minimally invasive neuroendoscopy for cSDH as a minimally invasive surgery with high-efficiency, rapidness, reliable hemostasis and less bleeding in combination with CT imaging positioning will further improve the treatment efficacy and efficiency for cSDH. With the continuous improvement of neuroendoscopy and imaging technology, minimally invasive neuroendoscopy for cSDH will be more complete, accurate and popular.

CONCLUSION

Patients with Chronic Subdural Hematoma (CSH) can achieve good therapeutic effect by using our way to positioning and design to assist the operation of CSH according to CT scan and image, and our way is very useful and necessary.

ARTICLE HIGHLIGHTS

Research background

This technology can be further promoted and applied in clinical practice, which will certainly achieve better clinical therapeutic effect, improve the curative effect of surgery, and be more minimally invasive and reasonable.

Research motivation

Patients with Chronic Subdural Hematoma (CSH) can achieve good therapeutic effect by using our way to positioning and design to assist the operation of CSH according to computed tomography (CT) scan and image, and our way is very useful and necessary.

Research objectives

We designed a new surgical incision method of neuroendoscopy under CT imaging technology for chronic subdural hematoma (cSDH), and achieved satisfactory therapeutic effect through the application of the above methods.

Research methods

A minimally invasive surgical incision design suitable for cSDH under neuroendoscopy was designed by using neuroendoscopy technology, combined with the study of CT and other imaging technologies.

Research results

To study more convenient methods of surgical incision and bone window size for the treatment of cSDH under neuroendoscopy, so as to make the operation more minimally invasive.

Research conclusions

The bone window for the treatment of cSDH under neuroendoscopy needs to vary from person to person; otherwise, the bone window may be too large or too small during the operation, which may affect the operation.

Research perspectives

Neuroendoscopy is a very useful technique to CSH. But how to achieve the goal of treatment more minimally invasive? How can incisions be designed and positioned to be more minimally invasive?

FOOTNOTES

Author contributions: Wang XJ and Yin YH conceived and designed the trial; Wang XJ and Wang ZF collected the date; Sun C and Cui ZM analyzed the date; Wang XJ and Zhang LY wrote the manuscript; and all authors contributed to the article and approved the submitted version.

Institutional review board statement: This research has been approved by the ethics committee of our department.

Informed consent statement: Informed consent has been obtained and this investigation has been conducted according to the principles expressed in the Declaration of Helsinki. And the authors have obtained written informed consent of all the patients.

Conflict-of-interest statement: All the authors have no any conflict-of-interest statement.

Data sharing statement: All data is saved by corresponding author. If you need relevant information, you can contact corresponding author.

Country/Territory of origin: China

ORCID number: Xue-Jian Wang 0000-0003-0389-5674; Yu-Hua Yin 0000-0003-3760-0264; Long-Yao Zhang 0000-0001-7460-7903; Zhi-Feng Wang 0000-0001-8154-0356; Cheng Sun 0000-0003-3388-9179; Zhi-Ming Cui 0000-0002-0939-5550.

Corresponding Author's Membership in Professional Societies: Senior Member of the American Society of Peripheral Neurosurgery.

S-Editor: Liu XF
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Pevehouse BC**, Bloom WH, Mckissock W. Ophthalmologic aspects of diagnosis and localization of subdural hematoma. An analysis of 389 cases and review of the literature. *Neurology* 1960; **10**: 1037-1041 [PMID: 13735079 DOI: 10.1212/WNL.10.11.1037]

2 **Hashimoto N**, Sakakibara T, Yamamoto K, Fujimoto M, Yamaki T. Two fluid-blood density levels in chronic subdural

hematoma. Case report. *J Neurosurg* 1992; **77**: 310-311 [PMID: 1625021 DOI: 10.3171/jns.1992.77.2.0310]

3 **Masopust V**, Netuka D, Häckel M. Chronic subdural haematoma treatment with a rigid endoscope. *Minim Invasive Neurosurg* 2003; **46**: 374-379 [PMID: 14968410 DOI: 10.1055/s-2003-812507]

4 **Scotton WJ**, Kolias AG, Ban VS, Crick SJ, Sinha R, Gardner A, Massey K, Minett T, Santarius T, Hutchinson PJ. Community consultation in emergency neurosurgical research: lessons from a proposed trial for patients with chronic subdural haematomas. *Br J Neurosurg* 2013; **27**: 590-594 [PMID: 23767683 DOI: 10.3109/02688697.2013.793291]

5 **Ueba T**, Yasuda M, Inoue T. Endoscopic burr hole surgery with a curettage and suction technique to treat traumatic subacute subdural hematomas. *J Neurol Surg A Cent Eur Neurosurg* 2015; **76**: 63-65 [PMID: 25306208 DOI: 10.1055/s-0033-1358606]

6 **Berhouma M**, Jacquesson T, Jouanneau E. The minimally invasive endoscopic management of septated chronic subdural hematomas: surgical technique. *Acta Neurochir (Wien)* 2014; **156**: 2359-2362 [PMID: 25223748 DOI: 10.1007/s00701-014-2219-1]

7 **Callovini GM**, Bolognini A, Callovini G, Gammone V. Primary enlarged craniotomy in organized chronic subdural hematomas. *Neurol Med Chir (Tokyo)* 2014; **54**: 349-356 [PMID: 24305027 DOI: 10.2176/nmc.oa2013-0099]

8 **Ducruet AF**, Grobelny BT, Zacharia BE, Hickman ZL, DeRosa PL, Andersen KN, Sussman E, Carpenter A, Connolly ES Jr. Erratum to: The surgical management of chronic subdural hematoma. *Neurosurg Rev* 2015; **38**: 771 [PMID: 26138024 DOI: 10.1007/s10143-015-0644-0]

9 **Asghar M**, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly--a North Wales experience. *J R Soc Med* 2002; **95**: 290-292 [PMID: 12042376 DOI: 10.1258/jrsm.95.6.290]

10 **Kudo H**, Kuwamura K, Izawa I, Sawa H, Tamaki N. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. *Neurol Med Chir (Tokyo)* 1992; **32**: 207-209 [PMID: 1378564 DOI: 10.2176/nmc.32.207]

11 **Haines DE**, Harkey HL, al-Mefty O. The "subdural" space: a new look at an outdated concept. *Neurosurgery* 1993; **32**: 111-120 [PMID: 8421539 DOI: 10.1097/00006123-199301000-00017]

12 **Kim IS**, Son BC, Lee SW, Sung JH, Hong JT. Comparison of frame-based and frameless stereotactic hematoma puncture and subsequent fibrinolytic therapy for the treatment of supratentorial deep seated spontaneous intracerebral hemorrhage. *Minim Invasive Neurosurg* 2007; **50**: 86-90 [PMID: 17674294 DOI: 10.1055/s-2007-982503]

13 **Yadav YR**, Ratre S, Parihar V, Bajaj J, Sinha M, Kumar A. Endoscopic Management of Chronic Subdural Hematoma. *J Neurol Surg A Cent Eur Neurosurg* 2020; **81**: 330-341 [PMID: 32176925 DOI: 10.1055/s-0039-1698388]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3211-3223

DOI: 10.12998/wjcc.v11.i14.3211

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Evaluation of chronic idiopathic tinnitus and its psychosocial triggers

Sherifa Ahmed Hamed, Fadia Ahmed Attiah, Mohamed Fawzy, Mohamed Azzam

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sahin Y, Turkey; Sfera A, United States

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: February 2, 2023
Revised: February 18, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: May 16, 2023

Sherifa Ahmed Hamed, Fadia Ahmed Attiah, Mohamed Fawzy, Department of Neurology and Psychiatry, Assiut University, Faculty of Medicine, Assiut 71516, Egypt

Mohamed Azzam, Department of Otolaryngology, Assiut University, Faculty of Medicine, Assiut 71516, Egypt

Corresponding author: Sherifa Ahmed Hamed, MD, Professor, Department of Neurology and Psychiatry, Assiut University, Faculty of Medicine, Assiut University Street, Nayla Khatoun, Gharb District, Assiut 71516, Egypt. hamedsherifa@aun.edu.eg

Abstract

BACKGROUND

The tinnitus susceptibility patterns in relation to different psychological and life stressors are unknown in different cultures.

AIM

To determine the comorbid psychosocial factors and behaviors associated with tinnitus and the predictors for the increase in its severity.

METHODS

Participants were 230 adults (males = 70; females = 160; mean age = 38.6 ± 3.3). They underwent audiograms, speech discrimination and masking testing, and neuropsychiatric evaluation. Measures used for assessment included tinnitus handicap inventory, depression anxiety stress scale 21 (DASS-21), perceived stress scale (PSS), and insomnia severity index (ISI).

RESULTS

Patients had mean duration of tinnitus of 11.5 ± 2.5 mo. They had intact hearing perception at 250-8000 Hz and 95 (41.3%) had aggravation of tinnitus loudness by masking noise. Decompensated tinnitus was reported in 77% (n = 177). The majority had clinically significant insomnia (81.3%), somatic symptoms (75%) other than tinnitus and perceived moderate (46.1%) and high (44.3%) stress to tinnitus. The severe/extremely severe symptoms of depression, anxiety and stress were reported in 17.4%, 35.7% and 44.3%, respectively. Patients with decompensated type had significantly higher scores for ISI (P = 0.001) and DASS-21 (depression = 0.02, anxiety = 0.01, stress = 0.001) compared to those with compensated tinnitus. Psychiatric interviewing showed that 35.7% had non-specific anxiety disorder, 17.4% had major depression, and 19.6% fulfilled the criteria of

somatization disorder. Multivariate analysis showed that the only independent predictors for tinnitus severity were the duration of tinnitus [odd ratios (OR) = 0.832, 95%CI: 0.640-1.158; *P* = 0.001] and PSS (OR = 0.835, 95%CI: 0.540-1.125; *P* = 0.001) scores.

CONCLUSION

To the best of our knowledge, this is the first study in our culture to evaluate the causal relationship between psychological factors and tinnitus onset, severity and persistence. Tinnitus could be the earliest and dominant somatic symptom induced by life stressors and psychological vulnerabilities. Therefore, multidisciplinary consultation (psychologists, psychiatrists, and neurologists) is important to acknowledge among the audiologists and otolaryngologists who primarily consult patients.

Key Words: Chronic tinnitus; Idiopathic; Stress; Anxiety; Insomnia; Somatization; Psychosocial factors

Core Tip: Tinnitus is a frequent subjective symptom in adults. About 15%-30% of patients with tinnitus have no clinically manifested hearing loss or no subclinical sensorineural hearing loss when evaluated using advanced auditory testing. There are several comorbid psychiatric conditions and disorders in sufferers of tinnitus, which may contribute to its persistence and increased severity. They include stress, anxiety, depression, sleep disturbance, increased forgetfulness, major depression and anxiety, and somatoform disorders. However, the relationship of these comorbidities with tinnitus onset is unclear. Also the psychosocial triggers for initiation, increased severity, and chronicity of tinnitus are understudied in many areas of the world.

Citation: Hamed SA, Attiah FA, Fawzy M, Azzam M. Evaluation of chronic idiopathic tinnitus and its psychosocial triggers. *World J Clin Cases* 2023; 11(14): 3211-3223
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3211.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3211

INTRODUCTION

Tinnitus is the most common subjective auditory symptom with an estimated prevalence of 8%-20% (~14.4%) in adults and 35%-45% (~40%) in individuals aged ≥ 55-years-old. The prevalence of tinnitus is reduced after the 7th decade[1]. It has also been reported that tinnitus is a life-lasting disabling problem in 0.5%-2.5% of patients[1-3] and a handicapping problem in 1%-2%[4]. Tinnitus is defined as a sound heard in the ears or ears and head in absence of external auditory source. It is commonly described as ringing, whistling, buzzing, roaring and clicking and rarely as a combination of sounds or a non-defined sound. Some audiologists suggested that the majority of patients with tinnitus (~90%) might have a degree of hearing loss which varied from severe to very mild or subclinical[5]. However, others found tinnitus in 30% of patients without clinically manifest sensorineural hearing loss (SNHL) and in 15% of patients without evidence of hearing impairment using advanced testing for detection of subclinical deficits[6]. They also suggested that persistence of tinnitus and aggravation of its severity overtime (decompensated tinnitus) highly indicate the presence of psychological or other physical (to less extent) comorbid conditions, because tinnitus due to lesions in the auditory system is often transient and disappears overtime due to brain filtering mechanisms regardless to the cause[6]. The common comorbid conditions in patients with chronic tinnitus include emotional stresses, mood swings and anxiety symptoms (28%-49%)[7-9], sleep problems (10%-80%)[10,11], poor attention and concentration (up to 70%)[9], and chronic physical diseases (21%-47%)[12]. Research studies have also reported that 45%-78% of patients with chronic tinnitus satisfied the criteria of at least one psychiatric disorder(s), for example, affective (~23.5%), anxiety (~35%) and somatoform (~25%) disorders[2,8,9,13-20].

Various medications and interventions are used in the treatment of tinnitus including vasodilators, vitamins, calcium channel blockers, antihistamines, anticonvulsants (*e.g.*, valproate), gabapentin, antidepressants, anxiolytics, psychotherapy, biofeedback, and hypnosis. However, none have been approved by the United States Food and Drug Administration. Many clinicians agree that combined management strategies are more effective for the treatment of tinnitus[7,21-24].

Whether psychological/psychiatric factors are risk factors for tinnitus is understudied in different countries. Therefore, in this work, we aimed to determine the comorbid psychosocial factors and behaviors associated with tinnitus's onset, severity, and chronicity; as well as the predictors for the increase in its severity.

MATERIALS AND METHODS

Study design and participants

This was a cross-sectional study, which included 230 adults (males = 70; females = 160) with chronic tinnitus. Patients were recruited from January 2020 to July 2022 from the outpatient Otolaryngology and Neuropsychiatry Clinics of Assiut University Hospital, Assiut Egypt. The inclusion criteria were: (1) Adults (20-55-years-old); (2) self-reported tinnitus as a main physical problem at presentation; (3) duration of tinnitus ≥ 6 mo; (4) normal results of previous routine audiometric testing which were done at different time points; and (5) normal imaging (computed tomography or magnetic resonance imaging) of the brain and cervical spine or cord. Exclusion criteria were: (1) Pulsatile tinnitus; (2) manifested hearing loss; (3) local cause that explains tinnitus, for example, impacted wax, infections/inflammation of the ear, Meniere disease, otosclerosis, and presbycusis; (4) medical, neurological, or psychiatric disease, which can cause hearing impairment (*e.g.*, diabetes, anemia, thyroid disease, stroke, small vessel disease, demyelinating lesions, migraine, epilepsy, tumor as acoustic neuromas, and psychosis); (5) head or cervical vertebra injuries; and (6) ototoxic drug use (*e.g.*, aspirin, quinine, aminoglycosides, cancer chemotherapy as cisplatin).

Procedures

Data collection included: (1) Demographics: age, sex, residence, marital state, educational level (classified as low if could not read or write, can read, primary or secondary school education; or high if high school, college, *etc*.) and socioeconomic state. The socioeconomic scale (SES) was used for determination of socioeconomic state. SES is a structured questionnaire used to gather data related to parents' education, family income per month, sanitation, and crowding index. SES total score is 30. SES was classified as high (score > 25 to ≥ 30), middle (score > 20 to ≥ 25), low (score ≥ 15 to ≤ 20), or very low (score < 15)[25]. Clinical characteristics were: completion of otological, medical, neurological, and psychiatric histories and examinations. Tinnitus inquiries included: Its duration, origin, description, laterality, intensity, pattern, and time of occurrence. The results of previous evaluations (audiograms, laboratory investigations and drug prescriptions for tinnitus) were also collected. The diagnosis of a psychiatric disorder was done according to the Structured Clinical Interviewing using Arabic version of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised (DSM-IV-TR)[26,27].

The diagnostic work-up questionnaires included: The Tinnitus handicap inventory (THI)[28] consists of 25 items, with 3 responses for each which are 1st response or "yes" equals 4 points, 2nd response or "sometimes" equals 2 points, or a 3rd response "no" equals 0. Its total scores range from 0 to 100 points. Higher scores indicate greater perceived handicap. Tinnitus severity was classified as: (1) Grade 1 or slight (score 0-16) if tinnitus was heard only in quite environment, masked easily with environmental noise and did not interfere with sleep or daily activities; (2) Grade 2 or mild (score 18-36) if tinnitus was masked easily by environmental noise, neglected during life activities and occasionally interfered with sleep, but did not interfere with daily activities; (3) Grade 3 or moderate (score 38-56) if tinnitus could be noticed in noisy environment but the individual could still perform the daily activities; (4) Grade 4 or severe (score 58-76) if tinnitus was always heard, disturbed sleep and could interfere with daily activity; and (5) Grade 5 or catastrophic (score 78-100) if tinnitus was severe enough to interfere with any life activity. For comparative statistics, tinnitus was divided according to its severity into compensated tinnitus if THI grades were 1or 2 (*i.e.* slight or mild) and decompensated tinnitus if THI grades were 3, 4, or 5 (*i.e.* moderate, severe or catastrophic).

Insomnia severity index (ISI) is a 7-item questionnaire[29]. The total score categories are: (1) No clinically significant insomnia (score 0-7); (2) sub-threshold insomnia (score 8-14); (3) moderately severe clinically significant insomnia (score 15-21); and (4) severe clinically significant insomnia (score 22-28).

Depression anxiety stress scale 21 (DASS-21)[30] is 21 items, which produces results for the recent (past week) symptoms. The DASS-21 scores for depression or anxiety or stress symptoms were determined separately. They were classified as normal, mild, moderate, severe, and extreme.

Perceived stress scale (PSS)[31,32] is a 14-item scale. Each item is rated by a 5-point Likert scale which range from 0: "never" to 4: "very often." The total score of each individual was calculated by reversing the scores on these positive seven items (B4, B5, B6, B7, B9, B10, and B13), followed by adding the responses to the rest of the 14 items. PSS does not reflect a specific diagnosis or course for treatment; therefore, it has no cut-off value. PSS scores range from 0 to 56. Accordingly, subjects were classified according to the perceived stress level to tinnitus (as stressor) into: (1) Perceived low stress if scores were 0 to 13; (2) perceived moderate stress if scores were 14 to 26; and (3) perceived high stress if scores were 27 to 40.

A designed questionnaire for determination of life stressors. The term "life stressor" is defined as extraordinary and undesirable major life events or conditions of clear onset and offset. We designed a simple questionnaire based on the common major stressors in our population which included financial, marital, siblings, changes in personal work or home activities, troubles with law, and problems with close relatives or a friend.

Basic audiologic evaluation: It included pure tone audiometry, which was assessed at frequency ranges from 250 Hz to 8000 Hz (interacoustic model AC 40), tympanometry (interacoustic model AZ 26), measurement of acoustic reflex threshold (interacoustic model AZ 26), and speech discrimination test. Speech discrimination score (SDS) is defined as the hearing level to understand and repeat at least 25 Arabic phonetically balanced monosyllabic words. SDS of 90% to 100% was considered normal. For patients who noticed tinnitus at quite occasions (*e.g.*, at bedtime), a masking test was also done using a white noise machine.

Statistical analysis

Data were analyzed with SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, United States). The distributional properties of variables and appropriateness of the analyses of covariance were confirmed. Comparative statistics were done using the two-sided Student's *t*-test, χ^2 test, and one way analysis of variance with Bonferroni post hoc correction. Inferential statistics were performed using Spearman's correlation coefficient between: (1) Scores of THI and age, duration of tinnitus, and scorings of DASS-21 (depression, anxiety, and stress), PSS and ISI; (2) scores of DASS-21 and PSS and ISI; and (3) scores of PSS and ISI. Multivariate analysis was done to detect the independent variables associated with THI. First, univariate analysis was done between scores of THI and duration of tinnitus and scores of ISI, DASS-21, and PSS. Variables that showed significant values in the univariate model were entered into the multivariate model. Results are expressed as the odds ratio (OR) and 95%CI. Significance was calculated at $P < 0.05$.

RESULTS

Demographics and clinical characteristics

Participants were 230 adults with chronic tinnitus, ranging in age from 25 years to 50 years (mean = 38.6 ± 3.3). The mean duration of tinnitus at the time of the study was 11.5 ± 2.5 mo (range: 6 to 24 mo). The majority were in their 3rd decade and 4th decade (n = 147, 64%), females (69.6%), rural residents (62.6%), married (63.5%), of low education (79.1%), and low/middle socioeconomic states (53%). They had intact hearing perception at 250-8000 Hz, SDS, and type A tympanometry. One hundred and forty patients(60.87%) had tinnitus at quite (or bedtime) and 95 of them (or 67.86%) had aggravation of tinnitus loudness by masking noise. Decompensated tinnitus was reported in 77% (n = 177; G3 = 52 or 22.6%, G4 = 62 or 27% and G5 = 63 or 27.4%) and compensated tinnitus was reported in 23% (n = 53; G1 = 15 or 6.5%, and G2 = 38 or 16.5%). Figure 1 shows the demographics of the studied patients and the differences in demographics between patients with compensated *vs* decompensated tinnitus. There were no significant differences between the two groups of patients in relation to different variables. Table 1 shows the characteristics of tinnitus. It showed that the most frequently encountered sounds were whistling (33.04%) and different sounds' descriptions in different occasions (27%), while clicking (7.4%) and sound echo (4%) were the least described types. Bilateral tinnitus of equal intensity in both ears was more frequent than unilateral. Tinnitus was either continuous or periodic. Thirty percent of patients found that ear plugging resulted in reduced tolerance to tinnitus loudness. There were no significant differences in the tinnitus characteristics between patients with compensated and decompensated types, except that the latter had significantly longer duration of tinnitus at presentation (P = 0.03).

Psychological characteristics and stressors

Table 2 shows the results of the diagnostic work-up questionnaires and psychiatric interviewing of patients. It showed that the majority had clinically significant insomnia (n = 187, 81.3%). The severe and extremely severe symptoms of depression, anxiety and stress were reported in 17.4% (n = 40), 35.7% (n = 82), and 48.7% (n = 112) of patients, respectively. Also, the majority of patients had perceived moderate (n = 106 or 46.1%) and high (n = 102 or 44.3%) stress to tinnitus. There were no sex differences in scores of ISI, DASS-21, and PSS. Patients with decompensated type had significantly higher scores for ISI (P = 0.001) and DASS-21 (depression = 0.02, anxiety = 0.01, stress = 0.001) compared to those with compensated tinnitus.

There were high frequencies of patients with somatic symptoms (75%) other than tinnitus. They included non-specific headache (47.9%), gastrointestinal symptoms (41.3%) (*e.g.*, vomiting, bloating, diarrhea, abdominal gaseous distention, and colic without definite etiology or similar concurrent conditions in close household contacts), poor concentration (38.3%), and erectile dysfunction (31.7%). Psychiatric interviewing showed that 35.7% had non-specific anxiety disorder, 17.4% had major depression, and 19.6% fulfilled the criteria of somatization disorder. Higher frequency of somatization disorder (23.7% *vs* 5.7%) and sexual dysfunction (49% *vs* 26.6%) were reported in patients with decompensated compared to those with compensated tinnitus. Family history of psychiatric disorders was reported in only 9.57% of patients.

Table 1 Characteristics of tinnitus in the studied patients, *n* (%)

Characteristics	Patients, *n* = 230	Compensated tinnitus, *n* = 53	Decompensated tinnitus, *n* = 177	*P* value
Duration of tinnitus in mo	6-24 (11.5 ± 2.5)	10.6 ± 2.2	14.3 ± 2.3	0.03
≥ 6 to ≤ 12	55 (23.9)	8 (15.1)	47 (26.6)	
> 12 to ≤ 18	127 (55.2)	7 (13.2)	120 (67.8)	
> 18	48 (20.9)	38 (71.7)	10 (5.7)	
Origin of sound				
Ear	147 (63.9)	38 (71.7)	109 (61.6)	
Ear and head	83 (36.1)	15 (28.3)	68 (38.4)	
Description				
Ringing	32 (14)	14 (26.4)	18 (10.2)	
Whistling	76 (33)	14 (26.4)	62 (35)	
Roaring	34 (14.8)	13 (24.5)	21 (11.9)	
Clicking	17 (7.4)	0	17 (9.6)	
Sound echo	9 (4)	0	9 (5.1)	
Different descriptions	62 (27)	12 (22.6)	50 (28.3)	
Laterality				
Unilateral, either right or left	63 (27.4)	3 (5.7)	60 (33.9)	
Bilateral	132 (57.4)	38 (71.7)	94 (53.1)	
Equal intensity	98 (43.6)	30 (56.6)	68 (38.4)	
Unequal intensity	34 (14.8)	8 (15.1)	26 (14.7)	
Alternating	35 (15.2)	12 (22.6)	23 (13)	
Pattern				
Continuous	120 (52.2)	28 (42.8)	92 (52)	
Periodic	110 (47.8)	25 (47.2)	85 (48)	
Time of occurrence				
In silence, *e.g.*, at bed time	140 (60.8)	25 (47.2)	115 (65)	
In presence of noise or silence	90 (39.1)	28 (42.8)	62 (35)	

Significance: Compensated *vs* decompensated tinnitus.

The most frequently reported life stressors were financial (77.4%), marital (73%), and sibling (69.6%) issues. Few (8.83%) denied the presence of life stressors (Table 3). We observed that there were no significant differences in the frequencies of life stressor for patients with decompensated compared to those with compensated tinnitus.

Results of correlation analyses

Significance correlations were found between the duration of tinnitus and its severity and perceived stress towards it and severities of depression, anxiety and stress symptoms, and insomnia; between perceived stress towards tinnitus and severities of depression, anxiety and stress symptoms, and insomnia; and between severities of insomnia and depression, anxiety and stress symptoms (Table 4). Univariate analysis showed that there were significant correlations between THI scores and duration of tinnitus (OR = 0.913, 95%CI: 0.758-1.262; *P* = 0.02) and scores of ISI (OR = 0.853, 95%CI: 0.650-1.128; *P* = 0.001), DASS21 (depression: OR = 0.430, 95%CI: 0.320-0.656; *P* = 0.01; anxiety: OR = 1.156, 95%CI: 0.886-1.902; *P* = 0.001; stress: OR = 0.932, 95%CI: 0.843-1.230; *P* = 0.001) and PSS (OR = 0.923, 95%CI: 0.643-1.258; *P* = 0.001). Multivariate analysis showed that the only independent predictors for tinnitus severity (THI score) were the duration of tinnitus (OR = 0.832, 95%CI: 0.640-1.158; *P* = 0.001) and PSS score (OR = 0.835, 95%CI: 0.540-1.125; *P* = 0.001).

Table 2 Results of the diagnostic work-up questionnaires and psychiatric interviewing, *n* (%)

Characteristics	Patients, *n* = 230	Compensated, *n* = 53	Decompensated, *n* = 177	*P* value
Type of insomnia				
Sub-threshold insomnia	43 (18.7)	10 (18.9)	33 (18.6)	
Moderately severe clinical insomnia	129 (52.2)	25 (47.2)	104 (58.8)	
Severe clinical insomnia	58 (23.2)	18 (34)	40 (22.6)	
ISI score	20.6 ± 5.3	14.3 ± 2.4	28.6 ± 2.3	0.001
DASS-21				
Depression				
No, score: 0-9	45 (19.6)	14 (26.4)	31 (17.5)	
Mild, score: 10-13	85 (37)	23 (43.4)	62 (35)	
Moderate, score: 14-20	60 (26.1)	12 (22.6)	48 (27.1)	
Severe, score: 21-27	28 (12.2)	4 (7.6)	24 (13.6)	
Extremely severe, score: 28+	12 (5.2)	0	12 (6.8)	
Score	15.88 ± 3.26	14.08 ± 2.46	22.68 ± 2.26	0.02
Anxiety				
No, score: 0-7	12 (5.2)	12 (22.6)	0	
Mild, score: 8-9	16 (7)	14 (26.4)	2 (1.1)	
Moderate, score: 10-14	120 (52.2)	8 (15.1)	112 (63.3)	
Severe, score: 15-19	58 (25.2)	19 (35.9)	39 (22)	
Extremely severe, score: 20+	24 (10.4)	0	24 (13.6)	
Score	28.65 ± 2.80	22.42 ± 2.33	30.55 ± 2.08	0.01
Stress				
No, score: 0-14	10 (4.4)	2 (3.8)	8 (4.5)	
Mild, score: 15-18	12 (5.2)	3 (5.7)	9 (5.1)	
Moderate, score: 19-25	106 (46.1)	40 (75.5)	66 (37.3)	
Severe, score: 26-33	60 (26.1)	8 (26.1)	52 (29.4)	
Extremely severe, score: 34+	42 (18.3)	0	42 (23.7)	
Score	38.32 ± 3.86	23.82 ± 2.40	42.88 ± 2.23	0.001
PSS				
Perceived low stress	12 (5.2)	3 (5.7)	9 (5.1)	
Perceived moderate stress	106 (46.1)	30 (56.6)	76 (42.9)	
Perceived high stress	112 (48.7)	20 (37.7)	92 (51.98)	
Comorbid physical and psychiatric conditions				
Major depression	40 (17.4)	8 (26.1)	32 (18.1)	
Non-specific anxiety disorder	82 (35.7)	18 (34)	64 (35)	
Somatization disorder	45 (19.6)	3 (5.7)	42 (23.7)	
Poor concentration	88 (38.3)	23 (43.4)	65 (36.7)	
Non-specific headache	110 (47.9)	32 (60.4)	78 (44.1)	
Gastrointestinal tract symptoms	95 (41.3)	20 (37.7)	75 (42.4)	
Sexual dysfunction	73 (31.7)	26 (49.1)	47 (26.6)	
Family history of psychiatric disorders	18 (7.8)	6 (11.3)	12 (6.8)	

P value: Compensated *vs* decompensated tinnitus. DASS21: Depression, anxiety, stress scale 21; ISI: Insomnia severity index; PSS: Perceived stress scale.

Table 3 Life stressors of studied patients, *n* (%)

No.	Most stressful life events or changes	Total, *n* = 230	Compensated, *n* = 53	Decompensated, *n* = 177
1	Financial issues: Change in financial state; Accumulation of loans; Stopped work or fired at work (either subject or a spouse)	178 (77.39)	27 (50.94)	151 (85.31)
2	Marital issues: Trouble with spouse; Marital separation; Divorce; Death of spouse	168 (73.04)	3 (5.66)	165 (93.22)
3	Siblings' issues: Change in health; Death; Left home; Poor achievement at school or college or work; Stopped work	160 (69.57)	20 (37.74)	140 (79.10)
4	Change in personal issues: Lower home daily activities; Lower work activities; Poor social activities; Change in personal habits; Change in religion habits	120 (52.17)	0	120 (67.80)
5	Work or home activities' issues: Work readjustment; Change in work hours or conditions; Change to a different line of work; Change a different responsibility at work; Change in sleeping habits or frequent daytime shifts	63 (27.39)	0	63 (35.59)
6	Trouble with law issues	0	0	0
7	A close relatives' or a friends' issues: Change in health; Death	50 (21.74)	3 (5.66)	47 (26.55)
8	None	18 (8.83)	0	18 (10.17)

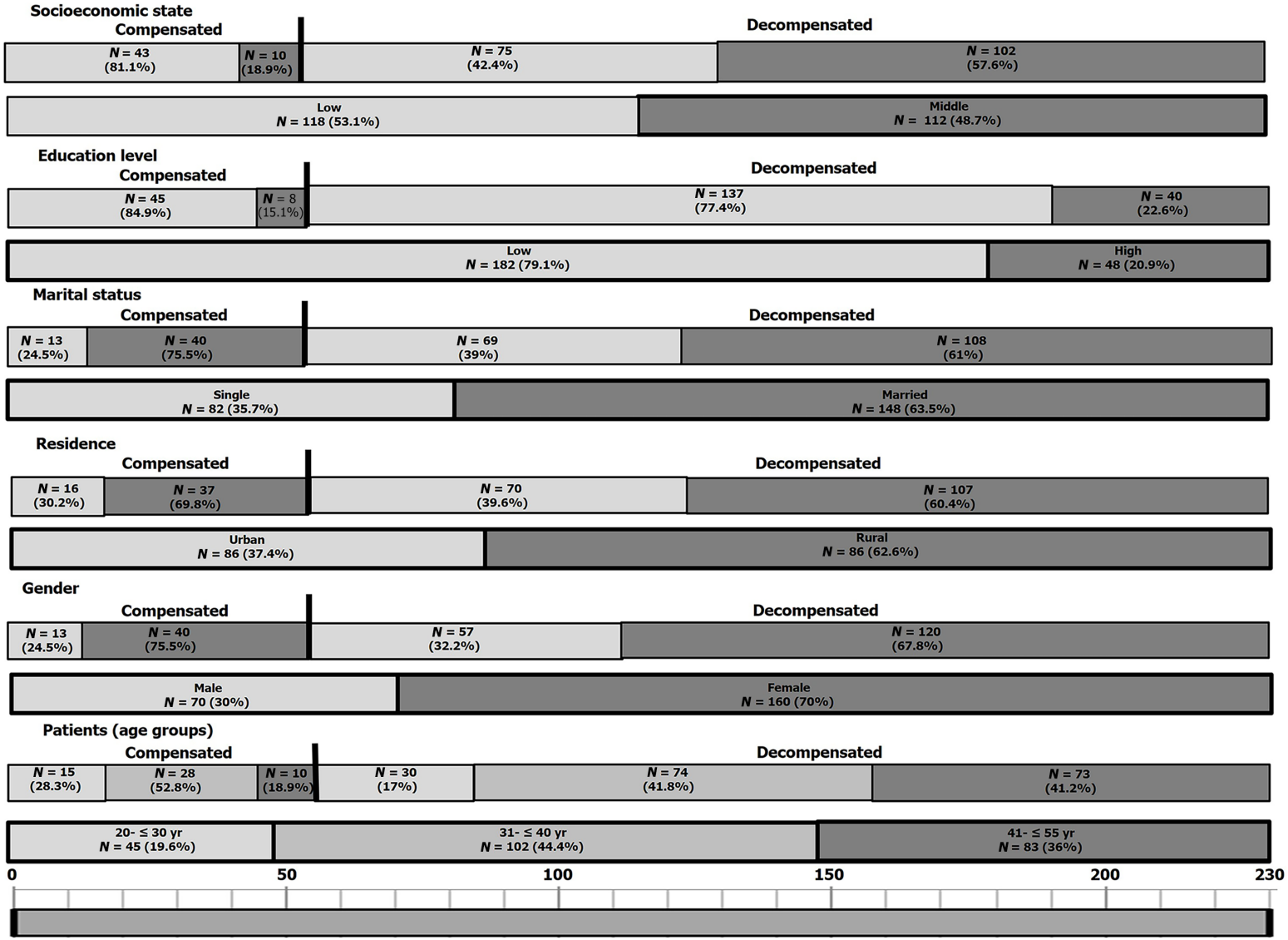
Table 4 Results of correlation analysis between tinnitus and psychological variables, *r* (*P* value)

Parameter	Duration	THI	ISI	PSS
Duration				
THI	0.358 (0.01)			
ISI	0.520 (0.001)	0.653 (0.001)		
DASS-21				
Depression	0.362 (0.04)	0.325 (0.033)	0.350 (0.02)	0.358 (0.01)
Anxiety	0.540 (0.001)	0.386 (0.02)	0.520 (0.001)	0.626 (0.001)
Stress	0.565 (0.001)	0.543 (0.001)	0.624 (0.001)	0.580 (0.001)
PSS	0.338 (0.01)	0.545 (0.001)	0.545 (0.001)	

DASS-21: Depression, anxiety, stress scale 21; ISI: Insomnia severity index; PSS: Perceived stress scale; THI: Tinnitus handicap inventory.

DISCUSSION

The topic of chronic idiopathic tinnitus and its relationship to psychological factors is understudied in different countries. The core outcome domain of this study was identification of psychosocial associates with tinnitus's onset, severity, and persistence. Generally speaking, previous studies have included the following information about tinnitus: (1) Lesions in the auditory sensory pathway and its brain circuits often produce high-pitched tinnitus (*i.e.* hearing loss is dominant in high-frequency tone sound stimuli with ranges more than 4000 Hz. These ranges are not routinely tested in audiology clinics[5]. Tinnitus caused by auditory pathway lesions is often transient and disappears spontaneously within short time regardless to its etiology. This is due to the activation of thalamic filtering processes by the superior brain centers (*i.e.* switch-off the aberrant signals expressed as noisy ear sounds). This process is termed habituation or adaptation[6]; (2) Clinicians observed that it is impossible at onset to predict the course of tinnitus or whether an individual will develop compensated or decompensated tinnitus overtime. However, audiologist and otologists usually advice the majority (~80%) of individuals with tinnitus against frequent consultations as long as there is no hearing deficits and intact comprehensive of speech, and to become accustomed to tinnitus[16,20] as there is/are no standard symptomatic treatment(s) for tinnitus. The clinicians also observed that there is no direct relation between tinnitus loudness and the severity of SNHL. There are individuals with very severe hearing loss but never experienced tinnitus [6]. In contrast, some clinicians reported an association between the estimates of hearing loss and



DOI: 10.12998/wjcc.v11.i14.3211

Figure 1 Demographics of the studied patients.

tinnitus loudness. However, such studies were criticized as their authors did not exclude (during analyses) the co-variables which could associate with tinnitus severity (as emotional stress or psychosocial factors)[5,15]; (3) Most studies are focused on tinnitus as a somatic stressor, *i.e.* the cause of adverse mental health. They also suggested that the suffers of tinnitus seem to be more vulnerable to significant stress[16]. However, few indicated that tinnitus may begin in times of severe stress or after a period of significant stress[20]; and (4) In many countries, the management of chronic tinnitus may include interdisciplinary approach (*i.e.* neurologists, audiologists, psychologists and psychiatrists)[1-3].

In our sample, the women to men ratio, was 2.3:1. The sex difference in prevalence of chronic tinnitus is a subject of debate. Some studies have reported higher frequencies in females. Others found the reverse[12,18]. In this study, the higher frequency of participants from females could be explained by the following: (1) Females may be vulnerable to develop chronic tinnitus than male; (2) being housewives, females had free times for consultations than males; (3) females are commonly express their somatic symptoms, feelings and stress more easily and frequently compared to males; and (4) females with or without tinnitus had higher psychological risks throughout their lives and were more likely to exhibit emotional disturbances (*e.g.*, mood swings, anxiety and stress), while males tended to experience depression and social isolation[9].

In this study, psychiatric interviewing revealed that participants had higher frequencies and severities of insomnia, anxiety and stress symptoms. Many patients (75%, n = 172) had repeated somatic symptoms in addition to tinnitus, which are distressing or result in significant disruption of daily life. They included insomnia, headache, gastrointestinal tract (GIT) symptoms (*e.g.*, vomiting, bloating, diarrhea) without explanatory cause, erectile dysfunction, and memory deficits. These manifestations were marked in patients with decompensated tinnitus.

Considering the age of participants at presentation, ~20% satisfied the DSM-IV criteria of somatization disorder, a class of somatoform disorders[26,27]. The same criteria were applied for the classification in DSM-IV as "somatic symptom disorder," a class of somatic symptom and related disorder[33]. These criteria were previously termed "psychosomatic or psycho-physiologic disorders." Non-specific anxiety disorder was reported in 35.65%. Major depressive disorder was reported in 17.39%.

Exploring the psychosocial stressors, the majority (77%) had drastic financial, marital, or sibling stressful life events. Accordingly, previous studies have reported that 45%-78% of patients with chronic idiopathic tinnitus satisfied the criteria of one or more psychiatric disorders[2,7-14,16-18]. Some studies have considered the role of stress-reactivity in tinnitus onset[6,19,20]. Belli *et al*[17] showed that 27% of patients with tinnitus had at least one psychiatric diagnosis (as anxiety disorders in 28%, somatoform and mood disorders in 15%, and personality disorders in 3%) *vs* 5.6% for control subjects. The authors suggested that, the psychological stressor greatly impacts the body physiological function with improper stimulation of the autonomic nervous system, excess adrenaline secretion and severe stress and anxiety and somatization. Fagelson[34] did a chart review for enrolled patients to tinnitus service in the Veterans Affairs Medical Center. The authors reported that 34% of patients with tinnitus also fulfilled the criteria for the diagnosis of posttraumatic stress disorder (PTSD). They also reported that the following tinnitus inquiries were more frequent in patients with tinnitus and PTSD compared to those with tinnitus only, they include sudden onset of tinnitus, increased tinnitus severity, poor tolerance to sounds and exaggeration of tinnitus with sounds. The authors suggested that there might be several shared neural mechanisms between tinnitus and PTSD and affect auditory behaviors (*i.e.* mutual reinforcement of symptoms of both tinnitus and PTSD). Furthermore, several studies reported that the chronic and severe tinnitus, which followed traumatic brain injury, whether the involved individuals were from military or civil personnel, is due to the emotional trauma or the higher distress level which was experienced during the trauma event and not directly associated with the specific head or neck injury[35,36].

We observed the following associates and characteristics of tinnitus in the majority of patients, which highly suggest a contribution of non-sensorineural auditory problem: (1) There was no deterioration of hearing over time with repeated audiometric tests despite increase in tinnitus severity in the majority (77%); (2) In the same individual in different occasions, tinnitus originated from inside the head or the ear or both (36.09%), alternate in origin from either left or right (15.22%) and had different descriptions (*e.g.* ringing at sometimes and another description at another time) (27%); (3) The bilateral presentation and equal intensity in both ears since onset (43.61%); (4) The descriptions of tinnitus as whistling (33.04%), roaring (14.78%), clicking (7.4%) or sound echo (4%), which are non-familiar descriptions for tinnitus associated with SNHL; (5) The non-continuous or periodic pattern (47.83%); (6) Tinnitus was aggravated or became intolerable with ear plugging or masking noise (41.30%); and (7) Tinnitus severity and its perceived stress were associated with the severity of anxiety, stress and depression symptoms and insomnia[15,16,20].

Research studies have shown that insomnia reduces tolerance and increases the perceived annoyance to tinnitus[10,17,37]. Authors have linked the conscious perception of tinnitus and its loudness with time and insomnia to the hyperarousal induced by hyperactivity of the sympathetic nervous system [38]. We also found that the only independent associates to severe tinnitus were its chronicity and higher perceived stress towards it. We suggested that psychological factors influence the conscious perception of tinnitus, result in worsening of tinnitus (*e.g.*, became continuous, increase in its loudness,

and prolonged its duration) and also generate other functional somatic conditions such as headache, poor concentration, and GIT manifestations, erectile dysfunction. Research studies have found an independent association between neuroticism, obsession and anxiety traits and tinnitus severity[15,16]. It has been suggested that focusing attention on tinnitus increases fear, tension and anxiety, and emotional reinforcements followed by emotional exhaustion, neuronal hyperexcitability, establishment of a neuronal plasticity in the limbic system, particularly the amygdala and a vicious circle, resulting in chronic and severe continuous perception of tinnitus[13,14,17,39].

The results of this study support the fact that the psychological factors play an important role in the processes of perception, interpretation, treatment, and complications of tinnitus[40]. Therefore, combined multidisciplinary management of patients with tinnitus is required. Neuropsychiatric evaluation has to include counseling, education, and reassurance, and reduction of depression, anxiety and stress, and improving sleep pattern by psychotropic medication, psychotherapy or other interventions[21-24]. Psychotropic drugs improve tinnitus by improving the depression anxiety, stress and sleep disturbance. The previously used medication which have shown efficacy included tricyclic antidepressants (as amitriptyline, nortriptyline and trimipramine) and selective serotonin reuptake inhibitors (SSRIs) (as sertraline, citalopram, escitalopram, fluoxetine, venlafaxine, fluvoxamine, and paroxetine)[21]. Folmer *et al*[21] in their retrospective study on 30 patients with depression and started treatment with SSRIs and psychotherapy for 20.6 mo after tinnitus onset, the authors demonstrated a significant improvement of tinnitus as evidenced by reduction of tinnitus severity index scores. The authors concluded that, SSRIs elevated affectivity which accompanied tinnitus and therefore reduced the intensity and frequency of tinnitus. However, some studies found that although SSRIs improve symptoms of depression and anxiety but may worsen tinnitus[22,41]. In tinnitus mouse models, Tang *et al*[42] analyzed the brain tissue which focused on the response of neurons in the dorsal cochlear nucleus to serotonin. The dorsal nucleus is the portion of the cochlear nucleus with inhibitory characteristics and involved in sensory processing. It is the portion of the cochlear nucleus which is affected by tinnitus. The authors observed hyperactivity and hypersensitivity of the mice to sounds when the fusiform cells in the dorsal cochlear nucleus were exposed to serotonin, indicating that serotonin raises neuronal activity in the dorsal cochlear nucleus. They also suggested that serotonin suppresses signaling through the auditory pathway and enhances transmission through a multisensory pathway. Previous studies have also suggested that the main aim for the use of psychotropic medications is to treat the co-morbid anxiety/depression in patients with tinnitus and not as a main symptomatic treatment of tinnitus. Because not all psychotropic medications can worsen tinnitus, it is plausible to suggest that it is better to switch to another psychotropic drug to improve depression and anxiety symptoms without deterioration of tinnitus.

To the best of our knowledge, this is the first study in our culture to evaluate the causal relationship between psychological factors and tinnitus onset, severity and persistence. However, this study has limitations which include a female predominance (*i.e.* sex bias), however, we do not consider this a major weakness as statistical analyses were also done after classification of patients from both sex into those with compensated *vs* decompensated tinnitus.

CONCLUSION

Tinnitus was an infrequent earliest and dominant somatic symptom induced by severe life stressors and psychological vulnerabilities. In many patients, the characters of tinnitus were distinguished from that of solely auditory system lesions. Psychiatric interviewing revealed the diagnosis of anxiety disorder in 35.7%, somatization disorder in 19.6% and major depression in 17.4% of patients. Tinnitus severity was independently associated with the longer duration of tinnitus and the individual's perceived stress towards tinnitus. Therefore, multidisciplinary consultation (psychologists, psychiatrists and neurologists) is important to acknowledge.

ARTICLE HIGHLIGHTS

Research background

Tinnitus is the most common auditory symptom with an estimated prevalence of 8%-40% and life-long disabling problem in ~2.5%. Tinnitus is an aberrant sound heard in the ears or in both ears and head. It is believed to be a symptom of hearing impairment. However, many audiologists observed that approximately 15%-30% of subjects with tinnitus had neither manifest nor subclinical hearing impairment. Research studies have indicated that psychosocial factors as stress, anxiety, depression and insomnia are strong risks for the chronic and severe tinnitus. They also reported comorbid psychiatric disorders as anxiety, somatization and major depressive disorders in 23%-35% of patients with tinnitus. Others reported improvement of tinnitus after the use of antidepressant or anxiolytic medications. Many audiologist and otolaryngologist believe that tinnitus requires multidisciplinary evaluation and

management. As chronic idiopathic tinnitus and evaluation of its psychosocial triggers is an understudied topic in many parts of the world, therefore, it has to be addressed in different populations.

Research motivation

The research hotspots include determination of: (1) Characteristics of chronic tinnitus in group of patients with no obvious hearing loss as a cause; (2) comorbid psychosocial stressors and psychiatric conditions and disorders which are associated with tinnitus initiation, aggravation and chronicity; and (3) predictors that are independently associated with increase in the severity of tinnitus.

Research objectives

This study systematically assessed patients with chronic idiopathic tinnitus and the psychosocial factors associated with its onset, increased severity and chronicity.

Research methods

Tinnitus handicap inventory, depression anxiety stress scale 21, perceived stress scale, insomnia severity index, and a designed questionnaire for determination of life stressors.

Research results

This study included 230 adult patients from both sex. They had chronic tinnitus with a mean duration of approximately 11 mo. Their previous ear, nose and throat and audiology evaluations including pure tone audiometry at frequencies ranged from 250 to 8000 Hz did not reveal obvious cause for tinnitus. Decompensated tinnitus was reported in 77%. The characters of tinnitus in many patients are distinguished from that of tinnitus due to pure auditory pathway lesions, which included being originated from ears and/or head, bilateral or alternate ear side, described as whistling, roaring, clicking, or combined sound, aggravated by ear plugging, stress, anxiety and insomnia and absence of hearing deterioration overtime. Psychiatric evaluation revealed frequent comorbid conditions and disorders including stress, anxiety, somatic problems, depression, enhanced perceived stress towards tinnitus and anxiety, somatization and major depressive disorders. We also reported that the variables which were highly significant and independently associated with tinnitus were its duration and increased stress perception towards tinnitus.

Research conclusions

Tinnitus was a common and predominant somatic symptom in response to severe life stressors and psychological susceptibility. The tinnitus variables showed distinct characteristics which differentiate it from tinnitus caused by pure auditory system lesions. Psychiatric interviewing revealed that the majority of patients had symptoms of stress, anxiety, depression, and sleep disturbance of variable severities. Anxiety and somatization disorders were reported in 35.7% and 19.6% of patients, respectively. Major depressive disorder was reported in 17.4%. The interindividual variability to stress perception and anxiety were strong triggers for tinnitus, its severity and chronicity.

Research perspectives

In our locality, the importance of the psychosocial factors for the initiation, aggravation and chronicity of tinnitus are understudied. Multidisciplinary consultation (psychologists, psychiatrists and neurologists) is important to acknowledge among the audiologists and otolaryngologists who primarily consult patients. Also future longitudinal studies are required to determine the tinnitus outcomes before and after treatment with psychotropic medications.

FOOTNOTES

Author contributions: Hamed SA was the guarantor and designed the study, conducted the data collection and neurologic evaluation of the patients, applied the diagnostic work-up questionnaires on the patients, and contributed to the statistical analyses and manuscript drafting; Attiah FA and Fawzy M conducted the psychiatric interviewing, and participated in the acquisition, analysis, and interpretation of the data; Azzam M did the ENT evaluation, and participated in the acquisition, analysis, and interpretation of the data; Attiah FA, Fawzy M, and Azzam M revised the article critically for important intellectual content.

Institutional review board statement: The Ethics Committees of Faculty of Medicine of Assiut University, Assiut Governorate, Egypt, approved the study protocol.

Informed consent statement: All study participants, or their guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: Egypt

ORCID number: Sherifa Ahmed Hamed 0000-0002-1441-3530; Fadia Ahmed Attiah 0000-0002-4768-0782.

S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Chen YX

REFERENCES

1 **Shargorodsky J**, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. *Am J Med* 2010; **123**: 711-718 [PMID: 20670725 DOI: 10.1016/j.amjmed.2010.02.015]
2 **Krog NH**, Engdahl B, Tambs K. The association between tinnitus and mental health in a general population sample: results from the HUNT Study. *J Psychosom Res* 2010; **69**: 289-298 [PMID: 20708451 DOI: 10.1016/j.jpsychores.2010.03.008]
3 **Martinez-Devesa P**, Perera R, Theodoulou M, Waddell A. Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst Rev* 2010; CD005233 [PMID: 20824844 DOI: 10.1002/14651858.CD005233.pub3]
4 **Heller AJ**. Classification and epidemiology of tinnitus. *Otolaryngol Clin North Am* 2003; **36**: 239-248 [PMID: 12856294 DOI: 10.1016/s0030-6665(02)00160-3]
5 **Schlee W**, Kleinjung T, Hiller W, Goebel G, Kolassa IT, Langguth B. Does tinnitus distress depend on age of onset? *PLoS One* 2011; **6**: e27379 [PMID: 22125612 DOI: 10.1371/journal.pone.0027379]
6 **Georgiewa P**, Klapp BF, Fischer F, Reisshauer A, Juckel G, Frommer J, Mazurek B. An integrative model of developing tinnitus based on recent neurobiological findings. *Med Hypotheses* 2006; **66**: 592-600 [PMID: 16226392 DOI: 10.1016/j.mehy.2005.08.050]
7 **Robinson SK**, McQuaid JR, Viirre ES, Betzig LL, Miller DL, Bailey KA, Harris JP, Perry W. Relationship of tinnitus questionnaires to depressive symptoms, quality of well-being, and internal focus. *Int Tinnitus J* 2003; **9**: 97-103 [PMID: 15106282]
8 **Stobik C**, Weber RK, Münte TF, Walter M, Frommer J. Evidence of psychosomatic influences in compensated and decompensated tinnitus. *Int J Audiol* 2005; **44**: 370-378 [PMID: 16078732 DOI: 10.1080/14992020500147557]
9 **Zöger S**, Svedlund J, Holgers KM. Relationship between tinnitus severity and psychiatric disorders. *Psychosomatics* 2006; **47**: 282-288 [PMID: 16844885 DOI: 10.1176/appi.psy.47.4.282]
10 **Erlandsson SI**, Hallberg LR, Axelsson A. Psychological and audiological correlates of perceived tinnitus severity. *Audiology* 1992; **31**: 168-179 [PMID: 1642568 DOI: 10.3109/00206099209072912]
11 **Folmer RL**, Griest SE. Tinnitus and insomnia. *Am J Otolaryngol* 2000; **21**: 287-293 [PMID: 11032291 DOI: 10.1053/ajot.2000.9871]
12 **Zirke N**, Seydel C, Arsoy D, Klapp BF, Haupt H, Szczepek AJ, Olze H, Goebel G, Mazurek B. Analysis of mental disorders in tinnitus patients performed with Composite International Diagnostic Interview. *Qual Life Res* 2013; **22**: 2095-2104 [PMID: 23292277 DOI: 10.1007/s11136-012-0338-9]
13 **Sullivan MD**, Katon W, Dobie R, Sakai C, Russo J, Harrop-Griffiths J. Disabling tinnitus. Association with affective disorder. *Gen Hosp Psychiatry* 1988; **10**: 285-291 [PMID: 3417130 DOI: 10.1016/0163-8343(88)90037-0]
14 **Halford JB**, Anderson SD. Anxiety and depression in tinnitus sufferers. *J Psychosom Res* 1991; **35**: 383-390 [PMID: 1920169 DOI: 10.1016/0022-3999(91)90033-k]
15 **Hiller W**, Janca A, Burke KC. Association between tinnitus and somatoform disorders. *J Psychosom Res* 1997; **43**: 613-624 [PMID: 9430074 DOI: 10.1016/s0022-3999(97)00188-8]
16 **Møller AR**. Misophonia, phonophobia, and "exploding head" syndrome. In Møller AR, Langguth B., De Ridder D, Kleinjung T. Textbook of tinnitus. New York: Springer, 2011: 25-27 [DOI: 10.1007/978-1-60761-145-5_4]
17 **Belli H**, Belli S, Oktay MF, Ural C. Psychopathological dimensions of tinnitus and psychopharmacologic approaches in its treatment. *Gen Hosp Psychiatry* 2012; **34**: 282-289 [PMID: 22285367 DOI: 10.1016/j.genhosppsych.2011.12.006]
18 **Aytac I**, Baysal E, Gulsen S, Tumuklu K, Durucu C, Mumbuc LS, Kanlikama M. Masking Treatment and its Effect on Tinnitus Parameters. *Int Tinnitus J* 2017; **21**: 83-89 [PMID: 29336124 DOI: 10.5935/0946-5448.20170017]
19 **Mazurek B**, Olze H, Haupt H, Szczepek AJ. The more the worse: the grade of noise-induced hearing loss associates with the severity of tinnitus. *Int J Environ Res Public Health* 2010; **7**: 3071-3079 [PMID: 20948948 DOI: 10.3390/ijerph7083071]
20 **Abbas J**, Aqeel, M, Jaffar A, Nurunnabi M, Bano S. Tinnitus perception mediates the relationship between physiological

and psychological problems among patients. *J Exp Psychopathol* 2019; 1-15 [DOI: 10.1177/2043808719858559]

21 **Folmer RL**, Shi YB. SSRI use by tinnitus patients: interactions between depression and tinnitus severity. *Ear Nose Throat J* 2004; **83**: 107-108, 110, 112 passim [PMID: 15008444]

22 **Zöger S**, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering--a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2006; **26**: 32-39 [PMID: 16415703 DOI: 10.1097/01.jcp.0000195111.86650.19]

23 **Aazh H**, El Refaie A, Humphriss R. Gabapentin for tinnitus: a systematic review. *Am J Audiol* 2011; **20**: 151-158 [PMID: 21940981 DOI: 10.1044/1059-0889(2011/10-0041)]

24 **Savage J**, Waddell A. Tinnitus. *BMJ Clin Evid* 2014; **2014** [PMID: 25328113]

25 **El-Gilany A**, El-Wehady A, El-Wasify M. Updating and validation of the socioeconomic status scale for health research in Egypt. *East Mediterr Health J* 2012; 18: 962-968 [PMID: 23057390 DOI: 10.26719/2012.18.9.962]

26 **First MB**, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition (SCID-I/P) biometrics research. New York: New York State Psychiatric Institute, 2002

27 **Khalil AH**, Abou El Ella EI, Hamed MAM, Lotfy MM. Systematic review of some epidemiological studies on psychiatric disorders in Egypt. M.Sc. Thesis, Ain Shams University. 2009

28 **Barake R**, Rizk SA, Ziade G, Zaytoun G, Bassim M. Adaptation of the Arabic Version of the Tinnitus Handicap Inventory. *Otolaryngol Head Neck Surg* 2016; **154**: 508-512 [PMID: 26671903 DOI: 10.1177/0194599815621551]

29 **Suleiman KH**, Yates BC. Translating the insomnia severity index into Arabic. *J Nurs Scholarsh* 2011; **43**: 49-53 [PMID: 21342424 DOI: 10.1111/j.1547-5069.2010.01374.x]

30 **Moussa MT**, Lovibond P, Laube R, Megahead HA. Psychometric Properties of an Arabic Version of the Depression Anxiety Stress Scales (DASS). *Res Soc Work Pract* 2017; **27**: 375-386 [DOI: 10.1177/1049731516662916]

31 **Cohen JN**, Taylor Dryman M, Morrison AS, Gilbert KE, Heimberg RG, Gruber J. Positive and Negative Affect as Links Between Social Anxiety and Depression: Predicting Concurrent and Prospective Mood Symptoms in Unipolar and Bipolar Mood Disorders. *Behav Ther* 2017; **48**: 820-833 [PMID: 29029678 DOI: 10.1016/j.beth.2017.07.003]

32 **Almadi T**, Cathers I, Hamdan Mansour AM, Chow CM. An Arabic version of the perceived stress scale: translation and validation study. *Int J Nurs Stud* 2012; **49**: 84-89 [PMID: 21851941 DOI: 10.1016/j.ijnurstu.2011.07.012]

33 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Association, 2013

34 **Fagelson MA**. The association between tinnitus and posttraumatic stress disorder. *Am J Audiol* 2007; **16**: 107-117 [PMID: 18056879 DOI: 10.1044/1059-0889(2007/015)]

35 **American Tinnitus Association**. ATA's top 10 most frequently asked questions. [cited 2 July 2012]. Available at: http://www.ata.org/for-patients/faqs

36 **Kreuzer PM**, Landgrebe M, Schecklmann M, Staudinger S, Langguth B; TRI Database Study Group. Trauma-associated tinnitus: audiological, demographic and clinical characteristics. *PLoS One* 2012; **7**: e45599 [PMID: 23049821 DOI: 10.1371/journal.pone.0045599]

37 **Malouff JM**, Schutte NS, Zucker LA. Tinnitus-related distress: A review of recent findings. *Curr Psychiatry Rep* 2011; **13**: 31-36 [PMID: 21080115 DOI: 10.1007/s11920-010-0163-1]

38 **Rauschecker JP**, Leaver AM, Mühlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron* 2010; **66**: 819-826 [PMID: 20620868 DOI: 10.1016/j.neuron.2010.04.032]

39 **Salvi R**, Sun W, Ding D, Chen GD, Lobarinas E, Wang J, Radziwon K, Auerbach BD. Inner Hair Cell Loss Disrupts Hearing and Cochlear Function Leading to Sensory Deprivation and Enhanced Central Auditory Gain. *Front Neurosci* 2016; **10**: 621 [PMID: 28149271 DOI: 10.3389/fnins.2016.00621]

40 **Hallam RS**. Psychological Approaches to the Evaluation and Management of Tinnitus Distress. In: Hazzel JWP. Tinnitus. Edinburg: Churchill Livingstone, 1987: 156-175

41 **Miller CW**. Development of Tinnitus at a Low Dose of Sertraline: Clinical Course and Proposed Mechanisms. *Case Rep Psychiatry* 2016; **2016**: 1790692 [PMID: 27703829 DOI: 10.1155/2016/1790692]

42 **Tang ZQ**, Trussell LO. Serotonergic Modulation of Sensory Representation in a Central Multisensory Circuit Is Pathway Specific. *Cell Rep* 2017; **20**: 1844-1854 [PMID: 28834748 DOI: 10.1016/j.celrep.2017.07.079]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3224-3237

DOI: 10.12998/wjcc.v11.i14.3224

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Intestinal complications in patients with Crohn's disease in the Brazilian public healthcare system between 2011 and 2020

Ligia Yukie Sassaki, Adalberta Lima Martins, Rodrigo Galhardi-Gasparini, Rogerio Saad-Hossne, Alessandra Mileni Versut Ritter, Tania Biatti Barreto, Taciana Marcolino, Bruno Balula, Claudia Yang-Santos

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Jin X, China; Zhou W, China

Received: January 9, 2023
Peer-review started: January 9, 2023
First decision: February 15, 2023
Revised: February 27, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Ligia Yukie Sassaki, Department of Internal Medicine, São Paulo State University - UNESP, Medical School, 18618687, Botucatu, Brazil

Adalberta Lima Martins, Department of Gastroenterology, State Office for Pharmaceutical Assistance at Espírito Santo Health Office, Vitoria 29017-010, Espirito Santo, Brazil

Rodrigo Galhardi-Gasparini, Department of Gastroenterology, SETE – Specialized Medical Center, Marilia 17502-020, Sao Paulo, Brazil

Rogerio Saad-Hossne, Department of Surgery, São Paulo State University - UNESP, Medical School, 18618687, Botucatu, Brazil

Alessandra Mileni Versut Ritter, Bruno Balula, Real World Evidence, IQVIA Brazil, 04719-002, Sao Paulo, Brazil

Tania Biatti Barreto, Taciana Marcolino, Medical Affairs, Takeda Pharmaceuticals Brazil, 04794-000, Sao Paulo, Brazil

Claudia Yang-Santos, Clinical Research, Takeda Pharmaceuticals Brazil, 04794-000, Sao Paulo, Brazil

Corresponding author: Claudia Yang-Santos, BPharm, MSc, PhD, Research Scientist, Clinical Research, Takeda Pharmaceuticals Brazil, Av. das Nações Unidas, 14.401 - Torre Jequitibá - 10º, 11º e 12º andares, 04794-000, Sao Paulo, Brazil. clausantos2910@gmail.com

Abstract

BACKGROUND

This is a secondary database study using the Brazilian public healthcare system database.

AIM

To describe intestinal complications (ICs) of patients in the Brazilian public healthcare system with Crohn's disease (CD) who initiated and either only received conventional therapy (CVT) or also initiated anti-tumor necrosis factor (anti-TNF) therapy between 2011 and 2020.

METHODS

This study included patients with CD [international classification of diseases – 10th

revision (ICD-10): K50.0, K50.1, or K50.8] (age: ≥ 18 years) with at least one claim of CVT (sulfasalazine, azathioprine, mesalazine, or methotrexate). IC was defined as a CD-related hospitalization, pre-defined procedure codes (from rectum or intestinal surgery groups), and/or associated disease (pre-defined ICD-10 codes), and overall (one or more type of ICs).

RESULTS

In the 16809 patients with CD that met the inclusion criteria, the mean follow-up duration was 4.44 (2.37) years. In total, 14697 claims of ICs were found from 4633 patients. Over the 1- and 5-year of follow-up, 8.3% and 8.2% of the patients with CD, respectively, presented at least one IC, of which fistula (31%) and fistulotomy (48%) were the most commonly reported. The overall incidence rate (95%CI) of ICs was 6.8 (6.5–7.04) per 100 patient years for patients using only-CVT, and 9.2 (8.8–9.6) for patients with evidence of anti-TNF therapy.

CONCLUSION

The outcomes highlighted an important and constant rate of ICs over time in all the CD populations assessed, especially in patients exposed to anti-TNF therapy. This outcome revealed insights into the real-world treatment and complications relevant to patients with CD and highlights that this disease remains a concern that may require additional treatment strategies in the Brazilian public healthcare system.

Key Words: Crohn's disease; Intestinal complications; Anti-tumor necrosis factor; Conventional therapy; Public healthcare system

Core Tip: This real-world study assessed intestinal complications (ICs) in patients with Crohn's disease (CD) undergoing therapy available in the Public Healthcare System in Brazil over the last 10 years. Outcomes suggests that patients that received conventional therapy and eventually anti–tumor necrosis factor therapy have an active and progressive illness, developing relevant ICs that might imply in considerable use of resources from the health system, CD remains a concern which may require additional strategies in the Brazilian public health care system.

Citation: Sassaki LY, Martins AL, Galhardi-Gasparini R, Saad-Hossne R, Ritter AMV, Barreto TB, Marcolino T, Balula B, Yang-Santos C. Intestinal complications in patients with Crohn's disease in the Brazilian public healthcare system between 2011 and 2020. *World J Clin Cases* 2023; 11(14): 3224-3237
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3224.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3224

INTRODUCTION

Inflammatory bowel diseases are chronic relapsing immune-mediated disorders of the intestine, and Crohn's disease (CD) is one of its main representatives. CD is a global disease with rising incidence and prevalence across several countries[1]. In 2018, Martins *et al*[2] found a prevalence of 14.1 cases per 100000 inhabitants in Brazil[2]. The prevalence of CD in the State of São Paulo, Brazil, in December 2015 was 24.3 cases per 100000 inhabitants[3]. CD can affect the entire intestinal tract and is characterized by symptoms such as diarrhea, abdominal pain, and mucosal ulcerations, among others. In addition, the disease presents complications such as malnutrition, stenosis, hemorrhage, perforation, obstruction, and fistula, which compromise the patient's quality of life[1,4]. Disease flares and complications may result in the need for hospitalization and even surgery resulting in high direct healthcare costs[5].

Currently, there is no cure for CD, and the goal of medical treatment is to reduce the inflammation that triggers signs and symptoms and improve long-term prognosis by limiting complications. The choice of drug therapy for CD is influenced by several factors, including efficacy, need for induction and/or maintenance of remission, side-effect profiles, long-term risks, and patient choice. The treatments available include aminosalicylates, corticosteroids, immunosuppressants, and advanced therapies, such as tumor necrosis factor (TNF) inhibitors (anti-TNF), anti-integrins, and anti-interleukins. However, from 2011 to 2020, only the anti-TNF drugs infliximab, adalimumab, and certolizumab were available through the Brazilian public healthcare system. Several studies in humans have reported the positive impact of anti-TNF drugs on disease progression[6,7]. They are efficacious in inducing remission and reducing the need for surgery, hospitalization, and other complications[5].

Although effective, anti-TNF therapy are associated with a risk of serious and sometimes life-threatening treatment-related adverse events, such as potential for development of skin lesions, immune reactions, perioperative complications, infections, cancers, and decreased fertility/adverse effects on pregnancy[8].

Strategies have changed over the past decades to alter the progressive course of the disease[5]. The ultimate goal of medical therapy in CD, beyond achieving clinical response and sustained remission, would be to alter disease progression and prevent complications that lead to surgery[9]. An international study has reported that conventional therapy (CVT) might not decrease intestinal complications (ICs) or surgeries[9], whereas anti-TNF agents may present this ability. However, some population-based studies have documented the evolution of CD phenotype[9,10]. The present study aims to describe the ICs of patients with CD who initiated CVT between January 2011 and January 2020 in the Brazilian public healthcare system. An exploratory objective was to establish the ICs for patients who received infliximab, adalimumab, and/or certolizumab (anti-TNF subgroup) and patients who did not receive them (CVT-only subgroup).

MATERIALS AND METHODS

Study design

This is a descriptive, non-interventional, retrospective claims database study using the Brazilian public healthcare system (DATASUS) to characterize ICs in patients with CD. Patients with at least one claim of CD international classification of diseases – 10th revision (ICD-10) code (K50.0, K50.1, or K50.8) and at least one claim of CVT (sulfasalazine, mesalazine, methotrexate, azathioprine, or associations) between 2011 and 2020 were included. The date of the first CD-specific claim for CVT was considered the index date.

All individuals aged ≥ 18 years at the index date (first claim of CVT) and who had at least one diagnosis record for CD [ICD-10 code of CD (K50.0, K50.1, or K50.8)] with a claim of CVT (sulfasalazine, mesalazine, methotrexate, azathioprine, or associations) were included. Patients who had anti-TNF therapy claims (infliximab, adalimumab, or certolizumab pegol) prior to CVT (index date), were non-Sistema Único de Saúde (SUS)-exclusive patients, had any ulcerative colitis ICD-10 codes (K51.0, K51.8, and K51.9) 12 mo prior to the index date, or had < 6 mo of follow-up in the database were excluded. Patients with any ulcerative colitis ICD-10 codes (K51.0, K51.8, and K51.9) 12 mo prior to the index date were excluded; for this reason, ICD-10 codes for ulcerative colitis were verified since January 2010. To capture the initial treatment stage, patients must have neither CVT claims 12 mo prior to the index date nor anti-TNF drug (infliximab, adalimumab, or certolizumab) claims prior to the index date.

Therefore, only the period from January 2010 to December 2010 was considered to assess the medical history, and the period from January 2011 to January 2020 was considered as the study period. After the index date, patients might have received anti-TNF therapy; therefore, a subgroup analysis was also considered: (1) Anti-TNF therapy cohort: Patients who presented at least one claim of anti-TNF therapy available at the public healthcare system (infliximab, adalimumab, or certolizumab), and patients who presented anti-TNF therapy either isolated or combined with CVT; and (2) CVT-only cohort: Patients who did not present any claim of anti-TNF drugs.

Four groups/categories of types of ICs in patients with CD were assessed: (1) CD hospitalization-related; (2) Procedure-related; (3) Associated diseases; and (4) Overall (one or more types of ICs). To be classified as an IC case, patients must present with at least one medical claim in one or more specific categories. Thus, IC was classified as CD hospitalization-related if the patient presented with a hospitalization claim due to CD (K50); procedure-related due to CD complications if the patient presented with a claim of procedure for rectum or intestinal surgeries described in SIGTAP (System of Table of procedures, medications and orthoses, prostheses, and special materials); and associated disease if the patient presented with any claim of the 33 ICD-10 codes predefined as common complications of the disease according to the literature and four independent clinical expert opinions. The ICD-10 codes include malignant neoplasm of the colon; stenosis; hemorrhage; ulcer; and diseases of the anus and rectum, megacolon, volvulus, intussusception, and erythema nodosum. The complete ICD-10 code list is described in Supplementary Figure 1, and overall CD complications if patient present one or more types of ICs previously mentioned (associated disease, procedures or hospitalization).

The primary endpoint was to assess the IC rate in patients with CD who received CVT, regardless of whether anti-TNF therapy was administered after CVT. As secondary endpoints, the IC rates were assessed in patients with no evidence of anti-TNF therapy (CVT-only cohort) and those with evidence of anti-TNF therapy (anti-TNF therapy cohort). The annual rate and incidence of ICs were assessed during the observational study period for patients with CD. Since each individual attended at different time intervals in the database, the incidence of ICs was converted to per patient/per year units, dividing them for all patients by the person-years of follow-up. Incidence rate (IR) was calculated as the number of intestinal events in the database divided by the total person-time at risk. Rates were stratified based on the definition of ICs: All types of ICs combined was denominated as overall and ICs segregated by types were expressed by associated disease, procedurerelated, and CD hospitalization-related, per 100

patient years (PY).

Additionally, secondary outcomes were used to describe patients who switched from CVT to anti-TNF drugs irrespective of whether the patient had prior ICs or switched from CVT to anti-TNF therapy after ICs. The treatment switch was identified as at least one claim of different drug (s) than the previous one independently of the gap (length of time without therapy) between drugs.

A further secondary outcome included ranking the 10 most frequent IC procedure-related and associated diseases (ICD-10 codes) according to the number of patients with at least one claim. Finally, demographic (age, sex, and location) profile of patients with CD included in the study was extracted from the database and expressed according to the cohorts: General patients with CD and subgroups, CVT-only, and anti-TNF therapy cohorts.

An exploratory outcome was to establish ICs (general and categorized by each type of IC) for patients who received infliximab, adalimumab, and/or certolizumab (anti-TNF subgroup) and those who did not receive them (CVT-only subgroup). For both groups, the total number of patients and claims for ICs, as well as the annual rate of ICs, were assessed.

Data source

DATASUS is the Informatics Department of the SUS (https://datasus.saude.gov.br/). SUS is available to the whole population and is the only source of healthcare for 75% of the Brazilian population[11], responsible for collecting, processing, and disseminating healthcare data in Brazil, of which most information is from the public healthcare system (SUS). All information in the database is constantly updated.

DATASUS databases are administrative claim data that include data on inpatient information systems (SIH[11]) and outpatient information systems (SIA[12]), which are used for payments and auditing in the public setting. SIH includes the causes of hospitalization according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Data are presented as procedure codes from billing records and include demographic information, all procedures (whether the patient is hospitalized), number of procedures, and other additional information. All outpatient or inpatient procedures available in SUS follow the standardized procedure list SIGTAP. The ID code in SIA is able to link outpatient procedures to a single patient[13]; however, SIH does not have this ID coding. Thus, to allow for a longitudinal assessment in both systems at the patient level, a probabilistic record linkage was performed using multiple steps with different combinations of patient data from both the databases[14,15]. Ethical approval was not necessary as this was a secondary study that used anonymized data.

There is a supplemental system that coexists with the public system in Brazil, where nearly of 22%–25% of the Brazilian population is covered by private health insurance[16]. Some patients with private health insurance seek SUS to access high-cost medications while not seeking additional care within SUS, and no overall control is in place for dispensing most medications. To mitigate misleading results, patients that only used SUS to receive high-cost medications, but conduct treatment and healthcare partially by their private health insurance, were excluded. They were identified as patients who only had claims related to medication delivery (procedure code 06) without any claims related to other procedures (laboratory tests, exams, other therapies, hospitalizations, *etc.*).

Statistical analysis

As an observational secondary database descriptive study, no statistical hypothesis was intended, and only descriptive analysis was performed to describe ICs in patients who reported CD ICD-10 codes and underwent CVT in a public setting in Brazil.

The outcomes were summarized as absolute frequencies and percentages (%) for categorical variables and measures of central tendency and dispersion for continuous variables. Additionally, percentages were calculated over the number of patients with available (non-missing) data and Kaplan–Meier curves for time-to-event data. According to the type of variable the 95% confidence intervals (95%CIs), as applicable: Normal distribution for continuous variable, normal approximation to binominal distribution for proportion, and Poisson distribution for IR, as applicable.

The difference between the date of birth was used to calculate the age of patients and the first CVT and the time of follow-up according to the difference between the index date (CVT first claim) and the last date of patients available in the database. Timing of using CVT or anti-TNF therapy was calculated according to the date of the first and last claims of each drug reported by each patient, regardless of the gaps between them. The time taken for each drug was expressed as a continuous variable, such as mean, SD, median, and quartiles of the mean.

The CVT profile was expressed as the percentage of patients with at least one claim for sulfasalazine, mesalazine, azathioprine, or methotrexate. The anti-TNF therapy profile was expressed as the percentage of patients with at least one claim of infliximab, adalimumab, or certolizumab after the index date. The patients may have used a combination of therapies during the study period; however, this segregation was not performed. Switching CVT to anti-TNF therapy was defined as patients that had one or more claim (s) of a different drug than the previous claim.

The primary outcome was the IC profile of patients with CD after the initiation of CVT. ICs were assessed and expressed according to the total number of patients and total number of claims of each type of ICs per year after CVT initiation (annual ICs from 1 to 5 years). The mean (SD) and percentage of ICs per year were also calculated.

The total number of IC events (total number of claims), number of patients with at least one IC (first event), and total number of PY (defined as the time between the first claim of CVT therapy [index date] up to the last information available in the database for each patient) were expressed and used to calculate the IR (95%CI).

For the time-to-event analysis (Kaplan–Meier curve), it will be considered as censored the date of the last claim of the patient in the database or the date of the end of the study period for those patients without claim of ICs. The depiction of time to ICs in general population with CD and its subgroups (CVT-only and anti-TNF therapy) was described for all types of ICs (overall, procedure-related, associated diseases, and hospitalization-related). The time to switch from CVT to antiTNF therapy and time from the first evidence of anti-TNF to the first IC in the antiTNF therapy subgroup were also assessed.

ICs were not assessed according to CVT received or based on whether the patient discontinued or continued CVT. No imputation methods were used. Data were analyzed using Python version 3.6.9.

RESULTS

Demographics

A patient attrition flowchart is presented in Figure 1. A total of 16809 patients with CD who received CVT met the inclusion criteria. Of these, 12163 (72.2%) had no evidence of anti-TNF (CVT-only) and 4646 (27.8%) had evidence of anti-TNF therapy after the index date. The patient's demographic parameters are presented in Table 1 for all groups: Overall population with CD, CVT-only population, and anti-TNF therapy population. Over half of the patients resided in the southeast region and a minority in the North region of Brazil in all cohorts. Across cohorts, most of the patients were female (60%, 61%, and 54%) and Caucasian (53%, 51%, and 57%) for the general, CVT-only, and anti-TNF therapy populations, respectively. The mean age of 44 (± 15), 46 (± 15), and 40 (± 14) years and median (interquartile range) follow-up period of 4.34 (2.42–6.34), 4.17 (2.25–6.17), and 4.84 (2.92–6.84) years were found in the overall, CVT-only, and anti-TNF therapy populations, respectively.

Treatment characteristics

According to the inclusion criteria, all patients with CD had received CVT, and the mean time (SD) using CVT was 3.22 years (2.46; Table 1). Most patients used mesalazine (74%), followed by azathioprine (42%), sulfasalazine (15%), and methotrexate (2%). The percentage of patients who used each CVT drug was comparable across cohorts.

The mean time (SD) using CVT was 3.16 (2.46) years in patients with CD not exposed to anti-TNF therapy (CVT-only) and 1.84 years (1.75) in those who used CVT prior to anti-TNF therapy in the anti-TNF therapy cohort; in the anti-TNF therapy cohort, the mean time of anti-TNF therapy was 2.39 (2.06) years.

Among the 4646 patients who had evidence of anti-TNF therapy, 59% used infliximab, 51% used adalimumab, and 3% used certolizumab pegol, at some point in the study. Of these, 2603 (56%) patients presented with at least one claim of immunosuppressor drugs before anti-TNF therapy initiation.

ICs

Table 2 shows the IR of ICs in all cohorts. In the general CD group, patients had an overall IR (95%CI) of 7.48 (7.27–7.68) per 100 patients. The IR stratified by associated disease (ICD-10–related), procedure-related, and CD hospitalization-related ICs was 6.59 (6.39–6.78), 4.00 (3.98–4.15), and 0.61 (0.55–0.67) per 100 PY, respectively. In total, 14697 claims of ICs were reported from 4633 patients, of which 9429 claims were reported for IC associated diseases, 4707 for procedure-related ICs, and 561 as CD hospitalization-related ICs reported from 4162, 2706, and 454 patients, respectively.

The IR of ICs was also expressed in the CVT-only subgroup (Table 2). In total, 6415 claims (reports) of ICs from 3026 patients were identified. The overall IR (95%CI) of ICs was 6.8 (6.5–7.04) per 100 PY, and the IR of associated disease, procedurerelated, and hospitalization-related ICs was 6.1 (5.9–6.3), 3.7 (3.5–3.9), and 0.58 (0.42–0.54) per 100 PY, respectively. Table 2 also shows the ICs in patients with CD with evidence of anti-TNF therapy. In total, 3928 claims for ICs from 1607 patients were found. The overall IR of ICs (95%CI) was 9.2 (8.8–9.6) per 100 PY, and the IR of associated disease, procedure-related, and hospitalization-related ICs was 7.9 (7.5–8.3), 4.8 (4.5–5.1), and 0.9 (0.8–1.1) per 100 PY, respectively.

The annual rates of ICs (1–5-year period) in general, CVT-only, and anti-TNF therapy in patients with CD are described in Figure 2, respectively. In the first year after CVT initiation, 8.3% of patients in the general CD cohort, 7.4% in the CVT-only cohort, and 10.7% in the anti-TNF therapy cohort presented with at least one IC (overall), and in the fifth year, 8.3%, 7.4%, and 9.9% of patients presented with at

Table 1 Demographic characteristics and follow-up of patients with Crohn's disease at Sistema Único de Saúde: General, conventional therapy-only, and anti-tumor necrosis factor therapy population, n (%)

	General patients with CD	CVT-only	Anti-TNF therapy
Patients	16809 (100)	12163 (72)	4646 (28)
Age, yr			
Mean (SD)	44.09 (15.38)[4]	46.37 (15.42)	39.98 (13.72)[5]
Median (IQR)	43.27 (31.31–55.33)[4]	46.06 (34.10-57.62)	37.53 (28.59-50.47)[5]
Gender			
Male	6804 (40)	4686 (39)	2118 (46)
Female	10005 (60)	7477 (61)	2528 (54)
Ethnicity, *n* (%)			
Caucasian	8877 (53)	6214 (51)	2663 (57)
Mixed	5002 (29)	3108 (26)	1330 (29)
Black	622 (4)	451 (4)	171 (4)
Missing/others	2308 (14)	2390 (19)	482 (10)
Region of residence			
Southeast	10241 (61)	7085 (58)	3156 (68)
South	2369 (14)	1765 (15)	604 (13)
Midwest	756 (4)	491 (4)	265 (6)
Northeast	3188 (19)	2668 (22)	520 (11)
North	254 (2)	153 (1.3)	101 (2)
Missing	1 (0)	1 (0.01)	0 (0)
Follow-up time[1], yr			
Mean (SD)	4.44 (2.37)	4.3 (2.36)	4.86 (2.35)
Median (IQR)	4.34 (2.42–6.34)	4.17 (2.25–6.17)	4.84 (2.92–6.84)
CVT			
Mesalazine	12423 (74)	9376 (77)	3145 (68)
Sulfasalazine	2458 (15)	1864 (15)	619 (13)
Azathioprine	7078 (42)	4012 (33)	3126 (67)
Methotrexate	318 (2)	180 (1.5)	140 (3)
Anti-TNF therapy			
Infliximab	2737 (16)	-	2737 (59)
Adalimumab	2378 (14)	-	2378 (51)
Certolizumab	145 (0.8)	-	145 (3)
Time using CVT[2], years			
Mean (SD)	3.22 (2.46)	3.16 (2.46)	1.84 (1.75)
Median (IQR)	2.67 (1.08–5.00)	2.59 (1.00–4.92)	1.25 (0.50–2.61)
Time using anti-TNF therapy[3], yr			
Mean (SD)	-	-	2.39 (2.06)
Median (IQR)	-	-	1.76 (0.67–3.67)
Time using CVT therapy prior to anti-TNF therapy			
Mean (SD)	-	1.84 (1.75)	-

Median (IQR)	-	1.25 (0.50–2.61)	-
Immunosuppressant therapy prior to anti-TNF therapy, *n* (%)	-	-	2603 (56)

[1]Time since index date conventional therapy up to the last date of patient information available in the database.
[2]Calculated based on the index date and the last claim of conventional therapy.
[3]Calculated based on the anti-tumor necrosis factor drug initiation date and the last date of patient information available in the database.
[4]Age at the index date (conventional therapy initiation).
[5]Age at the initiation of anti-tumor necrosis factor therapy.
Conventional therapy and/or anti-tumor necrosis factor therapy describes the proportion of patients who have used each drug. Patients could use one or more drugs, alone or in combination. Immunosuppressant therapy: Azathioprine and/or methotrexate. CD: Crohn's disease; CVT: Conventional therapy; SUS: Sistema Único de Saúde; TNF: Tumor necrosis factor; IQR: Interquartile range.

Table 2 Incidence rate of intestinal complications (combined and segregated by type of intestinal complications) in general population with Crohn's disease (*n* = 16809), patients with no evidence of anti-tumor necrosis factor therapy (conventional therapy-only, *n* = 12163), and patients with evidence of anti-tumor necrosis factor therapy (*n* = 4646)

	Total number of events	First event[1] (*n*)	PY	IR per 100 PY (95%CI)
General patients with CD (*n* = 16809)				
Overall (combined)	14697	4633	61931.84	7.48 (7.27–7.68)
Associated disease	9429	4162	63123.61	6.59 (6.39–6.78)
Procedure-related	4707	2706	67528.54	4.00 (3.85–4.15)
CD hospitalization-related	561	454	73645.51	0.61 (0.55–0.67)
CVT-only (*n* = 12163)				
Overall	6415	3026	44431.39	6.8105 (6.5763–7.0447)
Associated disease	5890	2739	45060.27	6.0785 (5.8579–6.2991)
Procedure-related	2934	1768	47820.30	3.6972 (3.5281–3.8663)
CD-related hospitalization	286	247	51654.41	0.5782 (0.4187–0.5377)
Evidence of anti-TNF therapy (4646)				
Overall	3928	1607	17500.45	9.1826 (8.7548–9.6105)
Associated disease	3539	1423	18063.34	7.8778 (7.485–8.2707)
Procedure-related	1773	938	19708.24	4.7594 (4.4622–5.0567)
CD hospitalization-related	275	207	21991.1	0.9413 (0.8137–1.0689)

[1]Counted only the first intestinal complication (number of patients), but patients could present more than one intestinal complication or type of intestinal complications.
PY: Patient year [sum time of all patients under risk – since index date up to date of first intestinal complications (IC, patients with ICs) or date of last available data (patients without ICs)]. Prior to anti-tumor necrosis factor (anti-TNF) therapy: Since index date up to date of first IC or up to date of anti-TNF therapy initiation. After anti-TNF therapy: Since date of anti-TNF therapy initiation up to date of first IC or up to date of last available data (without ICs). Associated disease according to ICD-10 code: International Classification Disease - 10th edition. CD: Crohn's disease; CVT: Conventional therapy; ICs: intestinal complications; IR: Incidence rate = *n* of patients with event/PY × 100; TNF: Tumor necrosis factor.

least one IC (overall), respectively. The percentage and mean number of events per patient showed similar trends across the years.

Common ICD-10 codes and procedures

The most common IC according to the type of associated disease (ICD-10–related) was anal fistula (31%) and that according to the type of procedure-related was fistulotomy (48%) in the general population with CD (Table 3).

Time-to-event analysis

The visual representation of time-to-event (ICs) in the general cohort with CD according to the type of ICs is represented in the Kaplan–Meier curve (Figure 3), which suggests a decreasing trend of IC

Table 3 Description of the most common intestinal complications reported as associated disease or procedure predefined in general population with Crohn's disease (n = 16809)

Associated disease (ICD-10–related complications)	Description	Number of patients with ICs associated diseases (*n* = 4162)	Percentage (%)
K603	Anal fistula	1270	31
K610	Anal abscess	835	20
R100	Acute abdomen	422	10
K612	Anorectal abscess	406	10
K635	Polyp of colon	401	10
K629	Disease of anus and rectum, unspecified	350	8
K632	Fistula of intestine	267	6
K631	Perforation of intestine (nontraumatic)	251	6
K602	Anal fissure, unspecified	229	6
K601	Chronic anal fissure	174	4
Procedure-related ICs		**Number of patients with procedure-related ICs (*n* = 2706)**	
407020276	Fistulotomy	1308	48
407020136	Anorectal abscess drainage	785	29
407020217	Internal sphincterotomy	350	13
407020179	Enterectomy	129	5
407020144	Ischiorectal abscess drainage	110	4
407020403	Retossigmoidectomy	105	4
407020209	Enterotomy	92	3
407020101	Colostomy	89	3
407020390	Body removed – rectum or colon polyps	83	3
407020225	Excision of anorectal tumor	78	3

Enterectomy is a surgical procedure (incision) performed to remove a part of the intestine (either small or large). CD: Crohn's disease; ICs: Intestinal complications; ICD-10: International classification of diseases – 10th revision.

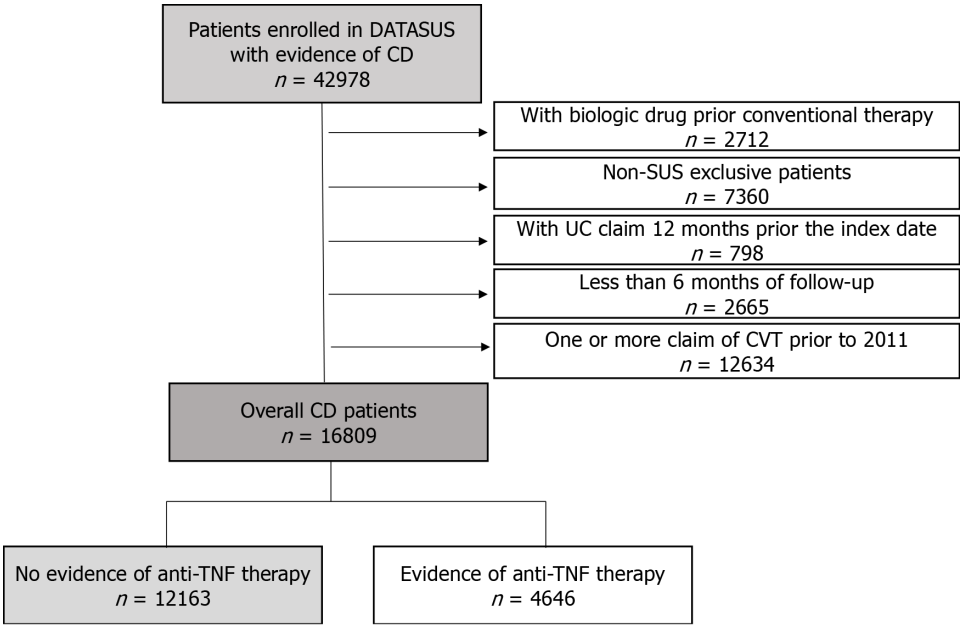
probability starting with the associated disease type, followed by procedure-related and CD hospitalization-related ICs.

Figure 4 depicts the time to overall IC in the general population with CD, CVT-only, and anti-TNF therapy cohorts. The anti-TNF therapy cohort was the subgroup that sustained a shorter duration before an IC or censoring event.

Supplementary Figure 1 presents the Kaplan–Meier curve depicting the proportion of patients who switched from CVT to anti-TNF therapy, irrespective of whether the patient has had IC status. Among the patients in the anti-TNF therapy cohort, nearly 20%, 27%, 32%, and 38% were at risk of switching from CVT to anti-TNF therapy at 2, 4, 6, and 8 years, respectively, following their first CVT. Supplementary Figure 2 illustrates the time from CVT to anti-TNF therapy after the first IC claim (overall ICs). Approximately 15%, 22%, 30%, and 35% of the patients were at risk of switching from CVT to anti-TNF therapy at 2, 4, 6, and 8 years following their first CVT.

DISCUSSION

The current study revealed insights into the clinical and treatment characteristics enhancing evolution and progression of the disease relevant to patients diagnosed with CD and treated with available drugs in the public healthcare system in Brazil between 2011 and 2020. Although, methodological factors could contribute to underestimating numbers of ICs within the DATASUS database, it is possible to note an important and constant number of events over the years either in patients that have used only



DOI: 10.12998/wjcc.v11.i14.3224

Figure 1 Patient attrition flowchart. CD: Crohn's disease; CVT: Conventional therapy; SUS: Sistema Único de Saúde; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

CVT or anti-TNF therapy.

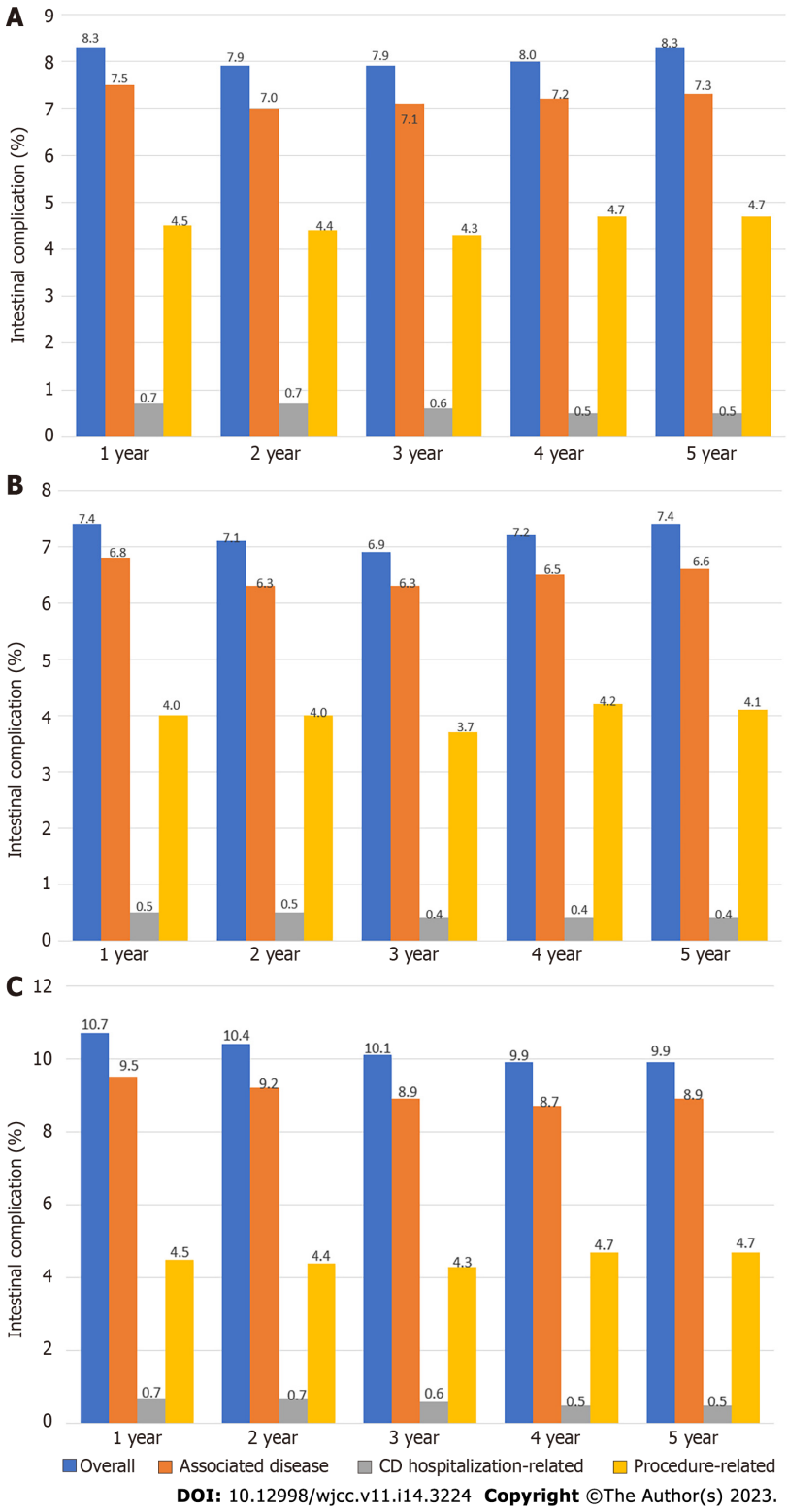
A large proportion of patients with CD in our study were from the southeast and the minority in northeast regions of Brazil, which might be a consequence of discrepancy in reports and/or assistance across the regions of the country and lack and/or delay in diagnosing CD patients.

CD is a progressive illness, and absence of timely and effective treatment results in considerable cumulative structural damage and complications[17]. The goal of CD treatment is to achieve clinical and endoscopic remission, avoid disease progression, and minimize surgical interventions[8]. Some evidences indicate that CVT, including immunosuppressant agents, may be insufficient to control CD progression, resulting in complications and/or considerable surgeries rates[18]. Accordingly, applying pre-defined and validated types of ICs in our study allowed for the longitudinal assessment of disease evolution and progression across the years. Our findings show that the IR of ICs is nearly 7.5 per 100 PY in patients who received either CVT or anti-TNF therapy (general cohort). Approximately 8% of general patients with CD present with at least one IC in the first year of CVT. This proportion of patients with some ICs was sustained across the years up to the last year observed in the study (5 years).

Anal fistula (31%) was the most common ICD-related IC, and fistulotomy (48%) was the most common procedure-related IC. Corroborating our findings, Schwartz *et al*[19] (2002) reported that fistulas occur in up to 35% of patients with CD and perianal fistulas occur in 20%[19]. In general, fistulas rarely heal without treatment and require pharmacological treatment, and most surgery rates can reach nearly 83%[19]. Based on previous observations, invasive procedures, such as intestinal surgeries, are most commonly indicated for medically refractory CD, medication side effects, and complications of disease, including hemorrhage, perforation, obstruction, and fistula formation[20]. Considering the current structure of healthcare delivery in Brazil, surgery and other complex procedures are not uncommon, and even complementary exams are postponed due to the lack of resources and specialists in the system[21]. These could prevent the achievement of a real and necessary treatment approach to control CD in the public system, keeping patients longer in pharmacological therapy, even if a further invasive approach is necessary. The higher lifetime risk of chronic uncontrolled inflammation may exacerbate symptoms and complications[22] and may influence the treatment pattern and procedures described in the present database. CD is a progressive disease, and it is important to closely monitor patients with a high risk of progression by risk stratification, escalation of therapy, and availability of therapies with different mechanisms of action[4].

Observing the same variables in the CVT-only and anti-TNF cohorts, it is possible to note that patients who used anti-TNF therapy at some point in their treatment tended to present earlier and/or more cases of ICs than patients who did not use anti-TNF therapy, although no formal comparisons were performed.

A robust literature shows that adding anti-TNF drugs to the CD therapeutic scheme helps in decreasing the risk of surgery, hospitalization, and disease-related complications[23], in addition to improving the quality of life[22]. The higher rate of ICs in patients with CD exposed to anti-TNF therapy than in the other cohorts in the present study is somewhat understandable. Anti-TNF is

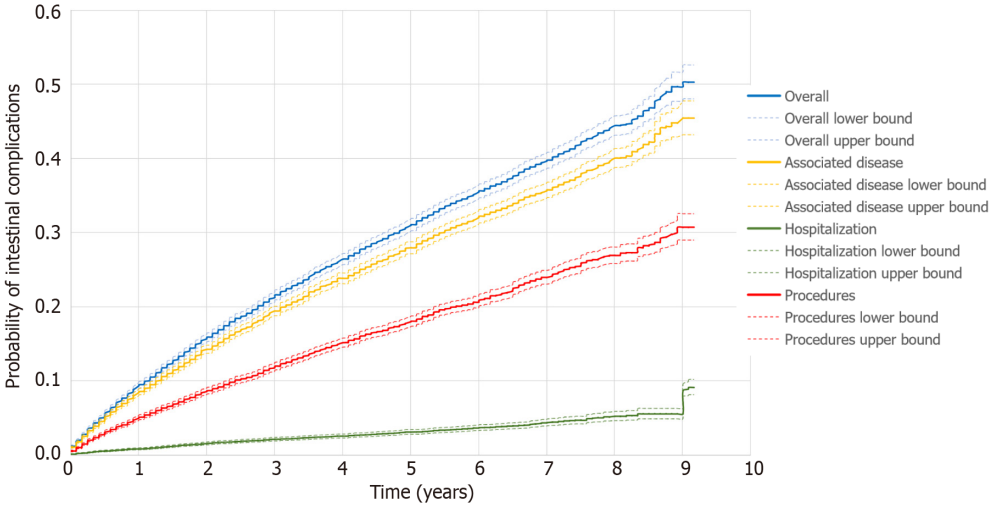


DOI: 10.12998/wjcc.v11.i14.3224

Figure 2 Annual rates of intestinal complications. A: The overall population with CD (*n* = 16809); B: CVT-only population (*n* = 12163); C: Anti-TNF therapy population (*n* = 4646). CD: Crohn's disease; CVT: Conventional therapy; TNF: Tumor necrosis factor.

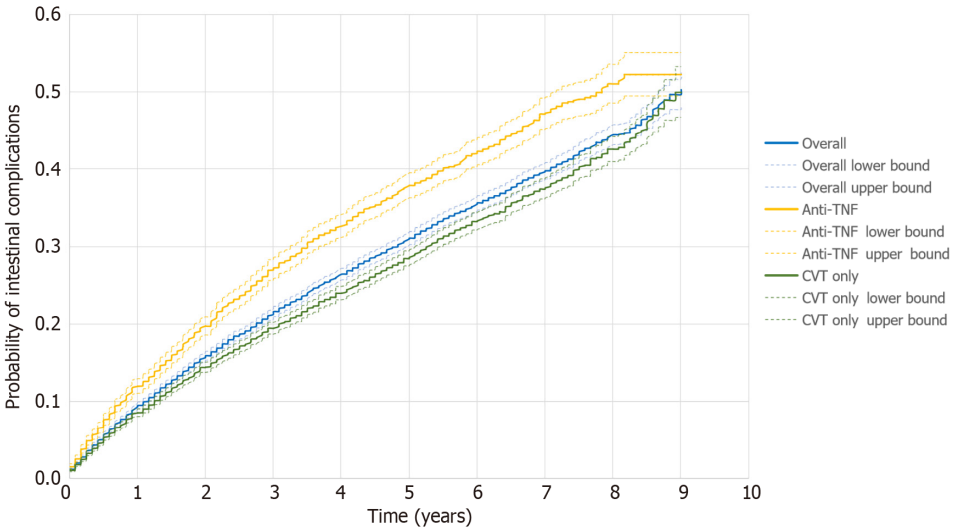
prescribed more often for the treatment of moderate-to-severe CD and/or for those who have become refractory to standard treatment[24]. Furthermore, it is inherent that this subgroup includes patients with advanced and/or longer disease periods who are non-responders and/or failures to anti-TNF therapy. As a consequence of the method limitations, the natural course, time, and severity of the disease were not contemplate in the analyses due to methodological limitations. Therefore, the rates may have been affected by different clinical aspects besides the treatment approach.

In addition to anti-TNF, other drugs with different mechanisms of action might offer potent alternatives for controlling disease and preventing ICs in patients with CD. Reinforcing this, clinical trials



DOI: 10.12998/wjcc.v11.i14.3224

Figure 3 Kaplan–Meier curve depicting time to intestinal complications in the general population with Crohn's disease (*n* = 16809) according to the type of intestinal complications (overall, associated disease, hospitalization-related, or procedure-related).



DOI: 10.12998/wjcc.v11.i14.3224

Figure 4 Kaplan–Meier curve depicting the time to intestinal complications in the general population with Crohn's disease (*n* = 16809) and subgroups conventional therapy-only cohort (*n* = 12163) and anti-tumor necrosis factor-therapy cohort (*n* = 4646). CVT: Conventional therapy; TNF: Tumor necrosis factor.

showing the induction and maintenance of durable remission of novel molecules with mechanisms of action different from those of anti-TNF agents in patients with CD naïve and/or previously anti-TNF failure are growing and consistent[25,26]. However, studies comparing the safety and efficacy of anti-TNF agents and novel molecules are limited[20]. Some studies indicated no difference in terms of effectiveness[27], while some have suggested considerable benefits with novel molecules, such as vedolizumab[28].

The optimal timing of anti-TNF therapy represents another important concern in CD management [5]. Our study indicates that nearly 30% of the patients switched from CVT to anti-TNF treatment for a long duration using CVT before switching, even if they had any IC. Of those, only 15% of patients switched after having an IC, which might be due to the lack of availability of medications with other mechanisms of action in the public healthcare system. Better outcomes have been observed when biologic drugs are introduced early in newly diagnosed patients[22,29-31]. Access to care and early intervention, including biologic agents to treat inflammatory disorders, can be difficult to achieve in the Brazilian public healthcare system[32], and usually leads to more severe morbidity and failure of prolonged courses of treatment.

Our study has several limitations that need discussion. First, longitudinal and timedependent analyses of outcomes and drug exposures of interest are dependent on greater completion and accuracy; however, DATASUS may be limited in the data captured for these variables due to the nature of the data entered (reimbursement purpose). Second, CVT and anti-TNF treatment coverage is based on the first claim of each drug in the database and the reason for anti-TNF use could not be determined. Third, it is not possible to distinguish whether a patient might be receiving their drug at private institutions (out of pocket). Medications used as part of CD treatment also include other drugs, such as corticosteroid agents; however, not all of them are described in SIGTAP. Also, the availability of each conventional and/or anti-TNF drug at the SUS varies over time due to strategies, policies, national guidelines, and other factors. Fourth, although associated diseases, procedures, and hospitalization related to CD were carefully pre-defined as ICs, they did not cover 100% of all possible complications related to CD. Therefore, the complication rates could have been underestimated. In addition, event rates might be underestimated because data such as comorbidities requiring hospitalization might not be captured because the record linkage used to build a patient-level longitudinal cohort is ICD-10 dependent. To reduce this bias, we used broad procedural terms and ICD-10 related to possible complications.

CONCLUSION

This study assessed the progression and evolution of patients with CD representative of the real-world treatment approach available in the Brazilian public healthcare system from 2020 to 2021. We were able to find a consistent and important number of ICs in patients treated with CVT and eventually anti-TNF therapy, capturing associated disease trends, procedures, and surgeries' patterns, as well as hospitalization rate due to the disease. Besides providing up-to-date IC estimates, our data indicate that CD remains a substantial public health problem in Brazil. Further strategies such as adequate access, earlier intervention, and/or inclusion of other drugs with different mechanisms of action might positively impact CD patients.

ARTICLE HIGHLIGHTS

Research background

Patients with Crohn's disease (CD) undergoing therapy available in the public healthcare system (Sistema Único de Saúde) in Brazil over the last decade.

Research motivation

Observe patients with CD who initiated and either only received conventional therapy (CVT) or also initiated anti-tumor necrosis factor (anti-TNF).

Research objectives

Verify the real-world intestinal complications (ICs) of patients with CD in the Brazilian public healthcare system.

Research methods

Patients with CD with at least one claim of CVT (sulfasalazine, azathioprine, mesalazine, or methotrexate). IC was defined as a CD-related hospitalization, pre-defined procedure codes (from rectum or intestinal surgery groups), and/or associated disease (pre-defined international classification of diseases – 10th revision codes), and overall (one or more type of ICs).

Research results

This study highlights a consistent rate of ICs over time in all the CD populations assessed, especially in patients exposed to anti-TNF therapy.

Research conclusions

The Brazilian public health care system should continue to develop additional strategies for treading CD.

Research perspectives

Effective CD treatment in Brazil's public healthcare system may require additional strategies.

FOOTNOTES

Author contributions: Sassaki LY, Galhardi-Gasparini R, Martins AL, Saad-Hossne R, Barreto TB, Marcolino T and Yang Santos C participated in designed, interpretation of the data and revised the article critically for important intellectual content; Ritter AMV and Balula B participated in the acquisition, analysis and draft the initial manuscript.

Supported by Takeda Pharmaceutical Brazil.

Conflict-of-interest statement: Dr. Yang-Santos reports grants from Takeda Pharmaceuticals Brazil, during the conduct of the study; Sassaki LY is a speaker for Janssen and Takeda and participates in the advisory boards of Takeda and AbbVie; Martins AL served on the advisory boards of Takeda, AbbVie, Janssen, Pfizer, and Amgen and is a speaker for Amgen and Janssen; Galhardi-Gasparini R is a speaker for Janssen, Takeda, and AbbVie; Saad-Hossne R is a speaker for Novartis and is on the advisory boards for AbbVie, Takeda, Janssen, Pfizer, Fresenius, and Amgen; Ritter AMV and Balula B are employees of IQVIA, Brazil; Marcolino T, Barreto TB, and Yang-Santos C are employees of Takeda Pharmaceuticals, Brazil.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Country/Territory of origin: Brazil

ORCID number: Ligia Yukie Sassaki 0000-0002-7319-8906; Adalberta Lima Martins 0000-0002-0273-5743; Rodrigo Galhardi-Gasparini 0000-0002-1032-5349; Rogerio Saad-Hossne 0000-0002-8166-0304; Alessandra Mileni Versut Ritter 0000-0002-4434-4791; Tania Biatti Barreto 0000-0003-1871-1815; Taciana Marcolino 0000-0003-2578-4537; Bruno Balula 0000-0002-1752-1422; Claudia Yang-Santos 0000-0002-6023-607X.

S-Editor: Li L
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **Torres J**, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020; **14**: 4-22 [PMID: 31711158 DOI: 10.1093/ecco-jcc/jjz180]

2 **Lima Martins A**, Volpato RA, Zago-Gomes MDP. The prevalence and phenotype in Brazilian patients with inflammatory bowel disease. *BMC Gastroenterol* 2018; **18**: 87 [PMID: 29914399 DOI: 10.1186/s12876-018-0822-y]

3 **Gasparini RG**, Sassaki LY, Saad-Hossne R. Inflammatory bowel disease epidemiology in São Paulo State, Brazil. *Clin Exp Gastroenterol* 2018; **11**: 423-429 [PMID: 30464570 DOI: 10.2147/CEG.S176583]

4 **Feuerstein JD**, Cheifetz AS. Crohn Disease: Epidemiology, Diagnosis, and Management. *Mayo Clin Proc* 2017; **92**: 1088-1103 [PMID: 28601423 DOI: 10.1016/j.mayocp.2017.04.010]

5 **Kwak MS**, Cha JM, Ahn JH, Chae MK, Jeong S, Lee HH. Practical strategy for optimizing the timing of anti-tumor necrosis factor-α therapy in Crohn disease: A nationwide population-based study. *Medicine (Baltimore)* 2020; **99**: e18925 [PMID: 32150045 DOI: 10.1097/MD.0000000000018925]

6 **Ha F**, Khalil H. Crohn's disease: a clinical update. *Therap Adv Gastroenterol* 2015; **8**: 352-359 [PMID: 26557891 DOI: 10.1177/1756283X15592585]

7 **Goulet O**, Abi Nader E, Pigneur B, Lambe C. Short Bowel Syndrome as the Leading Cause of Intestinal Failure in Early Life: Some Insights into the Management. *Pediatr Gastroenterol Hepatol Nutr* 2019; **22**: 303-329 [PMID: 31338307 DOI: 10.5223/pghn.2019.22.4.303]

8 **Adegbola SO**, Sahnan K, Warusavitarne J, Hart A, Tozer P. Anti-TNF Therapy in Crohn's Disease. *Int J Mol Sci* 2018; **19** [PMID: 30065229 DOI: 10.3390/ijms19082244]

9 **Thia KT**, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010; **139**: 1147-1155 [PMID: 20637205 DOI: 10.1053/j.gastro.2010.06.070]

10 **Lovasz BD**, Lakatos L, Horvath A, Szita I, Pandur T, Mandel M, Vegh Z, Golovics PA, Mester G, Balogh M, Molnar C,

Komaromi E, Kiss LS, Lakatos PL. Evolution of disease phenotype in adult and pediatric onset Crohn's disease in a population-based cohort. *World J Gastroenterol* 2013; **19**: 2217-2226 [PMID: 23599648 DOI: 10.3748/wjg.v19.i14.2217]

11 **Bittencourt SA**, Camacho LA, Leal Mdo C. [Hospital Information Systems and their application in public health]. *Cad Saude Publica* 2006; **22**: 19-30 [PMID: 16470279 DOI: 10.1590/S0102-311X2006000100003]

12 **Brasil**, Ministério da Saúde, Secretaria de Atenção à Saúde, Departamento de Regulação, Avaliação e Controle Coordenação-geral de Sistemas de Informação. Manual Técnico Operacional SIA/SUS Sistema de Informações Ambulatoriais. 2010:69 [DOI: 10.5123/s1679-49742006000200006]

13 **Ali MS**, Ichihara MY, Lopes LC, Barbosa GCG, Pita R, Carreiro RP, Dos Santos DB, Ramos D, Bispo N, Raynal F, Canuto V, de Araujo Almeida B, Fiaccone RL, Barreto ME, Smeeth L, Barreto ML. Administrative Data Linkage in Brazil: Potentials for Health Technology Assessment. *Front Pharmacol* 2019; **10**: 984 [PMID: 31607900 DOI: 10.3389/fphar.2019.00984]

14 **Justo N**, Espinoza MA, Ratto B, Nicholson M, Rosselli D, Ovcinnikova O, García Martí S, Ferraz MB, Langsam M, Drummond MF. Real-World Evidence in Healthcare Decision Making: Global Trends and Case Studies From Latin America. *Value Health* 2019; **22**: 739-749 [PMID: 31198192 DOI: 10.1016/j.jval.2019.01.014]

15 **Barbour J**, Araújo A, Zanoteli E, França Jr MC, Ritter AMV, Casarin F, Julian GS, Yazawa P, Mata VE, Carlos NS. Healthcare resource utilization of spinal muscular atrophy in the Brazilian Unified Health System: a retrospective database study. *J. Bras. Econ. da Saúde.* 2021; **13**: 94-107 [DOI: 10.21115/jbes.v13.n2.p94-107]

16 **Maia Diniz I**, Guerra AA Junior, Lovato Pires de Lemos L, Souza KM, Godman B, Bennie M, Wettermark B, de Assis Acurcio F, Alvares J, Gurgel Andrade EI, Leal Cherchiglia M, de Araújo VE. The long-term costs for treating multiple sclerosis in a 16-year retrospective cohort study in Brazil. *PLoS One* 2018; **13**: e0199446 [PMID: 29928006 DOI: 10.1371/journal.pone.0199446]

17 **Ferrante M**, Karmiris K, Newnham E, Siffledeen J, Zelinkova Z, van Assche G, Lakatos PL, Panés J, Sturm A, Travis S, van der Woude CJ, Reinisch W, Colombel JF, Panaccione R. Physician perspectives on unresolved issues in the use of conventional therapy in Crohn's disease: results from an international survey and discussion programme. *J Crohns Colitis* 2012; **6**: 116-131 [PMID: 22261537 DOI: 10.1016/j.crohns.2011.09.009]

18 **Cosnes J**, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; **54**: 237-241 [PMID: 15647188 DOI: 10.1136/gut.2004.045294]

19 **Schwartz DA**, Loftus EV Jr, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002; **122**: 875-880 [PMID: 11910338 DOI: 10.1053/gast.2002.32362]

20 **Chang MI**, Cohen BL, Greenstein AJ. A review of the impact of biologics on surgical complications in Crohn's disease. *Inflamm Bowel Dis* 2015; **21**: 1472-1477 [PMID: 25811432 DOI: 10.1097/MIB.0000000000000362]

21 **Viacava F**, Oliveira RAD, Carvalho CC, Laguardia J, Bellido JG. SUS: supply, access to and use of health services over the last 30 years. *Cien Saude Colet* 2018; **23**: 1751-1762 [PMID: 29972484 DOI: 10.1590/1413-81232018236.06022018]

22 **Rubin DT**, Griffith J, Zhang Q, Hepp Z, Keshishian A. The Impact of Intestinal Complications on Health Care Costs Among Patients With Inflammatory Bowel Disease Treated With Anti-Tumor Necrosis Factor Therapies. *Inflamm Bowel Dis* 2021; **27**: 1201-1209 [PMID: 33107564 DOI: 10.1093/ibd/izaa270]

23 **Singh S**, Heien HC, Sangaralingham LR, Schilz SR, Kappelman MD, Shah ND, Loftus EV Jr. Comparative Effectiveness and Safety of Anti-Tumor Necrosis Factor Agents in Biologic-Naive Patients With Crohn's Disease. *Clin Gastroenterol Hepatol* 2016; **14**: 1120-1129.e6 [PMID: 27058635 DOI: 10.1016/j.cgh.2016.03.038]

24 **Dalal SR**, Cohen RD. What to Do When Biologic Agents Are Not Working in Inflammatory Bowel Disease Patients. *Gastroenterol Hepatol (N Y)* 2015; **11**: 657-665 [PMID: 27330493]

25 **Tarabar D**, Hirsch A, Rubin DT. Vedolizumab in the treatment of Crohn's disease. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 283-290 [PMID: 26810276 DOI: 10.1586/17474124.2016.1135051]

26 **Hahn L**, Beggs A, Wahaib K, Kodali L, Kirkwood V. Vedolizumab: An integrin-receptor antagonist for treatment of Crohn's disease and ulcerative colitis. *Am J Health Syst Pharm* 2015; **72**: 1271-1278 [PMID: 26195652 DOI: 10.2146/ajhp140449]

27 **Laredo V**, Gargallo-Puyuelo CJ, Gomollón F. How to Choose the Biologic Therapy in a Bio-naïve Patient with Inflammatory Bowel Disease. *J Clin Med* 2022; **11** [PMID: 35160280 DOI: 10.3390/jcm11030829]

28 **Sandborn WJ**, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: 23964933 DOI: 10.1056/NEJMoa1215739]

29 **Ma C**, Beilman CL, Huang VW, Fedorak DK, Kroeker KI, Dieleman LA, Halloran BP, Fedorak RN. Anti-TNF Therapy Within 2 Years of Crohn's Disease Diagnosis Improves Patient Outcomes: A Retrospective Cohort Study. *Inflamm Bowel Dis* 2016; **22**: 870-879 [PMID: 26818419 DOI: 10.1097/MIB.0000000000000679]

30 **Pillai N**, Lupatsch JE, Dusheiko M, Schwenkglenks M, Maillard M, Sutherland CS, Pittet VEH; Swiss IBD Cohort Study group. Evaluating the Cost-Effectiveness of Early Compared with Late or No Biologic Treatment to Manage Crohn's Disease using Real-World Data. *J Crohns Colitis* 2020; **14**: 490-500 [PMID: 31630164 DOI: 10.1093/ecco-jcc/jjz169]

31 **Dulai PS**, Peyrin-Biroulet L, Demuth D, Lasch K, Hahn KA, Lindner D, Patel H, Jairath V. Early Intervention With Vedolizumab on Longer Term Surgery Rates in Crohn's Disease: Post Hoc Analysis of the GEMINI Phase 3 and Long-term Safety Programs. *J Crohns Colitis* 2020; **15**: 195-202 [PMID: 32691844 DOI: 10.1093/ecco-jcc/jjaa153]

32 **Tundia N**, Kotze PG, Rojas Serrano J, Mendes de Abreu M, Skup M, Macaulay D, Signorovitch J, Chaves L, Chao J, Bao Y. Economic impact of expanded use of biologic therapy for the treatment of rheumatoid arthritis and Crohn's disease in Argentina, Brazil, Colombia, and Mexico. *J Med Econ* 2016; **19**: 1187-1199 [PMID: 27376404 DOI: 10.1080/13696998.2016.1209508]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3238-3247

DOI: 10.12998/wjcc.v11.i14.3238

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of non-pharmacological treatment on the full recovery of social functioning in patients with attention deficit hyperactivity disorder

Ying-Bo Lv, Wei Cheng, Meng-Hui Wang, Xiao-Min Wang, Yan-Li Hu, Lan-Qiu Lv

Specialty type: Psychology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Joshipura KJ, United States; Sanz M, Spain

Received: March 2, 2023
Peer-review started: March 2, 2023
First decision: March 14, 2023
Revised: March 25, 2023
Accepted: April 7, 2023
Article in press: April 7, 2023
Published online: May 16, 2023

Ying-Bo Lv, Wei Cheng, Meng-Hui Wang, Xiao-Min Wang, Yan-Li Hu, Lan-Qiu Lv, Pediatric Health Care Section, Ningbo Women and Children's Hospital, Ningbo 315000, Zhejiang Province, China

Corresponding author: Lan-Qiu Lv, MD, Attending Doctor, Pediatric Health Care Section, Ningbo Women and Children's Hospital, No. 339 Liuting Street, Haishu District, Ningbo 315000, Zhejiang Province, China. lulanqiunb@sina.com

Abstract

BACKGROUND

Long-term treatment of attention deficit/hyperactivity disorder (ADHD) is associated with adverse events, such as nausea and vomiting, dizziness, and sleep disturbances, and poor maintenance of late ADHD medication compromises treatment outcomes and prolongs the recovery of patients' social functioning.

AIM

To evaluate the effect of non-pharmacological treatment on the full recovery of social functioning in patients with ADHD.

METHODS

A total of 90 patients diagnosed with ADHD between May 2019 and August 2020 were included in the study and randomly assigned to either the pharmacological group (methylphenidate hydrochloride and tomoxetine hydrochloride) or the non-pharmacological group (parental training, behavior modification, sensory integration therapy, and sand tray therapy), with 45 cases in each group. Outcome measures included treatment compliance, Swanson, Nolan, and Pelham, Version IV (SNAP-IV) scores, Conners Parent Symptom Questionnaire (PSQ) scores, and Weiss Functional Impairment Rating Scale (WFIRS) scores.

RESULTS

The non-pharmacological interventions resulted in significantly higher compliance in patients (95.56%) compared with medication (71.11%) ($P < 0.05$). However, no significant differences in SNAP-IV and PSQ scores, in addition to the learning/school, social activities, and adventure activities of the WFIRS scores were observed between the two groups ($P > 0.05$). Patients with non-pharmacological interventions showed higher WFIRS scores for family, daily life skills, and

self-concept than those in the pharmacological group ($P < 0.05$).

CONCLUSION

Non-pharmacological interventions, in contrast to the potential risks of adverse events after long-term medication, improve patient treatment compliance, alleviate patients' behavioral symptoms of attention, impulsivity, and hyperactivity, and improve their cognitive ability, thereby improving family relationships and patient self-evaluation.

Key Words: Non-pharmacological treatment; Attention deficit hyperactivity disorder; Social functioning; Recovery; Weiss Functional Impairment Rating Scale scores

Core Tip: This study evaluated the effect of non-pharmacological treatments on the full recovery of social functioning in patients with attention deficit hyperactivity disorder (ADHD). A total of 90 patients with ADHD were included in this study. The non-pharmacological intervention resulted in significantly higher patient compliance than the pharmacological treatment group. Patients in the non-pharmacological intervention group also had significantly higher Weiss Functional Impairment Rating Scale scores on family, daily living skills and self-concept than those receiving medication. Thus, non-pharmacological interventions had a positive impact on the overall recovery of social functioning in ADHD patients compared to long-term pharmacological treatment.

Citation: Lv YB, Cheng W, Wang MH, Wang XM, Hu YL, Lv LQ. Effect of non-pharmacological treatment on the full recovery of social functioning in patients with attention deficit hyperactivity disorder. *World J Clin Cases* 2023; 11(14): 3238-3247

URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3238.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3238

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common chronic neurodevelopmental disorder in childhood and adolescence[1,2], characterized by age-inappropriate distractibility, reduced attention span, overactivity, and emotional impulsivity regardless of the setting, and associated cognitive impairment, and learning difficulties. The age of onset of ADHD is uncertain, with a prevalence of 6–14 years and a peak of 8-10 years, with a significant gender difference of[3-8]: 1 between males and females. The prevalence of the disease also varies widely, ranging from 1.3% to 13.4%, with a mean prevalence of 3%. According to reports on ADHD, approximately 70% of children with ADHD develop symptoms into adolescence and are at significantly greater risk for disruptive behaviors and emotions than during childhood. The global prevalence of ADHD has been growing in the past decades [1]. Clinical studies reveal that symptoms continue in 70% of ADHD children throughout adolescence and 30% into adults, creating disturbances in family connections[9]. ADHD is a chronic condition with lifelong consequences, often associated with poor academic performance[10], emotional instability[3], and behavioral problems[4].

Studies have shown that long-term treatment of ADHD is associated with adverse events[5], such as nausea, vomiting, dizziness, and sleep disturbances, and poor maintenance of late ADHD medication compromises treatment outcomes and prolongs the recovery of patients' social functioning[11]. The American Academy of Child and Adolescent Psychiatry advises pharmaceutical therapies for ADHD above behavioral treatment alone[6], although the American Academy of Pediatrics favors behavioral interventions, particularly for preschool-aged children[7,12]. However, controversy persists regarding the optimal intervention paradigm for ADHD.

Currently, the treatment of ADHD is mainly pharmacological. Long-term drug use is prone to insomnia, loss of appetite, headache, abdominal pain, or risk of drug dependence. Moreover, pharmacological treatment has a negligible effect on children's deficits in social functioning caused by environmental and psychological factors. In addition to pharmacological treatment, non-pharmacological treatments such as biofeedback therapy, family therapy, and combined medical-educational interventions also constitute an important part of disease management, with more targeted correction of children's behavioral disorders, more lasting and stable improvement of social functions, and higher safety compared with pharmacological treatment. In traditional Chinese medicine (TCM), the disease mainly involves the kidney and the liver, and according to clinical observation, comorbidities from the two organs represent most of the evidence. Kidney deficiency is more prominent among the symptoms

of ADHD. TCM focuses on the combination of disease and evidence and coordinates the functions of the internal organs, resulting in significant therapeutic effects.

Thus, exploring the therapeutic effects of non-pharmacological interventions is of great value and long-term significance for patients with ADHD and their families. Therefore, this study investigated the effect of non-pharmacological treatment on the full recovery of social functioning in patients with ADHD.

MATERIALS AND METHODS

Data source

Children diagnosed with ADHD between May 2019 and August 2020 were assessed for eligibility. After excluding eight cases with discontinued treatment due to adverse events, two cases that revoked their consent, and two cases whose parents refused follow-up visits, 90 ADHD patients (73 males and 17 females, aged 6–18 years) were included in the study. The included patients were randomly assigned to receive either methylphenidate hydrochloride and tomoxetine hydrochloride (pharmacological group) or parental training, behavior modification, sensory integration therapy, and sand tray therapy (non-pharmacological group), with 45 cases in each group.

The randomization was conducted using an online web-based randomization tool (freely available at http://www.randomizer.org/). For concealment of allocation, the randomization procedure and assignment were managed by an independent research assistant who was not involved in the screening or evaluation of the participants.

The original sample size calculation estimated that 45 patients would be needed in each group to detect a 3-point difference between groups using a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

The normality of the sample was determined with the Shapiro–Wilk test. Exploratory analyses of descriptive statistical data were performed using the Tukey test. Inferential statistical analysis of quantitative mean data (PES/WES, ISQ, and B.L) was performed using the non-parametric Wilcoxon-Mann–Whitney *U*-test.

All included patients, or their guardians, provided written informed consent. The study was approved by the ethics committee of our hospital.

Inclusion and exclusion criteria

All patients met the diagnostic criteria established in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, regardless of sex. Patients with mental retardation, character disorder, mood disorder, tic disorder, childhood autism, and schizophrenia were excluded.

Clinical characteristics

Hyperactivity and impulsivity: Hyperactivity and impulsivity mostly manifest in early childhood and become obvious in elementary school. The children are hyperactive, talk much in class, and often fight with their classmates.

Inattention: Children have difficulty concentrating when learning and easily respond to external stimuli.

Learning difficulties: Children with normal intelligence have learning difficulties due to the above-mentioned symptoms, and some develop cognitive impairment and general analysis disorder. The onset of the disease is mostly observed before the age of seven and lasts for more than six months.

Dissonant personality or behavioral disorders: Children are more capricious, stubborn, impulsive, lack self-control, and uncomfortable with social interaction. A small number of cases still have personality and behavioral defects in adulthood.

Treatment methods

The pharmacological group received methylphenidate hydrochloride extended-release tablets and tomoxetine hydrochloride tablets.

The non-pharmacological group received parent training, behavior modification, sensory integration therapy, and sand tray therapy. Parent training involved four sessions, including disease awareness, pros and cons of drugs, parent-child relationship, and methods to improve attention span. Behavior modification involved two major courses covering the positive reinforcement method of behavior modification, temporary isolation method, fading method, demonstration method, cognitive behavior therapy, and applied behavior analysis.

In addition, sensory integration therapy involved 45–60 min of training per session over 3–6 mo. The training process included warm-up, vestibular sensory, proprioception, balance, hand-eye coordination, sedation, and fine motor. Warm-up included simple children's songs, finger rhymes, action songs, and

story reading. Vestibular sensor entailed rotating, moving, scooting, and crossing obstacles. Their proprioception was stimulated using "heavy work" activities, such as holding, lifting, pushing, and pulling heavy objects. Balance involved crossing the balance beam, walking along the hula hoop, one-legged games, and balance board. Furthermore, hand-eye coordination included throwing balloons and sandbags, hitting target objects, and throwing objects to partners. Sedation included relaxation activities, simple children's songs, finger rhymes, and storytelling. Finally, fine motor included making snacks, scrapbooking activities, art activities, and coloring.

Sand tray therapy involved 10–12 sessions with a unified sand tray therapist, with each session lasting about 40–60 min. The process includes instructional language, familiarization with the environment, feeling the sand, creating a sand tray, playing with the sand tray, dialogue and communication, dismantling the work, and discussion and analysis with parents. All programs were scheduled after school or during weekends for the children. All patients were followed up once a month for the first six months of drug administration and every 2–3 mo thereafter.

The two groups received Tiaoshen Yizhi Decoction consisting of 20 g of *Paeoniae Radix Alba*, 20 g of *Rehmanniae Radix Praeparata*, 6 g of *Acori Tatarinowii Rhizoma*, 20 g of *Angelicae Sinensis Radix*, 10 g of *Lycii Fructus*, 15 g of *Ostreae Concha*, 10 g of *Testudinis Carapax et Plastrum*, 15 g of *Os Draconis*, 6 g of *Polygalae Radix*, 15 g of *Margarita*, 10 g of *Uncariae Ramulus cum Uncis*, and 6 g of *liquorice root*, grounded into powder and one dose was administered daily. The powder was dissolved in 60 mL of boiling water, and half a dose was administered in the morning and in the evening.

Outcome measures

The compliance scale designed by our hospital was used to assess the patient's treatment compliance before the parental intervention. Compliance was rated by the parents using a 3-point scale: full compliance, partial compliance, and non-compliance.

In addition, the Swanson, Nolan, and Pelham, Version IV (SNAP-IV) was used for rating, which contains nine inattention problems and nine hyperactivity/impulsivity problems, each with a 4-point scale indicating different levels of severity.

The Conners Parent Symptom Questionnaire (PSQ) was used. The questionnaire has 48 items and includes six factors: character problems, learning problems, psychosomatic problems, impulsivity-hyperactivity, anxiety, and hyperactivity index. The higher the factor score, the more severe the problem.

Finally, the Weiss Functional Impairment Rating Scale (WFIRS) was used to assess patients' social functioning. The scale contains 50 items rated by parents on six domains of family, learning/school, life skills, self-concept, social activities, and adventure activities, each on a scale of 0–4, respectively. The lower the score, the better the social functioning

Statistical analysis

If the parameter beta is either a difference of means, a log odds ratio, or a log hazard ratio, then it is reasonable to assume that the beta is unbiased and normally distributed. GraphPad Prism 8 was used for image processing, and SPSS 26.0 software was used to organize the data and for statistical analysis. Measurement data were expressed as mean ± SD and analyzed using the *t*-test. Count data were expressed as a rate (%) and compared using the χ^2 test. $P < 0.05$ indicated that differences were statistically significant.

RESULTS

Patient characteristics

There were 35 males and 10 females in the pharmacological group, aged 6–18 (9.03 ± 1.78) years, with a duration of disease of 11–35 (23.89 ± 1.77) months and Wechsler IQ scores ≥ 85 (90.23 ± 2.91). In total, 39 cases attended school in urban areas, while 6 cases were schooled in non-urban areas. By contrast, there were 38 males and 7 females in the pharmacological group, aged 6–18 (9.23 ± 1.65) years, with a duration of illness of 11-37 (23.48 ± 2.13) months and Wechsler IQ scores ≥ 85 (90.37 ± 2.75). A total of 36 cases attended school in urban areas and 9 cases in non-urban areas. The characteristics of patients in the two groups were comparable ($P > 0.05$) (Table 1).

Treatment compliance

Before treatment, there was no significant difference in compliance between the two groups ($P > 0.05$). After treatment, 43 (95.56%) of the 45 patients in the non-pharmacological group were compliant. The number of partially compliant patients in the non-pharmacological group increased to 22 (48.89%), while the number of non-compliant patients decreased to 2 (4.44%), indicating that non-pharmacological treatment can improve patients' treatment compliance compared with pharmacological intervention, and the difference was statistically significant ($P < 0.05$) (Table 2).

Table 1 Patient characteristics

Characteristics	Pharmaceutical group (*n* = 45)	Non-pharmaceutical group (*n* = 45)	*t* value	*P* value
Sex, *n* (%)			0.653	0.419
Male	35 (77.78)	38 (84.45)		
Female	10 (22.22)	7 (15.55)		
Age (yr, mean)	6-18 (9.03 ± 1.78)	6-18 (9.23 ± 1.65)	0.553	0.582
Duration of disease (mo, mean)	11-35 (23.89 ± 1.77)	11-37 (23.48 ± 2.13)	0.993	0.323
Wechsler intelligence score (score, mean)	≥ 85 (90.23 ± 2.91)	≥ 85 (90.37 ± 2.75)	0.235	0.815
School, *n* (%)			0.720	0.396
Urban	39 (86.67)	36 (80.00)		
Non-urban	6 (13.33)	9 (20.00)		

Table 2 Treatment compliance, *n* (%)

Treatment compliance	Pharmaceutical group (*n* = 45)	Non-pharmaceutical group (*n* = 45)	χ^2	*P* value
Before treatment			0.179	0.673
Complete compliance	1 (2.22)	2 (4.44)		
Partial compliance	21 (46.67)	18 (40.00)		
Non-compliance	23 (51.11)	25 (55.55)		
Compliance	22 (48.89)	20 (44.44)		
After treatment				
Complete compliance	12 (26.67)	21 (46.67)	15.195	< 0.001
Partial compliance	20 (44.44)	22 (48.89)		
Non-compliance	13 (28.89)	2 (4.44)		
Compliance	32 (71.11)	43 (95.56)		

SNAP-IV

There was no statistically significant difference in SNAP-IV scores between the two groups of patients before treatment ($P > 0.05$). SNAP-IV scores were significantly reduced in both groups after treatment; the reduction was greater in the non-pharmacological intervention group (16.85 ± 2.48) than in the pharmacological group (17.69 ± 2.28). However, the differences in SNAP-IV scores between the two groups before and after treatment were not statistically significant ($P > 0.05$) (Figure 1).

Conners parenting inventory

After treatment, patients in the pharmacological group had character problems scores of 0.65 ± 0.11, learning problems scores of 0.88 ± 0.25, psychosomatic problems scores of 3.35 ± 1.05, impulsivity-hyperactivity scores of 1.02 ± 0.51, anxiety scores of 1.98 ± 1.21, and hyperactivity index scores of 0.85 ± 0.36. Patients in the non-pharmacological group had character problems scores of (0.61 ± 0.08), learning problems 0.81 ± 0.11, psychosomatic problems scores of 3.21 ± 0.77, impulsivity-hyperactivity scores of 0.87 ± 0.12, anxiety scores of 1.87 ± 0.89, and hyperactivity scores of 0.79 ± 0.35. There were no significant differences in Conners' PSQ scores between the two groups ($P > 0.05$) (Table 3).

Social functioning

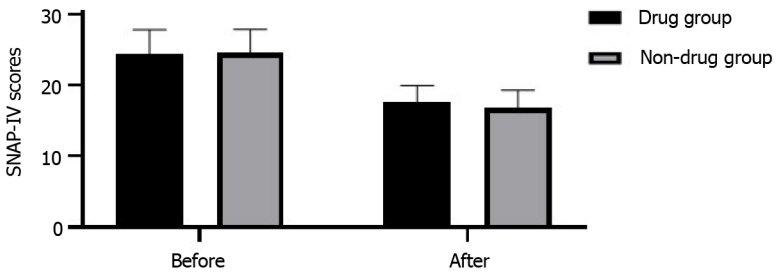
After treatment, the family score in the pharmacological group (0.78 ± 0.52) and non-pharmacological group (0.46 ± 0.41) were statistically significantly different ($t = 3.242$, $P < 0.05$). There was a statistically significant difference ($t = 5.335$, $P < 0.05$) in the life skills score of the pharmacological group (0.99 ± 0.38) and the non- pharmacological group (0.69 ± 0.31). In addition, the difference in the self-concept score of the pharmacological group (0.95 ± 0.42) and the non-pharmacological group (0.65 ± 0.35) was statistically significant ($t = 3.436$, $P < 0.05$). However, there was no significant difference in Weiss scores between the two groups in learning/school, social activities, and risk-taking activities ($P > 0.05$). Family, life skills, and self-concept scores indicated that the non-pharmacological treatment group scored significantly better than the pharmacotherapy group (Table 4).

Table 3 Conners scores (mean ± SD)

	Pharmaceutical group (*n* = 45)	Non-pharmaceutical group (*n* = 45)	*t* value	*P* value
Character problems	0.65 ± 0.11	0.61 ± 0.08	1.973	0.052
Learning problems	0.88 ± 0.25	0.81 ± 0.11	1.719	0.089
Psychosomatic problems	3.35 ± 1.05	3.21 ± 0.77	0.721	0.437
Impulsivity-hyperactivity	1.02 ± 0.51	0.87 ± 0.12	1.921	0.058
Anxiety	1.98 ± 1.21	1.87 ± 0.89	0.491	0.625
Hyperactivity index	0.85 ± 0.36	0.79 ± 0.35	0.802	0.425

Table 4 Weiss scores (mean ± SD)

	Pharmaceutical group (*n* = 45)	Non-pharmaceutical group (*n* = 45)	*t* value	*P* value
Family	0.78 ± 0.52	0.46 ± 0.41	3.242	0.002
Learning/school	0.52 ± 0.44	0.42 ± 0.35	1.193	0.236
Life skills	0.99 ± 0.38	0.69 ± 0.31	5.335	< 0.001
Self-concept	0.95 ± 0.42	0.65 ± 0.35	3.436	0.001
Social activities	0.45 ± 0.51	0.32 ± 0.21	1.581	0.117
Adventure activities	0.22 ± 0.21	0.20 ± 0.18	0.485	0.629



DOI: 10.12998/wjcc.v11.i14.3238

Figure 1 Swanson, Nolan, and Pelham, Version IV scores.

DISCUSSION

ADHD is a psychiatric disorder with significant symptoms that interfere with the child's daily life and learning. ADHD belongs to the categories of "forgetfulness", "deafness", and "false annoyance" in TCM. Approximately 20%–25% of children with ADHD exhibit symptoms that continue into adulthood. Early intervention once symptoms are detected is important to alleviate the symptoms and reduce the impairment of social functioning of the patients[13]. Pharmacotherapy is an effective treatment for ADHD that significantly relieves the core symptoms but is associated with adverse effects[7,14]. The efficacy of non-pharmacological interventions is more stable and efficient than pharmacological treatment.

This study found that the compliance of the non-pharmaceutical group (95.56%) was significantly higher than that of the pharmaceutical group (71.11%) after treatment. This difference in compliance suggests that, after treatment, patients in the non-pharmacological group, could follow their parents' advice and actively cooperate with the treatment, leading to significant improvements in their emotions and physical discomfort. Moreover, there were no significant differences in the SNAP-IV scores, PSQ scores, and the learning/school, social activities, and adventure activities of the WFIRS scores between the two groups. Patients who received non-pharmacological therapies had higher WFIRS ratings for family, life skills, and self-concept than those who received drugs. Compared to pharmaceutical therapies, non-pharmacological interventions provide more enrichment for children's competence development, family connection improvement, and self-evaluation. This finding contrasts with previous research findings, which may be attributed to personalized variances from the small sample size of this study.

In this study, non-pharmacological interventions included parent training, behavior modification, sensory integration therapy, and sand tray therapy. Parenting training is an established treatment for children with ADHD, whereas behavioral therapies focus on the functional recovery of ADHD children. Prior research has demonstrated marked symptom alleviation with parenting treatments for ADHD, and this correlation remains significant when trials with concurrent medication are omitted[15]. Different parenting behavior training programs have been proven effective, such as the 3P Positive Parenting Program[16], the New Forest Parenting Program[17], and the Barkley Program[18]. Some patients with ADHD experience perceptual problems and hand-eye coordination deficits. Research has shown that sensory-motor training could correct hyperactivity, impulsivity, and attention deficit, and adjust the vestibular response deficits of sensory integration disorders (vestibular balance organs form vague images and effects in the brain), tactile defenses (frontal cortical sensory acuity and control difficulties), use disorders in children (blurred body image formed in the brain by proprioceptive kinesthesia and vestibular balance organs, causing clumsy coordination of the five senses, especially hand-eye coordination and reading and writing difficulties), visuospatial shape perception disorder (the same principle as the use disorder, coupled with a lack of dexterity in the visual cortical coordination of the brain), and gravitational insecurity, which were reflected in the results of the current study.

In addition, sand tray therapy improves the ADHD hyperactivity index, character problems, hyperactivity/impulsivity, and anxiety in children. The reason may be that during the sand tray game, children with ADHD focus on the sand in their hands under the supervision of the host tester, which may gradually waken the children's inner ability of self-healing and self-development, effectively reducing anxiety and improving their emotional stability. The succession of sandbox imagery portrayed in the sandbox produces a continual dialogue between the sandbox player's conscious and unconscious thoughts, resulting in an effective improvement of character issues closely associated with personality. The combination of the above non-pharmacological interventions promotes emotional stability, gradually improves former interpersonal sensitivity, personality paranoia, and impulsive and aggressive behavior, and enhances self-esteem and self-confidence, which in turn facilitate the full recovery of patients' social functioning.

According to TCM theory, normal life activities and the mental state of the human body is a state of calmness of Yin and Yang[19,20]. Children's internal organs are delicate and vigorous and frequently suffer from a relative lack of essence, blood, fluid, and other material bases, predisposing them to a state of excitement, hyperactivity, impatience, irritability, and mental disturbance[21,22]. In TCM, treatment for ADHD lies on nourishing Yin and Yang, tonifying the liver, and benefiting the kidneys, for which Tiaoshen Yizhi Decoction was developed in our hospital for ADHD patients. The combination of drugs in the decoction focused on nourishing Yin and Yang without harming the spleen, and Angelicae Sinensis Radix was used to invigorate the blood. In addition, some herbs with sedative functions were used to prevent drowsiness in the children. Moreover, calm and warm medicines were used to avoid damage to the spleen and stomach, and protection of the righteous energy was emphasized in the use of drugs[23].

Our study has some limitations. The diversity of non-pharmacologic treatments increases the difficulty in controlling the operational criteria. Assessing the effectiveness of such non-pharmacologic treatments is closely related to the complexity of the intervention and the influence of different operational providers. Despite our rigorous control of the means and measures of non-pharmacological interventions, uncontrollable variation in the implementation of the treatment may still occur. Second, non-pharmacologic treatment alone is slow and time-consuming, so it is crucial that non-pharmacologic treatment be combined with appropriate pharmacologic treatments. The primary outcome measure in this study was based on self-reported symptoms and function. Therefore, we lacked more objective clinician-based measures. In addition, the sample size of ADAH patients in the study was not large enough, and future studies could be based on a larger sample size. Finally, long-term follow-up information could also be included in future studies to assess the long-term effects of non-pharmacological treatments on patients with ADAH.

No precise etiology or pathogenesis of ADHD has been identified to date, and a growing body of data suggests that the syndrome involves a combination of biopsychosocial factors. Therefore, combining pharmacological and non-pharmacological treatments is more appreciated for the biopsychosocial model. Compared with foreign studies, research in this area in China is still in its initial stage, and there are many problems to be addressed. Therefore, further promotion of research on the non-pharmacological treatment of ADHD in China is required.

CONCLUSION

In contrast to the potential risks of adverse events after long-term medication, non-pharmacological interventions improve the treatment compliance of patients, alleviate patients' behavioral symptoms of attention, impulsivity, and hyperactivity, and improve patients' cognitive ability, thereby enhancing family relationships and patient self-evaluation.

ARTICLE HIGHLIGHTS

Research background

Long-term treatment of attention-deficit hyperactivity disorder (ADHD) is associated with adverse events. Therefore, non-pharmacological treatment has attracted a lot of attention as a new treatment, but its impact on the full recovery of social functioning of ADHD patients is still unknown.

Research motivation

Clarifying the effects of non-pharmacological treatments on the social functioning of ADAH patients is of great value and long-term significance to ADHD patients and their families.

Research objectives

This study aimed to investigate the impact of non-pharmacological treatments on the full recovery of social functioning in patients with ADHD.

Research methods

A total of 90 patients diagnosed with ADHD were enrolled in the study and randomly assigned to either the pharmacological group or the non-pharmacological group, with 45 cases in each group. Treatment adherence, Swanson, Nolan and Pelham Fourth Edition (SNAP-IV) scores, Connors Parental Symptom Questionnaire (PSQ) scores, and Weil Functional Impairment Rating Scale (WFIRS) scores were measured.

Research results

Non-pharmacological interventions resulted in significantly higher compliance in patients compared to pharmacological intervention. No significant differences in the SNAP-IV scores, PSQ scores, and the learning/school, social activities, and adventure activities of the WFIRS scores were observed between the two groups. Patients in the non-pharmacological group showed higher WFIRS scores of family, daily life skills, and self-concept compared to those in the pharmacological group.

Research conclusions

In contrast to the potential risks of adverse events after long-term medication, non-pharmacological interventions improve patient treatment compliance, alleviate patients' behavioral symptoms of attention, impulsivity, and hyperactivity, and improve their cognitive ability, thereby improving family relationships and patient self-evaluation.

Research perspectives

This study demonstrates the positive impact of non-pharmacological treatment compared to long-term medication on the full recovery of social functioning in patients with ADAH.

FOOTNOTES

Author contributions: Lv YB and Cheng W proposed concepts for this study; Wang MH and Lv LQ collected data; Lv YB, Wang XM, and Hu YL contributed to formal analysis; Lv YB and Lv LQ contributed to the survey; Lv YB, Lv LQ, and Wang XM contributed to this method; Lv YB, Lv LQ, Hu YL, and Wang MH supervised the study; Lv LQ validated this study; Lv YB and Cheng W contributed to the visualization of research; Lv YB and Lv LQ initially drafted this manuscript; Lv YB, Cheng W, Wang MH, and Wang XM reviewed and edited the manuscript.

Supported by Ningbo Science and Technology Plan Project Public Welfare Plan (Municipal Level), No: 2019C50099; Ningbo Medical Key Supporting Discipline Child Health Science, No: 2022-F26.

Institutional review board statement: The study was approved by the Ethics Committee of Ningbo Women and Children's Hospital.

Clinical trial registration statement: This study is registered at https://www.researchregistry.com/browse-the-registry#home/registrationdetails/63f45f91a0f7f7002b4f0915/.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent.

Conflict-of-interest statement: We declare that there are no conflicts of interest.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: China

ORCID number: Ying-Bo Lv 0009-0007-7692-8664; Lan-Qiu Lv 0009-0008-1814-0833.

S-Editor: Wang JL
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Polanczyk GV**, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol* 2014; **43**: 434-442 [PMID: 24464188 DOI: 10.1093/ije/dyt261]
2 **Drechsler R**, Brem S, Brandeis D, Grünblatt E, Berger G, Walitza S. ADHD: Current Concepts and Treatments in Children and Adolescents. *Neuropediatrics* 2020; **51**: 315-335 [PMID: 32559806 DOI: 10.1055/s-0040-1701658]
3 **Sobanski E**, Banaschewski T, Asherson P, Buitelaar J, Chen W, Franke B, Holtmann M, Krumm B, Sergeant J, Sonuga-Barke E, Stringaris A, Taylor E, Anney R, Ebstein RP, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV. Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (ADHD): clinical correlates and familial prevalence. *J Child Psychol Psychiatry* 2010; **51**: 915-923 [PMID: 20132417 DOI: 10.1111/j.1469-7610.2010.02217.x]
4 **Biederman J**, Petty CR, Dolan C, Hughes S, Mick E, Monuteaux MC, Faraone SV. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychol Med* 2008; **38**: 1027-1036 [PMID: 18205967 DOI: 10.1017/S0033291707002668]
5 **Sonuga-Barke EJ**, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Stevenson J, Danckaerts M, van der Oord S, Döpfner M, Dittmann RW, Simonoff E, Zuddas A, Banaschewski T, Buitelaar J, Coghill D, Hollis C, Konofal E, Lecendreux M, Wong IC, Sergeant J; European ADHD Guidelines Group. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013; **170**: 275-289 [PMID: 23360949 DOI: 10.1176/appi.ajp.2012.12070991]
6 **Pliszka S**; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007; **46**: 894-921 [PMID: 17581453 DOI: 10.1097/chi.0b013e318054e724]
7 **Subcommittee on Attention-Deficit/Hyperactivity Disorder**; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011; **128**: 1007-1022 [PMID: 22003063 DOI: 10.1542/peds.2011-2654]
8 **National Collaborating Centre for Mental Health (UK)**. Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults. Leicester (UK): British Psychological Society (UK), 2009 [PMID: 22420012]
9 **Harpin VA**. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Arch Dis Child* 2005; **90** Suppl 1: i2-i7 [PMID: 15665153 DOI: 10.1136/adc.2004.059006]
10 **Biederman J**, Petty CR, Fried R, Kaiser R, Dolan CR, Schoenfeld S, Doyle AE, Seidman LJ, Faraone SV. Educational and occupational underattainment in adults with attention-deficit/hyperactivity disorder: a controlled study. *J Clin Psychiatry* 2008; **69**: 1217-1222 [PMID: 18681752 DOI: 10.4088/jcp.v69n0803]
11 **Miklós M**, Futó J, Komáromy D, Balázs J. Executive Function and Attention Performance in Children with ADHD: Effects of Medication and Comparison with Typically Developing Children. *Int J Environ Res Public Health* 2019; **16** [PMID: 31658722 DOI: 10.3390/ijerph16203822]
12 **Sprich SE**, Safren SA, Finkelstein D, Remmert JE, Hammerness P. A randomized controlled trial of cognitive behavioral therapy for ADHD in medication-treated adolescents. *J Child Psychol Psychiatry* 2016; **57**: 1218-1226 [PMID: 26990084 DOI: 10.1111/jcpp.12549]
13 **Felt BT**, Biermann B, Christner JG, Kochhar P, Harrison RV. Diagnosis and management of ADHD in children. *Am Fam Physician* 2014; **90**: 456-464 [PMID: 25369623]
14 **Manos MJ**, Giuliano K, Geyer E. ADHD: Overdiagnosed and overtreated, or misdiagnosed and mistreated? *Cleve Clin J Med* 2017; **84**: 873-880 [PMID: 29173249 DOI: 10.3949/ccjm.84a.15051]
15 **Coates J**, Taylor JA, Sayal K. Parenting Interventions for ADHD: A Systematic Literature Review and Meta-Analysis. *J Atten Disord* 2015; **19**: 831-843 [PMID: 24915737 DOI: 10.1177/1087054714535952]
16 **Sanders MR**. Triple P-Positive Parenting Program: towards an empirically validated multilevel parenting and family support strategy for the prevention of behavior and emotional problems in children. *Clin Child Fam Psychol Rev* 1999; **2**: 71-90 [PMID: 11225933 DOI: 10.1023/a:1021843613840]

17 **Sonuga-Barke EJ**, Daley D, Thompson M, Laver-Bradbury C, Weeks A. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 402-408 [PMID: 11314565 DOI: 10.1097/00004583-200104000-00008]

18 **Storebø OJ**, Elmose Andersen M, Skoog M, Joost Hansen S, Simonsen E, Pedersen N, Tendal B, Callesen HE, Faltinsen E, Gluud C. Social skills training for attention deficit hyperactivity disorder (ADHD) in children aged 5 to 18 years. *Cochrane Database Syst Rev* 2019; **6**: CD008223 [PMID: 31222721 DOI: 10.1002/14651858.CD008223.pub3]

19 **Schein J**, Childress A, Gagnon-Sanschagrin P, Maitland J, Bedard J, Cloutier M, Guérin A. Treatment Patterns Among Patients with Attention-Deficit/Hyperactivity Disorder and Comorbid Anxiety and/or Depression in the United States: A Retrospective Claims Analysis. *Adv Ther* 2023 [PMID: 36913128 DOI: 10.1007/s12325-023-02458-5]

20 **Fu D**, Guo HL, Hu YH, Chen F. A precision medication study of atomoxetine in children with attention deficit hyperactivity disorder: CYP2D6 genetic testing and therapeutic drug monitoring. *Zhongguo Dang Dai Er Ke Za Zhi* 2023; **25**: 98-103 [PMID: 36655671 DOI: 10.7499/j.issn.1008-8830.2208092]

21 **Çelik HEA**, Küçükgöncü S, Erdoğan A, Özerdem A. Response Inhibition and Interference Control in Adult Attention Deficit Hyperactivity Disorder. *Noro Psikiyatr Ars* 2023; **60**: 3-8 [PMID: 36911564 DOI: 10.29399/npa.28192]

22 **Chen SC**, Cheng HL, Han LF, Wu GT, Zhang RY, Suen LK, Chen X, Yeung WF. Parent-administered pediatric tuina for the treatment of attention deficit hyperactivity disorder symptoms: Process evaluation of a pilot randomized controlled trial. *Complement Ther Med* 2022; **70**: 102854 [PMID: 35842070 DOI: 10.1016/j.ctim.2022.102854]

23 **Pauli-Pott U**, Skoluda N, Nater UM, Becker K, Derz F, Kaspar E, Kasperzack D, Kehm K, Kött M, Mann C, Schurek P, Pott W, Schloß S. Long-term cortisol secretion in attention deficit hyperactivity disorder: roles of sex, comorbidity, and symptom presentation. *Eur Child Adolesc Psychiatry* 2023 [PMID: 36917355 DOI: 10.1007/s00787-023-02180-1]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3248-3255

DOI: 10.12998/wjcc.v11.i14.3248

ISSN 2307-8960 (online)

CASE REPORT

Diagnosis of tuberculous uveitis by the macrogenome of intraocular fluid: A case report and review of the literature

Yan-Kun Zhang, Yan Guan, Juan Zhao, Li-Fei Wang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Das Mohapatra SS, India

Received: September 3, 2022
Peer-review started: September 3, 2022
First decision: February 14, 2023
Revised: February 28, 2023
Accepted: March 24, 2023
Article in press: March 24, 2023
Published online: May 16, 2023

Yan-Kun Zhang, Yan Guan, Department of Ophthalmology, Hebei Chest Hospital, Shijiazhuang 050047, Hebei Province, China

Juan Zhao, Department of Respiratory, Hebei Chest Hospital, Shijiazhuang 050047, Hebei Province, China

Li-Fei Wang, Department of Ophthalmology, Hebei Eye Hospital, Xingtai 050010, Hebei Province, China

Corresponding author: Li-Fei Wang, Chief Physician, Doctor, Department of Ophthalmology, Hebei Eye Hospital, No. 399 Quanbei East Street, Xingtai 050010, Hebei Province, China. 928246030@qq.com

Abstract

BACKGROUND

Tuberculous uveitis caused by tuberculosis infection factors is common, but tuberculous uveitis caused by *Mycobacterium tuberculosis* found in the intraocular fluid is rare. This report describes the use of intraocular fluid in the diagnosis of tuberculous uveitis in a patient and reviews the relevant literature.

CASE SUMMARY

A 24-year-old woman who was 31-wk pregnant visited Hebei Chest Hospital due to intermittent chest pain, fever, and decreased vision for 3 mo. The hydrothorax test suggested "tuberculous pleurisy", and yellow effusion was extracted from the chest tube twice resulting in a total volume of approximately 800 mL. The patient chose to continue the pregnancy without treatment, and was hospitalized again due to high fever. Following 2 mo of anti-tuberculosis treatment, a healthy boy was delivered by cesarean section. Tuberculous uveitis was diagnosed using tuberculosis Xpert, and intraocular infection was detected by second-generation gene sequencing. Following systemic treatment, the patient gradually improved, and the corrected visual acuity of the left eye gradually increased from 0.08 to 1.0.

CONCLUSION

The etiology of uveitis is complex, and it is necessary to assess the patient's general condition and apply molecular biology methods to determine the pathogenesis and guide precise treatment, to improve clinicians' awareness and standardize treatment of the disease.

Key Words: Tuberculous uveitis; Metagenomic next-generation sequencing; Xpert; Case

report

Core Tip: Tuberculous uveitis caused by tuberculosis infection factors is common, but tuberculous uveitis caused by *Mycobacterium tuberculosis* found in intraocular fluid is rare. This report describes a 24-year-old pregnant patient who was diagnosed using tuberculosis Xpert and ophthalmologic multimodal imaging after 2 mo of anti-tuberculosis treatment and cesarean delivery of a healthy baby boy. Detection of intraocular infections can be performed by second-generation genetics. Folowing systemic treatment, the patient's vision recovered.

Citation: Zhang YK, Guan Y, Zhao J, Wang LF. Diagnosis of tuberculous uveitis by the macrogenome of intraocular fluid: A case report and review of the literature. *World J Clin Cases* 2023; 11(14): 3248-3255
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3248.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3248

INTRODUCTION

Uveitis is a common ophthalmic disease, and is an important cause of visual impairment in humans, accounting for 10% of blindness worldwide[1]. Tuberculous ocular lesions account for 1.40%-5.74% of systemic tuberculosis[2], among which tuberculous uveitis caused by tuberculosis infection is common. However, tuberculous uveitis in which *Mycobacterium tuberculosis* is found in intraocular fluid is clinically rare. A case was recently discovered in our hospital, and a summary report and literature review were carried out to analyze the results of tuberculosis-related testing, in order to improve clinicians' awareness and standardize treatment of the disease.

CASE PRESENTATION

Chief complaints

A 24-year-old woman who was 31-wk pregnant visited Hebei Chest Hospital due to intermittent chest pain, fever, decreased vision for 3 mo, temperature up to 39.4°C, with chills, dizziness, headache, fatigue and other symptoms, occasional cough, dry cough, and shortness of breath, aggravated after activity, The local fever clinic considered that the patient had "pneumonia", and she was given "cephalosporin" for 10 d, but the symptoms were not significantly relieved. Further examination of the thoracic cavity revealed "left pleural effusion", a pleural tube was placed and yellow effusion was extracted twice, with a total volume of approximately 800 mL. The pleural effusion test showed "tuberculosis pleurisy", and her temperature was better than before, fluctuating at around 37.5°C. As the patient chose to continue the pregnancy without treatment, she was again admitted to our hospital with high fever.

History of present illness

The patient developed pain at the left costal margin without obvious inducement 3 mo previously, which was prick-like pain, aggravated by deep inspiratory coughing and vomiting. There was no posterior sternal pressing sensation and radiating pain in the left shoulder. Electrocardiogram examination in the local hospital showed no abnormalities.

History of past illness

The patient had no previous history of disease.

Personal and family history

No family history of disease.

Physical examination

Body temperature was 38.9°C, the superficial lymph nodes were small, the left lower lung had percussion dullness, breath sounds were decreased on auscultation, and no wet or dry rales were heard. Ophthalmic examination showed that corrected visual acuity was 1.0 in the right eye, 0.08 in the left eye, no hyperemia in bulbar conjunctiva of the right eye, transparent cornea, a little keratic precipitate (KP) in the posterior cornea, good depth in the anterior chamber, normal pupil size, sensitive light reflex,

clear lens, clear edge of the optic disc in the fundus, yellow and white exudation and linear bleeding were seen below the center of the macula. Left eye bulbar conjunctival hyperemia, corneal transparency, KP (+++), aqueous humor opacification, drug-induced pupil dilation, clear lens, vitreous opacification, and invisible fundus were observed. Intraocular pressure was 16 mmHg in the right eye and 17 mmHg in the left eye.

Laboratory examinations

Routine blood tests revealed the following: White blood cells: 8.93 × 10^9/L, neutrophils 85.7%; C-reactive protein: 51.7 ng/mL; T-spot: 277; *Mycobacterium tuberculosis* 31.52; Procalcitonin: 0.370 ng/mL; erythrocyte sedimentation rate: 87 mm/h; metagenomic pathogen detection (metagenomic next-generation sequencing, mNGS) was sent for Xpert examination. The result of *Mycobacterium tuberculosis* detection by Xpert was positive. The PPT test was 10 mm × 10 mm positive.

Imaging examinations

Chest computed tomography (CT) showed hematogenous disseminated pulmonary tuberculosis.

FINAL DIAGNOSIS

A healthy baby boy (37 wk of intrauterine gestation) was delivered by cesarean section in the Department of Obstetrics and Gynecology in our hospital. Placenta Xpert examination showed that *Mycobacterium tuberculosis* was detected, with very low number of bacteria. At this time, the patient had received anti-tuberculosis therapy for 2 mo, and her general condition had improved, and the ocular aqueous humor turbidity was aggravated. Considering that the drug could not pass through the blood-eye barrier, the second-generation gene test of the left ocular aqueous humor was performed to determine intraocular infection, and four sequences of "*Mycobacterium tuberculosis*" were found in the aqueous humor test.

Destruction of the blood-eye barrier is often accompanied by destruction of the blood-brain barrier. Furthermore, brain magnetic resonance imaging (MRI) examination suggested multiple abnormal signal shadows in the brain parenchyma which were enhanced punctate and nodular, and miliary tuberculosis was considered.

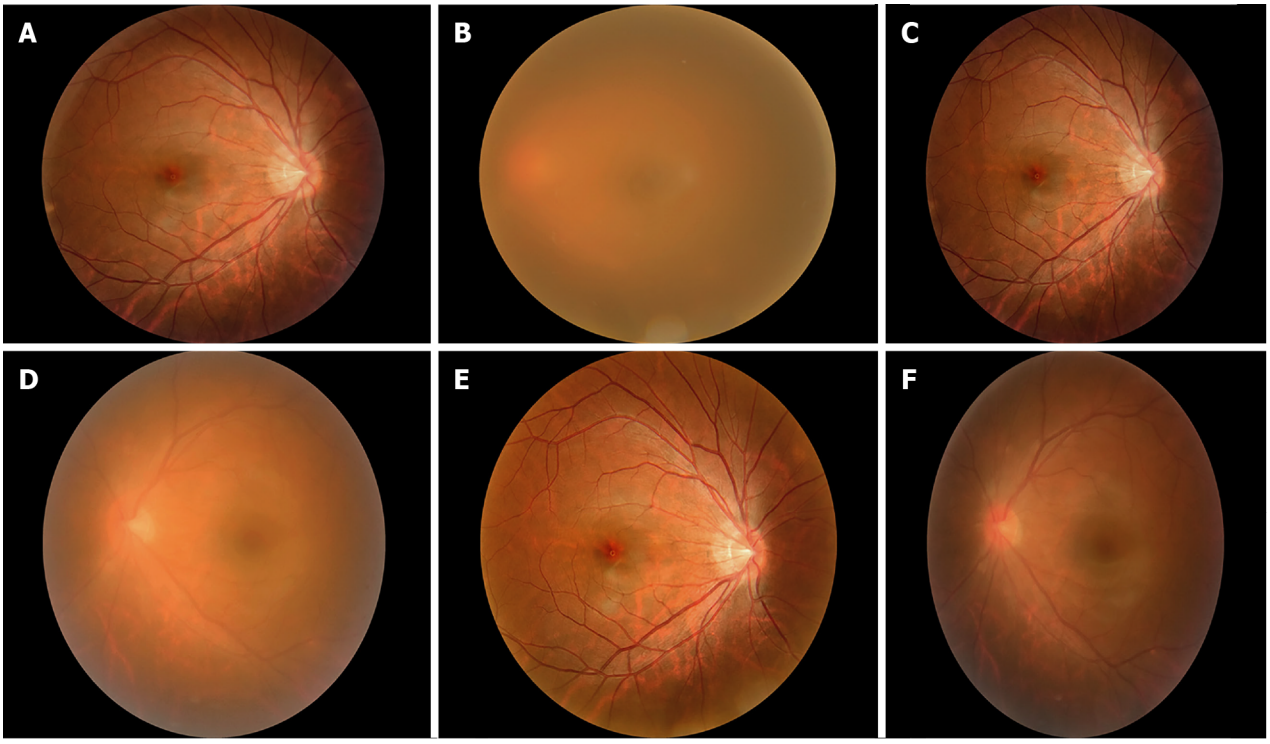
Systemic diagnosis included: Acute hematogenous disseminated pulmonary tuberculosis; tuberculous pleurisy; tuberculous encephalitis; left tuberculous meningitis. Ophthalmologic diagnosis included: Tuberculous uveitis in both eyes; retinal vasculitis in both eyes. A variety of molecular biology detection methods were performed to determine the diagnosis.

TREATMENT

With the cooperation of the Department of Tuberculosis, Obstetrics and Ophthalmology, the patient was given isoniazid 0.3 g orally 1/d, rifampicin 0.45 g orally 1/d, pyrazinamide capsule 0.5 g orally 3/d, and ethambutol 0.75 g orally 1/d. The Ophthalmology Department provided local anti-inflammatory mydriasis, and dexamethasone sodium phosphate 5 mg by peribulbar injection, twice a week. Tobramycin dexamethasone eye drops were administered to the left eye 6/d, pranoprofen eye drops to the left eye 4/d, and compound tropicamide eye drops to the left eye three times before bed.

OUTCOME AND FOLLOW-UP

After systemic treatment, the patient's general condition gradually improved, and corrected vision in the left eye gradually increased from 0.08 to 1.0. According to the uveitis standard working group (Standardization of Uveitis Nomenclature, SUN) standard assessment, the grade of anterior chamber cells and vitreous opacity was evaluated. The patient's anterior chamber aqueous humor was considered to be grade three: the anterior chamber had 21 to 50 cells/field of vision, and the iris and lens were difficult to recognize and classified as grade 1: The aqueous humor had no anterior chamber flash or weak anterior chamber flash, and no inflammatory cells. Vitreous opacity gradually changed from 4 + to 0.5 +. The results of fundus photography are shown in Figures 1A-F, and the changes in ocular B-ultrasound are shown in Figures 2A-D. The changes in anterior segment photography are shown in Figures 3A-B.



DOI: 10.12998/wjcc.v11.i14.3248

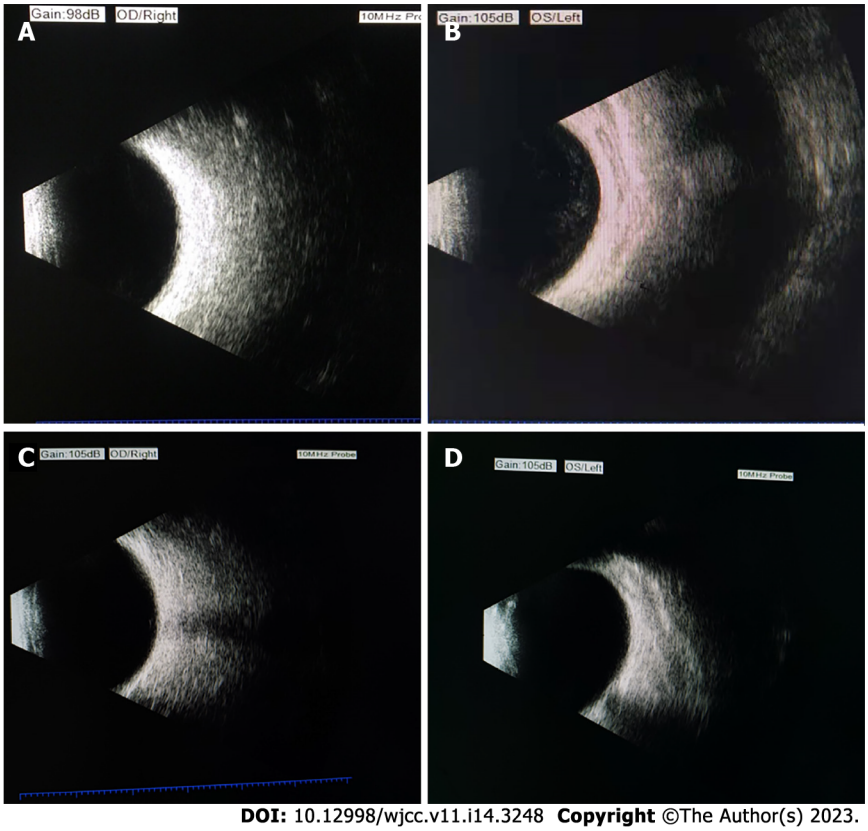
Figure 1 Fundus photography. A: The edge of the optic disc in the right eye is clear, and yellow-white exudation and linear hemorrhage can be seen below the center of the macula (August 31st); B: The refractive interstitium in the left eye is not clear, and the fundus is unclear (August 31st); C: The optic disc edge in the right eye is clear, yellow-white exudation and linear hemorrhage are absorbed below the center of the macula (October 13th); D: The refractive interstitium in the left eye is slightly clearer than before, and the optic disc and large blood vessels are vaguely visible in the fundus (October 13th); E: The fundus in the right eye is almost normal (November 19th); F: The refractive interstitium in the left eye is clearer than before, the edge of the optic disc is clear, and the large blood vessels can run (November 19th).

DISCUSSION

About one-third of the world's population is infected with *Mycobacterium tuberculosis*[3], but only 10% of those infected have clinical manifestations. Tuberculosis is most common in the lungs, but it can actually affect other organs, of which 16%-27% are extrapulmonary infections. Extrapulmonary tuberculosis can involve multiple systems and organs such as skin, eyes, cardiovascular system, digestive system, bones and joints, urinary system and the central nervous system. Intraocular tuberculosis is a unique form of extrapulmonary tuberculosis. All eye tissues except the lens can be infected with *Mycobacterium tuberculosis*[4]. The uvea is rich in blood vessels, containing 96% of the blood flow of the eyeball, and the flow rate in the eye is slow. Previous studies have shown that ocular tuberculosis is relatively rare, mostly secondary to tuberculosis foci in other parts of the body[5]. With the deepening of clinicians' understanding of the disease and improvements in imaging and laboratory testing methods, the detection rate of ocular tuberculosis is increasing. Tuberculous uveitis accounts for 6.9%-10.5% of unexplained uveitis, and 1.4%-6.8% of active tuberculosis patients are complicated by ocular tuberculosis[6-9]. Eye tuberculosis pathophysiology mechanisms include: (1) Active *Mycobacterium tuberculosis* infection - blood system spread of *Mycobacterium tuberculosis* directly into local eye tissue, such as choroid granuloma; and (2) The immune response, has nothing to do with copying an infection, and is related to extrapulmonary organs (eye) of *Mycobacterium tuberculosis* late-onset allergic reactions, such as stomach morphic choroiditis.

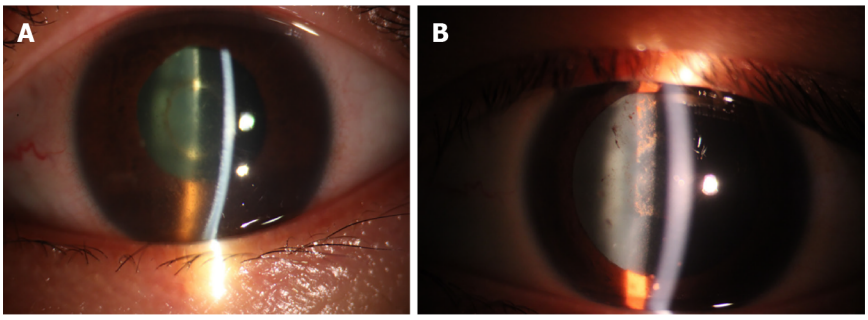
Ocular tuberculosis is usually monocular, but can be binocular. The left eye has been shown to have a higher incidence than the right eye. This is due to anatomical position, as the left common carotid artery emerges directly from the aortic arch, the tuberculous bacterium present in the blood flow *via* the aortic arch enters directly into the left ocular artery, and on the right side needs to pass the innominate artery.

In this case, the tuberculin skin test [postpartum depression (PPD)] was strongly positive, tuberculosis infection T-cell positive T-spot: 277 increased, and three positive findings were found. Brain MRI showed multiple intracranial nodules and diffuse miliary nodules, and chest CT showed miliary nodules in both lungs, which supported the diagnosis of hematogenous disseminated pulmonary tuberculosis. Diagnostic criteria for tuberculous uveitis are as follows: (1) History of systemic tuberculosis or previous history of tuberculosis; (2) Detection of tuberculous bacilli in body fluids or tissues; (3) Ocular lesions consistent with tuberculosis manifestations; (4) Strong PPD positive tuberculin skin test; (5) Effective anti-tuberculosis therapy; and (6) Differential diagnosis: Choroidal inflammation



DOI: 10.12998/wjcc.v11.i14.3248

Figure 2 Changes in ocular B-ultrasound. A: B-ultrasound showed no obvious abnormal echo in the vitreous cavity of the right eye (August 31st); B: B-ultrasound left eye vitreous haze 4+ (August 31st); C: B-ultrasound showed no obvious abnormal echo in the vitreous cavity of the right eye (November 19th); D: B-ultrasound left eye vitreous opacity changed to 0.5+ (November 19th).



DOI: 10.12998/wjcc.v11.i14.3248

Figure 3 The results of eye photography before and after treatment showed that the eye was significantly improved. A: Left eye anterior segment before treatment: Keratic precipitate (KP) (++), anterior chamber inflammatory cells 4+ (August 31st); B: Left eye anterior segment after treatment: Corneal suet-like KP (-), anterior chamber inflammatory cells 0.5+ (November 19th). The presence of KP indicates that the patient has chronic or granulomatous inflammation.

caused by syphilis, toxoplasmosis and other systemic diseases was excluded by laboratory examination. At present, in terms of diagnosis, aqueous humor or vitreous fluid sampling from intraocular fluid is performed under topical anesthesia, which is easier to obtain than other tissue fluid such as lumbar puncture for cerebrospinal fluid and thoracic puncture for pleural effusion. The incidence of intraocular tuberculosis in patients with uveitis has been reported in the literature, including 6.9% in Japan, 4% in China, 10.5% in Saudi Arabia and 20% in India[7,8,10]. The detection method used in this report was molecular biology technology, and the proportion of intraocular tuberculosis diagnosed by polymerase chain reaction (PCR) detection of intraocular fluid is up to 20%. This indicates that the proportion of intraocular tuberculosis in uveitis infection increases with the improvement of examination methods.

Previous studies have found that the positive rate of the tuberculin skin test and chest X-ray in patients with confirmed ocular tuberculosis is only 40% and 57%, respectively[11]. The positive detection rate of chest CT was higher at 68.6%. Therefore, it is necessary to consider the general condition of suspected patients. In the general population, the infection rate of latent tuberculosis is very high. Under the existing conditions, the correct interpretation of tuberculate-related test results can

improve the correct diagnostic rate of systemic tuberculosis and reduce the chance of missing the cause of tuberculosis in "idiopathic uveitis"[12]. PPD rhizomorph skin test and tuberculosis infected T cells are the two most basic methods to confirm previous tuberculosis[13]. The tuberculin test is a type of cellular immune response, low immunity will result in false positives, tuberculosis infected T cells is an immunology examination, it is not affected by immunity, and a positive result shows that the patient had a BCG vaccine or a previous tuberculosis infection. During tuberculosis infection, this test if positive is not significant, and should be based on the size of the value obtained, combined with the patient's own and other imaging examination indicators following a comprehensive analysis.

Intraocular fluid Xpert and metagenomic sequencing, as emerging detection methods, can also help in the diagnosis of tuberculous uveitis. These detection techniques based on molecular biology and polymerase reaction technology, are able to quickly detect *Mycobacterium tuberculosis* and rifampicin resistance, they can trace the tissue fluid in patients following tuberculosis DNA extraction, amplification of ropB genes, and more than 95% rifampicin resistant strains with ropB gene mutations. Most rifampicin resistant strains are also resistant to isoniazid at the same time. Therefore, this test can not only detect rifampicin resistant strains, but also, to a certain extent, indicate whether there are multiple drug-resistant strains. In this case, tuberculosis bacillus DNA was detected in sputum and placenta using this method. mNGS of the intraocular fluid in this case, and Xpert was not only used to evaluate sputum and placental tissue, but also used to extract intraocular fluid from the anterior chamber aqueous humor. As there were only a few samples, only mNGS samples were sent for examination, which is a next-generation sequencing technology based on metagenomics and directly extracts the DNA or RNA of all microorganisms from clinical samples, and studies the genetic composition and community functions of all microorganisms contained in the samples using genomic research strategies. The positive rate of *Mycobacterium tuberculosis* in patients with systemic active tuberculosis complicated by uveitis is relatively high. *Mycobacterium tuberculosis* is an intracellular bacterium with a thick cell wall, which is difficult to detect using conventional detection methods. In this case, the cell-free DNA extraction and library construction process was used to reduce the loss and contamination during the process of wall breaking genome extraction and enzyme digestion interruption, and to reduce contamination of the human sequence, effectively improving the detection rate of difficult-to-detect pathogens[14]. In this case, four sequences of *Mycobacterium tuberculosis* were detected in aqueous humor. Zhou *et al*[15] reported that the sensitivity of mNGS for the diagnosis of active tuberculosis was 44%. They proposed that intracellular bacteria release less extracellular nucleic acids, resulting in a high false-negative rate of mNGS results. Biswas *et al*[16] reported that the sensitivity of intraocular fluid PCR detection was 33.33% in tuberculous retinal vasculitis and 66.67% in granulomatous uveitis. In this case, sputum and placental tissue were detected by Xpert, and intraocular fluid was detected by metagenomic sequencing. At present, the sensitivity of Xpert and metagenomic sequencing for intraocular fluid samples is unclear. The study showed that the detection sensitivity of metagenomic sequencing for all active tuberculosis cases was 44%, which was similar to that of Xpert (42%). The sensitivity can be increased to 60%[15].

For the purpose of intraocular fluid detection in this patient, on the one hand, it was clear that there were pathogens in the eye, and on the other hand, the turbid inflammatory cells were directly removed during the extraction of aqueous humor, and new aqueous humor was generated to replace the aqueous humor lost. The positive rate of mNGS tuberculosis is high in patients with ocular manifestations of vitreous haze and endophthalmitis, and extraocular manifestations of hematogenous disseminated tuberculosis. The positive rate of mNGS tuberculosis was relatively low in patients with ischemic retinal vasculitis, choroidal tuberculoma, and choroiditis. Possible reasons for this are as follows: (1) There is no active replication of *Mycobacterium tuberculosis* in the eye, and the disease manifestation is caused by a delayed hypersensitivity reaction to *Mycobacterium tuberculosis*; and (2) The pathogen is located at the chorioretinal level and not released into the vitreous body[17]. The aqueous humor or vitreous fluid with planktonic cells should be selected to improve the positive rate of intraocular fluid detection.

This article should remind tuberculous physicians that when systemic problems such as hematogenous disseminated tuberculous lesions and tuberculous meningitis are found, attention should be paid to the diagnosis of possible tuberculous eye diseases, in order to avoid missing the diagnosis and delayed treatment, resulting in blindness. In addition, infection in other parts of the body should be considered in the diagnosis and treatment of tuberculous eye disease, and molecular biology detection methods can be used to improve the detection rate, providing patients with an early diagnosis and standardized treatment.

CONCLUSION

This article introduces the use of intraocular fluid in the diagnosis of tuberculous uveitis, the application of molecular biology methods for diagnosis, and the recovery of visual acuity following treatment. These findings illustrate the importance of intraocular fluid in the diagnosis of tuberculous uveitis.

FOOTNOTES

Author contributions: Zhang YK contributed to design and drafting the manuscript; Guan Y, Zhao J and Wang LF contributed to case collection; and all authors approved the final version of the manuscript.

Supported by the Medical Science Research Project of Hebei Province, No. 20191029.

Informed consent statement: The patient signed an informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Yan-Kun Zhang 0000-0001-6766-108X; Yan Guan 0000-0002-2835-6127; Juan Zhao 0000-0002-0183-0888; Li-Fei Wang 0000-0003-0804-8749.

S-Editor: Wang JJ
L-Editor: Webster JR
P-Editor: Li X

REFERENCES

1 **Krishna U**, Ajanaku D, Denniston AK, Gkika T. Uveitis: a sight-threatening disease which can impact all systems. *Postgrad Med J* 2017; **93**: 766-773 [PMID: 28942431 DOI: 10.1136/postgradmedj-2017-134891]
2 **Zhang MX**, Zhang JJ. [Diagnosis and treatment of choroidal tuberculosis]. *Chin J Ophthalmol* 2012; **48**: 4 [DOI: 10.3760/cma.j.issn.0412-4081.2012.02.022]
3 **Eurosurveillance editorial team**. WHO publishes Global tuberculosis report 2013. *Euro Surveill* 2013; **18** [PMID: 24176622]
4 **Wang JB**, Zhang Q, Zhao N, Yu HL, Guan J. [A case of choroidal tuberculoma]. *J Clin Ophthalmol* 2012; **20**: 2 [DOI: 10.3969/j.issn.1006-8422.2012.04.033]
5 **Liao MB**, Shen JK. [Clinicopathological analysis of ocular tuberculosis (report of 6 cases)]. *J Pract Ophthalmol* 1990; **8**: 3
6 **Mercanti A**, Parolini B, Bonora A, Lequaglie Q, Tomazzoli L. Epidemiology of endogenous uveitis in north-eastern Italy. Analysis of 655 new cases. *Acta Ophthalmol Scand* 2001; **79**: 64-68 [PMID: 11167291 DOI: 10.1034/j.1600-0420.2001.079001064.x]
7 **Wakabayashi T**, Morimura Y, Miyamoto Y, Okada AA. Changing patterns of intraocular inflammatory disease in Japan. *Ocul Immunol Inflamm* 2003; **11**: 277-286 [PMID: 14704899 DOI: 10.1076/ocii.11.4.277.18260]
8 **Islam SM**, Tabbara KF. Causes of uveitis at The Eye Center in Saudi Arabia: a retrospective review. *Ophthalmic Epidemiol* 2002; **9**: 239-249 [PMID: 12187422 DOI: 10.1076/opep.9.4.239.1507]
9 **Lara LP**, Ocampo V Jr. Prevalence of presumed ocular tuberculosis among pulmonary tuberculosis patients in a tertiary hospital in the Philippines. *J Ophthalmic Inflamm Infect* 2013; **3**: 1 [PMID: 23514121 DOI: 10.1186/1869-5760-3-1]
10 **Abrahams IW**, Jiang YQ. Ophthalmology in China. Endogenous uveitis in a Chinese ophthalmological clinic. *Arch Ophthalmol* 1986; **104**: 444-446 [PMID: 3954648 DOI: 10.1001/archopht.1986.01050150146047]
11 **Wroblewski KJ**, Hidayat AA, Neafie RC, Rao NA, Zapor M. Ocular tuberculosis: a clinicopathologic and molecular study. *Ophthalmology* 2011; **118**: 772-777 [PMID: 21055814 DOI: 10.1016/j.ophtha.2010.08.011]
12 **Peng XY**, Mao Y. [The dilemma and countermeasure of diagnosis and treatment in tuberculous uveitis]. *Ophthalmol China* 2019; **28**: 325-327
13 **Trad S**, Bodaghi B, Saadoun D. Update on Immunological Test (Quantiferon-TB Gold) Contribution in the Management of Tuberculosis-Related Ocular Inflammation. *Ocul Immunol Inflamm* 2018; **26**: 1192-1199 [PMID: 28700283 DOI: 10.1080/09273948.2017.1332232]
14 **Zeitz O**, Keserü M. Kallikrein-kinin activation by altered vitreous pH: New perspectives for treatment and pathogenesis of diabetic macular edema? Comment on: Gao BB *et al*. Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation. Nat Med. 2007 Feb; 13(2): 181-188. *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 1745-1747 [PMID: 17823811 DOI: 10.1007/s00417-007-0673-7]
15 **Zhou X**, Wu H, Ruan Q, Jiang N, Chen X, Shen Y, Zhu YM, Ying Y, Qian YY, Wang X, Ai JW, Zhang WH. Clinical Evaluation of Diagnosis Efficacy of Active Mycobacterium tuberculosis Complex Infection *via* Metagenomic Next-Generation Sequencing of Direct Clinical Samples. *Front Cell Infect Microbiol* 2019; **9**: 351 [PMID: 31681628 DOI: 10.3389/fcimb.2019.00351]
16 **Biswas J**, Madhavan HN, Gopal L, Badrinath SS. Intraocular tuberculosis. Clinicopathologic study of five cases. *Retina*

1995; **15**: 461-468 [PMID: 8747438]

17 **Ramanjulu R**, Dubey D, Shanmugam MP. Simultaneous mutually exclusive active tubercular posterior uveitis. *Indian J Ophthalmol* 2020; **68**: 2049-2050 [PMID: 32823477 DOI: 10.4103/ijo.IJO_1251_20]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3256-3260

DOI: 10.12998/wjcc.v11.i14.3256

ISSN 2307-8960 (online)

CASE REPORT

Intragastric fish bones migrate into the liver: A case report

Mu-Gen Dai, Jing-Jing Zheng, Jie Yang, Bin Ye

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Baryshnikova NV, Russia; Garbuzenko DV, Russia; Krishnan A, United States; Shelat VG, Singapore

Received: October 9, 2022
Peer-review started: October 9, 2022
First decision: January 17, 2023
Revised: January 29, 2023
Accepted: April 7, 2023
Article in press: April 7, 2023
Published online: May 16, 2023

Mu-Gen Dai, Bin Ye, Department of Gastroenterology, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui 323000, Zhejiang Province, China

Jing-Jing Zheng, Department of Gastrointestinal Surgery, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui 323000, Zhejiang Province, China

Jie Yang, Department of Infectious Disease, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui 323000, Zhejiang Province, China

Corresponding author: Bin Ye, MD, PhD, Chief Doctor, Chief Physician, Doctor, Department of Gastroenterology, The Fifth Affiliated Hospital of Wenzhou Medical University, No. 289 Kuocang Road, Lishui 323000, Zhejiang Province, China. 408252097@qq.com

Abstract

BACKGROUND

A foreign body in the digestive tract is a common disease in the clinic. However, it is rare for a foreign body to migrate into the liver. Most patients are diagnosed before or after perforation of the digestive tract. Laparoscopic removal of intrahepatic foreign bodies is an effective treatment method.

CASE SUMMARY

A 55-year-old male patient was admitted to the hospital due to fever for 3 d, in addition to pain and discomfort in the right side of his waist. After admission, abdominal computed tomography showed a foreign body in the liver, and gastroscopy did not indicate obvious erosion or ulcers. The patient then underwent laparoscopic surgery. During the operation, an abscess was seen near the gastric antrum and between the caudate lobes of the liver. It was approximately 30 mm × 31 mm × 23 mm in size. The abscess was cut open, and a fish bone was found inside. The fish bone had penetrated the liver and was successfully removed. It was confirmed that the fish bone migrated from the stomach to the liver.

CONCLUSION

Although intrahepatic foreign bodies are rare, they should be diagnosed and treated as early as possible to avoid serious complications such as intrahepatic abscess, which may lead to liver resection and even life-threatening events.

Key Words: Foreign body; Intrahepatic; Migrate; Stomach; Case report

Core Tip: Foreign bodies migrating into the liver are rare, but they may lead to liver resection and even life-threatening events. They should be diagnosed and treated as early as possible. We report a patient with a fish bone that migrated from the stomach to the liver and was successfully removed by laparoscopic surgery in the early stage. Early management is a prerequisite to ensure treatment efficacy.

Citation: Dai MG, Zheng JJ, Yang J, Ye B. Intragastric fish bones migrate into the liver: A case report. *World J Clin Cases* 2023; 11(14): 3256-3260
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3256.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3256

INTRODUCTION

Foreign bodies in the digestive tract are common clinical diseases. Most foreign bodies enter the digestive tract consciously, or the patients are aware of foreign body ingestion. Therefore, this can be removed through endoscopy in a timely manner. Perforation of hollow viscus by a foreign body is rare, representing 1% of cases of accidental foreign body ingestion. A few sharp foreign bodies can cause perforation, bleeding, or obstruction of the digestive tract. However, sharp foreign bodies can enter the digestive tract and pass through the stomach and duodenal mucosa and enter the liver, but this is even less common. We report a patient with a fish bone that migrated from the stomach to the liver and was successfully removed by laparoscopic surgery in the early stage, which avoided liver resection. There was no serious infection, bleeding, or other complications.

CASE PRESENTATION

Chief complaints

A 55-year-old male was hospitalized due to fever for 3 d.

History of present illness

The patient developed fever 3 d previously; the highest temperature was 39 °C. The patient also experienced paroxysmal dull pain and discomfort in the right waist, without chills, shivering, or any other digestive tract and respiratory tract symptoms. He self-administered antipyretic drugs, but his temperature did not significantly decrease. Therefore, he came to the hospital for treatment.

History of past illness

The patient's past medical history included hypertension, kidney stones, and gout but no history of the digestive system or other system diseases.

Personal and family history

The patient's personal and family history revealed no information relevant to the current case.

Physical examination

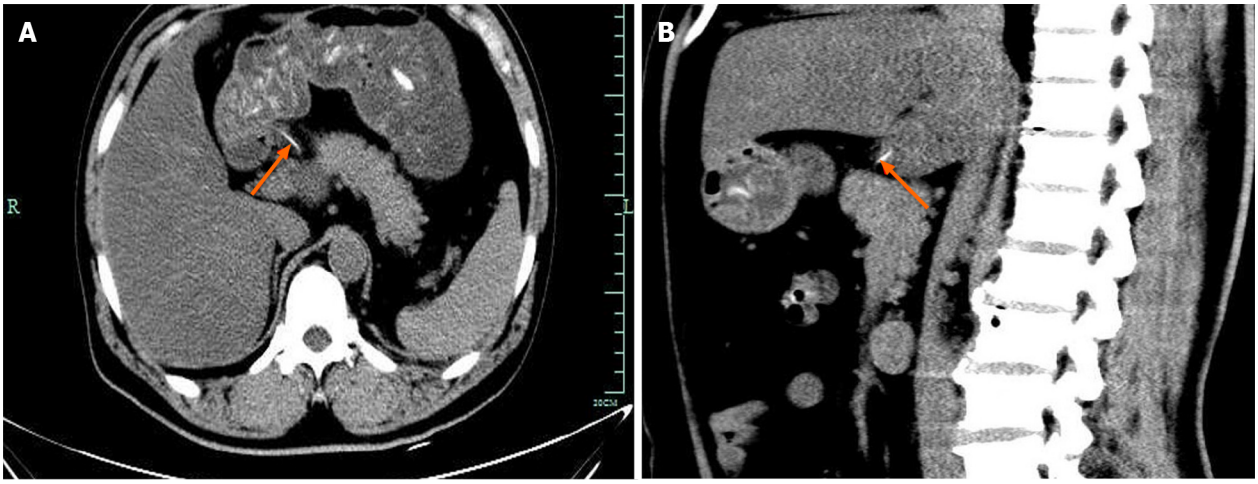
Upon initial evaluation, the patient was 170 cm tall and weighed 65 kg. The patient's temperature was 38.2 °C, heart rate was 90 bpm, and blood pressure (measured with an electronic cuff) was 146/96 mmHg. Heart and lung auscultation was normal, the abdomen was soft, without tenderness, rebound pain, or muscle tension, and percussion pain in the renal area was negative. The remaining examination showed no obvious positive signs.

Laboratory examinations

Laboratory examination results were as follows: C-reactive protein, 153.31 mg/L; white blood cells, 11.93 × 10^9/L (normal: 3.5-9.5 × 10^9/L); procalcitonin, 1.04 ng/mL (normal: < 0.05 ng/mL); and glutamic pyruvic transaminase, 57 U/L (normal: 9-50 U/L). All other tests were normal.

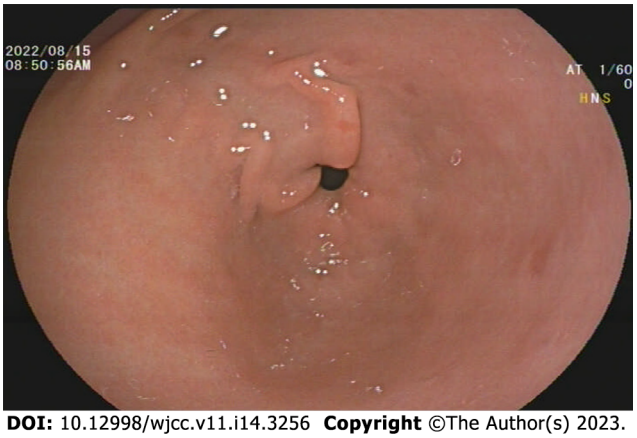
Imaging examinations

Abdominal computed tomography (CT) was performed after admission. It indicated a strip-shaped high-density focus in the stomach that had penetrated the caudate lobe of the liver. This was considered to be a foreign body in the stomach that had penetrated the liver (Figure 1). Emergency gastroscopy was performed to determine whether there were foreign bodies in the stomach. No obvious erosion or ulcers of the gastric mucosa was found during gastroscopy (Figure 2).



DOI: 10.12998/wjcc.v11.i14.3256 **Copyright** ©The Author(s) 2023.

Figure 1 Contrast-enhanced computed tomography. A: Gastric perforation caused by a foreign body in the stomach (arrow); B: The foreign body in the stomach had penetrated the liver (arrow).



DOI: 10.12998/wjcc.v11.i14.3256 **Copyright** ©The Author(s) 2023.

Figure 2 No obvious erosion or ulcers of the gastric mucosa was found during gastroscopy.

FINAL DIAGNOSIS

The patient was finally diagnosed with intrahepatic foreign body.

TREATMENT

After receiving routine intravenous antibiotics treatment, his temperature decreased but did not return to normal. Abdominal CT demonstrated that the foreign body in the stomach had migrated into the liver. Emergency gastroscopy was carried out, and no residue of the foreign body was found in the stomach. Therefore, the patient underwent emergency laparoscopic surgery. During the operation, abscess formation was seen in the hepatogastric space, the abscess was cut, and one end of the fish bone was visible. The fish bone was completely removed. Following removal of the abscess, the gastric wall was examined, and no obvious damage was found (Video 1). The operation went smoothly, and the patient recovered.

OUTCOME AND FOLLOW-UP

Following surgery, the patient's temperature gradually decreased to normal, without abdominal pain and other symptoms. He was discharged 1 wk after the operation and was followed up for 2 wk without experiencing obvious discomfort.

DISCUSSION

Chintamani *et al*[1] reported the world's first case of foreign body in the digestive tract migrating into the liver, causing liver abscess in 1898. Since then only 59 cases have been reported in the literature[1,2]. However, with the development of digestive endoscopy technology[3], most foreign bodies in the digestive tract can be removed. A small number of foreign bodies, such as fish bones, toothpicks, iron wires, *etc*.[4], are thin and sharp. Most do not cause obvious symptoms when penetrating the gastrointestinal tract, making them difficult to find. The most common site of perforation is the stomach [5]. After penetrating the digestive tract, the foreign body often migrates into the left liver[6]. The patient still has no obvious symptoms at this time. With time, bacteria can undergo microbial replication and dissemination, causing liver abscess. The patient may develop fever, abdominal pain, and other symptoms, including serious infection, liver bleeding, *etc*., resulting in serious consequences[7].

Although intragastric foreign body migration into the liver is rare[8], it occurs occasionally. Most patients cannot recall the history of foreign body ingestion[3]. Clinicians need to be alert, and diagnosis depends on ultrasound, CT, *etc*. Ultrasound may be a convenient and radiation-free screening tool that can be used to identify abscesses and possible foreign bodies. On the other hand, CT is the first choice for diagnosis[7] due to its high resolution and accuracy in identifying foreign bodies. It can also be used to assess the depth of penetration and complications.

When it is suspected that a foreign body in the digestive tract has migrated into the liver, it is necessary to conduct timely digestive endoscopy. Some patients may have residues in the digestive tract. Foreign bodies can be removed by digestive endoscopy to avoid traumatic surgery. If necessary, before the foreign body is removed, endoscopic ultrasonography should be performed to determine the relationship between the foreign body and the surrounding blood vessels[9] to avoid massive bleeding and protect the safety of patients. In addition, surgical treatment should be carried out as early as possible for foreign bodies without residues in the gastrointestinal tract[10] rather than after the abscess has liquefied. Timely surgical[11] removal of foreign bodies can reduce the occurrence of complications and preserve the liver.

In the present case, the fish bone transferred from the stomach to the liver, and gastroscopy was performed in a timely manner. No obvious wound was found in the stomach; thus, it could not be removed under endoscopy. Therefore, laparoscopic foreign body removal was selected. Because it was a short amount of time that the foreign body had entered the liver, no obvious damage was found on the gastric wall, hepatogastric space, or liver during the operation. Following removal of the foreign body, complete debridement was conducted to ensure a good treatment effect. Therefore, for liver abscesses of unknown cause, clinicians should consider the possibility of foreign bodies[12], carefully observe the patient's imaging findings, repeatedly ask about relevant medical history regarding ingestion of foreign bodies, carry out endoscopy as soon as possible when there is a high degree of suspicion of foreign bodies in the liver, and perform laparotomy if necessary. Surgery is the most effective method of treatment[13]. Early management is a prerequisite to ensure treatment efficacy.

CONCLUSION

We reported a case of intragastric foreign body that migrated into the liver. Although this is rare, it may cause serious infection and bleeding if not treated in time. This can lead to liver resection and can even be life-threatening, which should stimulate vigilance in clinicians.

FOOTNOTES

Author contributions: Dai MG, Zheng JJ, Yang J, and Ye B designed the research, performed the research, analyzed the data, and wrote the manuscript; all authors read and approved the final manuscript.

Supported by Zhejiang Province Administration Foundation of Traditional Chinese Medicine, No. 2020ZB305.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Bin Ye 0000-0001-7533-9963.

S-Editor: Liu GL
L-Editor: Filipodia
P-Editor: Yu HG

REFERENCES

1 **Chintamani**, Singhal V, Lubhana P, Durkhere R, Bhandari S. Liver abscess secondary to a broken needle migration--a case report. *BMC Surg* 2003; **3**: 8 [PMID: 14531934 DOI: 10.1186/1471-2482-3-8]
2 **Sobnach S**, Castillo F, Blanco Vinent R, Kahn D, Bhyat A. Penetrating cardiac injury following sewing needle ingestion. *Heart Lung Circ* 2011; **20**: 479-481 [PMID: 21315651 DOI: 10.1016/j.hlc.2011.01.006]
3 **Burkholder R**, Samant H. Management of Fish Bone-Induced Liver Abscess with Foreign Body Left In Situ. *Case Reports Hepatol* 2019; **2019**: 9075198 [PMID: 31285930 DOI: 10.1155/2019/9075198]
4 **Subasinghe D**, Jayasinghe R, Kodithuwakku U, Fernandopulle N. Hepatic abscess following foreign body perforation of the colon: A case report. *SAGE Open Med Case Rep* 2022; **10**: 2050313X221103357 [PMID: 35707053 DOI: 10.1177/2050313X221103357]
5 **Yan TD**, Leung PHY, Zwirewich C, Harris A, Chartier-Plante S. An unusual cause of pericardial effusion: A case report of a hepatic abscess following foreign body migration and duodenal perforation. *Int J Surg Case Rep* 2022; **93**: 106931 [PMID: 35279521 DOI: 10.1016/j.ijscr.2022.106931]
6 **Chong LW**, Sun CK, Wu CC. Successful treatment of liver abscess secondary to foreign body penetration of the alimentary tract: a case report and literature review. *World J Gastroenterol* 2014; **20**: 3703-3711 [PMID: 24707157 DOI: 10.3748/wjg.v20.i13.3703]
7 **Pan W**, Lin LJ, Meng ZW, Cai XR, Chen YL. Hepatic abscess caused by esophageal foreign body misdiagnosed as cystadenocarcinoma by magnetic resonance imaging: A case report. *World J Clin Cases* 2021; **9**: 6781-6788 [PMID: 34447825 DOI: 10.12998/wjcc.v9.i23.6781]
8 **Sim GG**, Sheth SK. Retained Foreign Body Causing a Liver Abscess. *Case Rep Emerg Med* 2019; **2019**: 4259646 [PMID: 31934467 DOI: 10.1155/2019/4259646]
9 **Zhang F**, Xu J, Zhu Y, Shi Y, Wu B, Wang H, Huang C. Endoscopic ultrasonography guided cutting scar of esophageal stricture after endoscopic injection sclerotherapy. *BMC Gastroenterol* 2022; **22**: 343 [PMID: 35840909 DOI: 10.1186/s12876-022-02420-9]
10 **Beckers G**, Magema JP, Poncelet V, Nita T. Successful laparoscopic management of a hepatic abscess caused by a fish bone. *Acta Chir Belg* 2021; **121**: 135-138 [PMID: 31433267 DOI: 10.1080/00015458.2019.1658353]
11 **Nassif AT**, Granella VH, Rucinski T, Cavassin BL, Bassani A, Nassif LT. Laparoscopy treatment of liver abscess secondary to an unusual foreign body (rosemary twig). *Autops Case Rep* 2021; **11**: e2021317 [PMID: 34458185 DOI: 10.4322/acr.2021.317]
12 **Dangoisse C**, Laterre PF. Tracking the foreign body, a rare cause of hepatic abscess. *BMC Gastroenterol* 2014; **14**: 167 [PMID: 25262330 DOI: 10.1186/1471-230X-14-167]
13 **Costa Almeida CE**, Caroço T, Silva M, Baião JM, Guimarães A, Ângelo M. Hepatic resection due to a fish bone. *Int J Surg Case Rep* 2021; **81**: 105722 [PMID: 33714000 DOI: 10.1016/j.ijscr.2021.105722]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3261-3266

DOI: 10.12998/wjcc.v11.i14.3261

ISSN 2307-8960 (online)

CASE REPORT

Primary seminal vesicle adenocarcinoma with a history of seminal vesicle cyst: A case report and review of literature

Yu Yao, Shuai Liu, Yu-Lu He, Lei Luo, Gui-Ming Zhang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chaturvedi HTC, India; Koubaa M, Tunisia; Sezer HF, Turkey

Received: November 28, 2022
Peer-review started: November 28, 2022
First decision: February 7, 2023
Revised: February 15, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: May 16, 2023

Yu Yao, Shuai Liu, Lei Luo, Gui-Ming Zhang, Department of Urology, The Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong Province, China

Yu-Lu He, Department of Pathology, The Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong Province, China

Corresponding author: Gui-Ming Zhang, MD, PhD, Doctor, Department of Urology, The Affiliated Hospital of Qingdao University, No. 16 Jiangsu Road, Qingdao 266003, Shandong Province, China. zhangguiming9@126.com

Abstract

BACKGROUND

Primary seminal vesicle adenocarcinoma is a rare malignancy that is difficult to diagnose.

CASE SUMMARY

A 54-year-old man with an 18-year history of a seminal vesicle cyst presented with worsening hematospermia that had persisted for one month. Dynamic contrast-enhanced computed tomography and pelvic magnetic resonance imaging indicated a mass with a cystic-solid component. Robot-assisted seminal vesicle tumor resection was performed, and primary seminal vesicle adenocarcinoma was confirmed pathologically. The patient received pelvic radiotherapy for six weeks, and to date, no evidence of recurrence has been found.

CONCLUSION

Seminal vesicle cysts should be monitored long-term. Seminal vesicle adenocarcinoma presents with non-specific symptoms and can be diagnosed by immunohistochemistry.

Key Words: Seminal vesicles; Adenocarcinoma; Cyst; Robot-assisted surgery; Radiotherapy; Case report

Core Tip: Primary seminal vesicle adenocarcinoma with a long history of seminal vesicle cyst has rarely been reported. Primary seminal vesicle adenocarcinoma is a rare malignancy that is difficult to diagnose. Herein, we present a case of pathologically confirmed primary adenocarcinoma of seminal vesicle with a long history of seminal vesicle cyst.

Citation: Yao Y, Liu S, He YL, Luo L, Zhang GM. Primary seminal vesicle adenocarcinoma with a history of seminal vesicle cyst: A case report and review of literature. *World J Clin Cases* 2023; 11(14): 3261-3266
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3261.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3261

INTRODUCTION

Adenocarcinoma of the seminal vesicle is an extremely rare tumor of the genitourinary system[1]. The early stage of the disease is often asymptomatic and is not easily detected and diagnosed. Seminal vesicle cyst combined with seminal vesicle carcinoma has been reported in a few cases[2-4]. However, adenocarcinoma of the seminal vesicle with a long history of seminal vesicle cysts has not been reported. When symptoms such as hematuria, hematospermia, or localized pain occur, it often means advanced or progressing disease with prostate or lung metastases, leading to a poor prognosis[5]. Notably, metastatic cancer of the seminal vesicles due to metastases from primary prostate, bladder, or rectal cancer invasion is more common; therefore, these conditions should be carefully differentiated[6, 7].

Owing to the rarity of seminal vesicle adenocarcinoma, there are no unified guidelines for treatment. Currently, the optimal treatment is radical resection[8]; however, because of the complex anatomy and the small space around the seminal vesicles and the proximity to the rectum, surgical resection is difficult[9]. Robot-assisted surgery, which has the advantages of fine operation and full exposure of the surgical field, is becoming more popular in the field of urology and appears to be more suitable for seminal vesicle tumors than other surgical approaches[10]. Chemotherapy, radiation, and hormonal therapy have been reported for the adjuvant treatment of seminal vesicle adenocarcinoma[2,5]. We report a case of primary seminal vesicle adenocarcinoma with a long history of seminal vesicle cyst resected by Da Vinci robot-assisted surgery.

CASE PRESENTATION

Chief complaints

A 54-year-old man presented to our outpatient clinic with a history of a seminal vesicle cyst found on physical examination 18 years previously.

History of present illness

The patient's symptoms started 18 years ago with a seminal vesicle cyst found on physical examination. The patient reported occasional hematospermia, hematuria, and perineal discomfort. His symptoms worsened one month prior to presentation.

History of past illness

When first identified, the seminal vesicle cyst was treated by unroofing and decompression; however, the cyst recurred. During regular surveillance, magnetic resonance imaging revealed seminal vesicle cyst.

Personal and family history

The patient had no personal or family history.

Physical examination

Digital rectal examination revealed no obvious abnormalities.

Laboratory examinations

The prostate specific antigen concentration was within the normal range at 0.587 ng/mL (normal range: 0-4 ng/mL).

Imaging examinations

Ultrasonography revealed a 6.9 cm × 5.1 cm × 4.8 cm cystic mass in the left seminal vesicle with a papillary hypoechoic mass in the vesicle wall. Pelvic dynamic contrast-enhanced computed tomography revealed a cystic-solid mass closely related to the seminal vesicles and prostate with an enhancing solid component (Figure 1A). Pelvic magnetic resonance imaging demonstrated a cystic-solid component mass (Figures 1B-D).

FINAL DIAGNOSIS

The final diagnosis of the present case was primary seminal vesicle adenocarcinoma.

TREATMENT

Robot-assisted seminal vesicle tumor resection was performed. A 7 cm light brown cystic mass was seen and was completely removed along with the left seminal vesicle after aspiration of the cystic fluid. A 2 cm × 1.5 cm nodular thickening was seen in the wall of the capsule, and the mass was grayish-white in cross-section. Postoperative pathology revealed that the tumor cells grew in a blister-like, solid, sieve-like, and papillary pattern, with necrosis, and some cells showed a boot-nail-like pattern (Figures 2A and B). The tumor cells invaded beyond the muscle into the extra-muscular tissue and nerves. The tumor did not involve the resection margin. Immunohistochemical staining was positive for cytokeratin (CK)7 (Figure 2C), partially positive for paired-box gene 8 (Figure 2D), and negative for carcinoembryonic antigen, prostate-specific antigen, CK20 (Figure 2E), calretinin, CK5/6, and Wilms' tumor-1. Considering the tumor morphology and the immunohistochemical results, moderately and poorly differentiated seminal vesicle adenocarcinoma was diagnosed pathologically.

OUTCOME AND FOLLOW-UP

The patient was in stable condition after surgery and was discharged seven days later. Two months after discharge, the patient received radiotherapy at a dose of 66 Gray in 30 fractions for six months. After four months of follow-up, no local recurrence or distant metastasis was found in imaging.

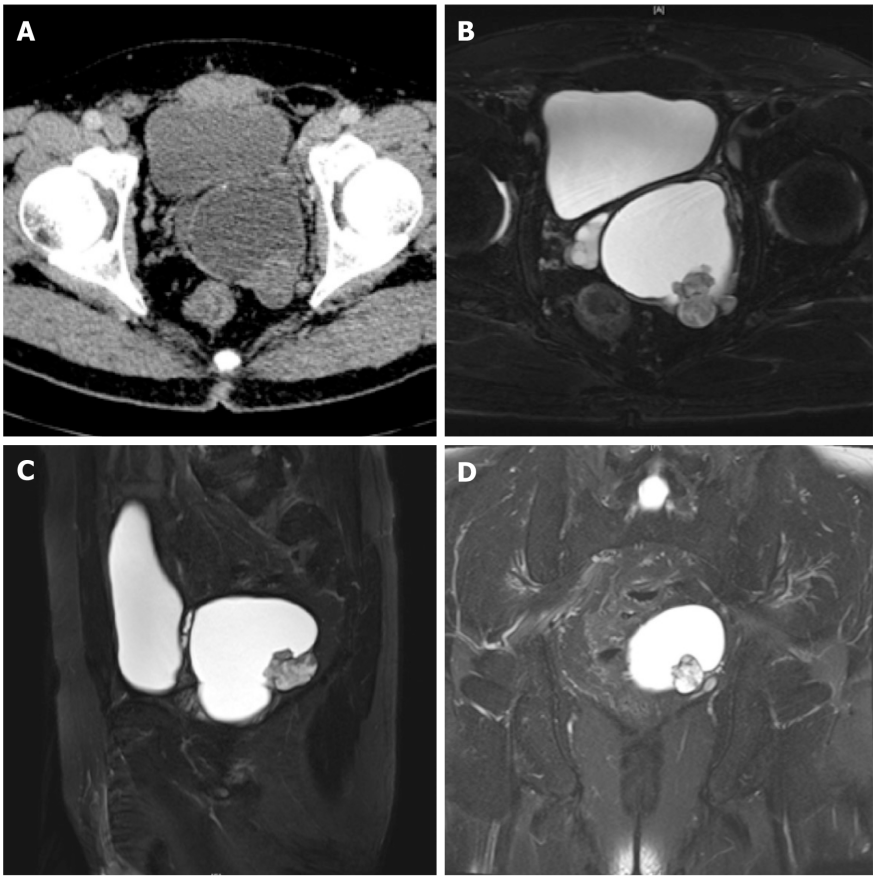
DISCUSSION

Adenocarcinoma of the seminal vesicle is the most common pathological type of seminal vesicle cancer originating from the lining epithelium of the seminal vesicle. Seminal vesicle adenocarcinoma was first reported in 1925[9]. Thiel and Effert collected and reviewed 52 cases of primary seminal vesicle adenocarcinoma[1]. In the following two decades, few cases were reported. The average age of the patients was 63 years; the youngest was only 19 years old, and the oldest was 90 years old[1].

In our case, the patient had an 18-year history of seminal vesicle cyst, which to our knowledge has not been reported previously. Seminal vesicle cyst is thought to be related to renal dysplasia and is caused by the accumulation of secretions owing to abnormal development of the urogenital tract[4]. Seminal vesicle cysts with renal agenesis have been reported in many cases[2-4,11]. In our case, bilateral kidneys and ureters developed normally. Hematospermia and hematuria are common with seminal vesicle adenocarcinoma[1]. Dysuria is uncommon unless the tumor invades the bladder triangle or is very large [12].

It is difficult to distinguish primary seminal vesicle adenocarcinoma from metastatic seminal vesicle carcinoma. Imaging examination is helpful in making the diagnosis, but the usefulness of this examination is limited. Dalgaard and Giertsen[13] proposed the following diagnostic criteria: Tumor confirmed as carcinoma microscopically and confined to the seminal vesicle; no primary carcinoma in other parts of the body; and preferably, the tumor has a papillary structure similar to that of a non-tumorous seminal vesicle. With developments in imaging technology, targeted core biopsy provides an opportunity for preoperative pathological diagnosis[6,14,15]. However, biopsy of a mass with a cystic component is impractical, and the cyst may be punctured, resulting in leakage of cyst fluid; therefore, biopsy was not performed in this case. With these considerations, it is often difficult to make a diagnosis of seminal vesicle adenocarcinoma preoperatively, and surgical resection is recommended to determine the next step in treatment based on the pathological features.

There are no standardized guidelines for the treatment of seminal vesicle adenocarcinoma, and Bhat *et al*[2] reported that robot-assisted laparoscopic surgery may be the preferred choice for localized disease. The stable robotic arms and clear magnification, which reveals a fuller field of vision, result in



DOI: 10.12998/wjcc.v11.i14.3261

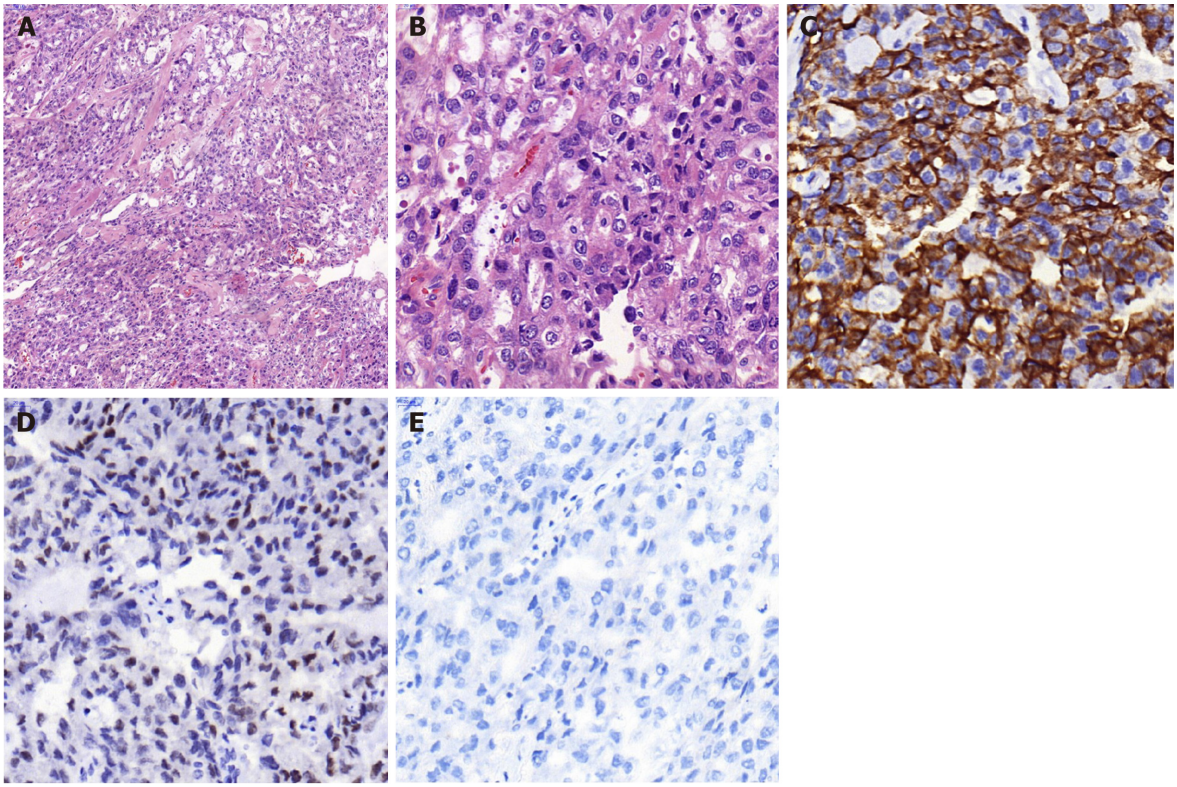
Figure 1 Imaging findings. A: Axial of pelvic dynamic contrast-enhanced computed tomography revealed a cystic-solid mass. B-D: T2-weighted MRI imaging: Axial (B), sagittal (C), and coronal (D) sections of the pelvis demonstrated a cystic-solid component mass.

less blood loss, shorter operation times, and shorter hospital stay compared with conventional surgery. The extent of the surgical resection depends on the degree of the tumor invasion to the surrounding tissue[16]. Prostatovesiculectomy with lymph node dissection has been reported in some localized cases because seminal vesicle adenocarcinoma is prone to invade the ejaculatory duct[6,17-19]. In some cases, seminal vesicle resection, only, was performed for localized disease, and no recurrence was observed within five years[2,4]. No recurrence was observed during the follow-up for localized margin-negative disease without adjuvant therapy[4,17,18]. Adjuvant chemotherapy or adjuvant radiotherapy has been reported in some localized margin-negative cases[2,6], but there is insufficient evidence of comparative survival differences with and without adjuvant therapy. In cases of positive margins, adjacent organ infiltration, metastasis, or recurrence, radiotherapy, chemotherapy or anti-androgen therapy has been reported to prolong recurrence-free survival or overall survival[5,9,20-23].

In the past, most seminal vesicle carcinomas were reported to have a poor prognosis, and patients died within two years because most had peripheral infiltration and distant metastasis at the time of diagnosis[1,2,20,24]. Some cases that were detected early and operated early were reported to achieve long-term survival[2,4,17,18].

CONCLUSION

We report a rare case of seminal vesicle adenocarcinoma with a long history of seminal vesicle cyst. Seminal vesicle cyst has the possibility of malignant transformation. The disease is diagnosed by histopathological and immunohistochemical analysis. We emphasize that seminal vesicle cyst should be followed-up long-term, especially when there are symptoms such as hematospermia and hematuria.



DOI: 10.12998/wjcc.v11.i14.3261

Figure 2 Microphotographs. A and B: Hematoxylin and eosin-stained of tumor (magnification, 100 × and 400 ×); C-E: IHC of cytokeratin (CK)7 (C), Pax-8 (D), and CK20 (E) (magnification, 400 ×).

FOOTNOTES

Author contributions: Yao Y and Liu S conceived of the concept and participated in drafting the manuscript; Luo L and He YL reviewed the pathological slides and revised the manuscript; Zhang GM performed the surgery, analyzed the radiologic imaging data, supervised the project, and revised the manuscript; and all the authors read and approved the final version and agreed to publish the manuscript.

Supported by the Natural Science Foundation of Shandong Province, No. ZR2021MH354.

Informed consent statement: Written informed consent was obtained from the patient for publication of this report and the accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Lei Luo 0000-0001-7281-4450; Gui-Ming Zhang 0000-0002-5856-5325.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhang YL

REFERENCES

1 **Thiel R**, Effert P. Primary adenocarcinoma of the seminal vesicles. *J Urol* 2002; **168**: 1891-1896 [PMID: 12394673 DOI: 10.1016/S0022-5347(05)64260-7]

2 **Bhat A**, Banerjee I, Kryvenko ON, Satyanarayana R. Primary seminal vesicle adenocarcinoma: a lethal yet cryptic malignancy with review of literature. *BMJ Case Rep* 2019; **12** [PMID: 31852695 DOI: 10.1136/bcr-2019-232994]

3 **Kondo N**, Shiono Y, Yoshino Y, Sugaya S, Abe M, Koshitaka Y. [Papillary adenocarcinoma in a seminal vesicle cyst associated with contralateral renal agenesis: a case report]. *Hinyokika Kiyo* 2007; **53**: 175-178 [PMID: 17447487]

4 **Lee BH**, Seo JW, Han YH, Kim YH, Cha SJ. Primary mucinous adenocarcinoma of a seminal vesicle cyst associated with ectopic ureter and ipsilateral renal agenesis: a case report. *Korean J Radiol* 2007; **8**: 258-261 [PMID: 17554197 DOI: 10.3348/kjr.2007.8.3.258]

5 **Campobasso D**, Fornia S, Ferretti S, Maestroni U, Cortellini P. Primary bilateral seminal vesicle carcinoma: description of a case and literature review. *Int J Surg Pathol* 2012; **20**: 633-635 [PMID: 22723505 DOI: 10.1177/1066896912450314]

6 **Bhardwaj N**, Rastogi P, Attri VS, Bora GS, Gorsi U. Primary seminal vesicle adenocarcinoma: A case report of rare entity and discussion of its differential diagnosis using immunohistochemical approach for the core biopsy specimen. *Andrologia* 2020; **52**: e13512 [PMID: 31961000 DOI: 10.1111/and.13512]

7 **Ormsby AH**, Haskell R, Jones D, Goldblum JR. Primary seminal vesicle carcinoma: an immunohistochemical analysis of four cases. *Mod Pathol* 2000; **13**: 46-51 [PMID: 10658909 DOI: 10.1038/modpathol.3880008]

8 **Navallas M**, Vargas HA, Akin O, Pandit-Taskar N, Fine SW, Eastham JA, Hricak H. Primary seminal vesicle adenocarcinoma. *Clin Imaging* 2011; **35**: 480-482 [PMID: 22040796 DOI: 10.1016/j.clinimag.2011.02.004]

9 **Yin T**, Jiang Y. A 5-year follow-up of primary seminal vesicle adenocarcinoma: A case report. *Medicine (Baltimore)* 2018; **97**: e12600 [PMID: 30313047 DOI: 10.1097/MD.0000000000012600]

10 **Poelaert F**, Joniau S, Roumeguère T, Ameye F, De Coster G, Dekuyper P, Quackels T, Van Cleynenbreugel B, Van Damme N, Van Eycken E, Mottrie A, Lumen N; Belgian RALP Consortium. Current Management of pT3b Prostate Cancer After Robot-assisted Laparoscopic Prostatectomy. *Eur Urol Oncol* 2019; **2**: 110-117 [PMID: 30929840 DOI: 10.1016/j.euo.2018.05.005]

11 **Okada Y**, Tanaka H, Takeuchi H, Yoshida O. Papillary adenocarcinoma in a seminal vesicle cyst associated with ipsilateral renal agenesis: a case report. *J Urol* 1992; **148**: 1543-1545 [PMID: 1433569 DOI: 10.1016/s0022-5347(17)36964-1]

12 **Martínez-Peñuela A**, Rosario Mercado M, Aldave J, Martínez-Peñuela JM. [Primary adenocarcinoma of the seminal vesicles]. *Arch Esp Urol* 2009; **62**: 671-673 [PMID: 19907060 DOI: 10.4321/s0004-06142009000800013]

13 **Dalgaard JB**, Giertsen JC. Primary carcinoma of the seminal vesicle; case and survey. *Acta Pathol Microbiol Scand* 1956; **39**: 255-267 [PMID: 13381470 DOI: 10.1111/j.1699-0463.1956.tb03400.x]

14 **Tochigi K**, Matsukawa Y, Ishida S, Funahashi Y, Fujita T, Kato M, Gotoh M. A case of primary adenocarcinoma of the seminal vesicle treated by total laparoscopic pelvic exenteration. *Aktuelle Urol* 2021; **52**: 50-53 [PMID: 32854127 DOI: 10.1055/a-1170-8373]

15 **Angulo JC**, Romero I, Cabrera P, González J, Rodríguez-Barbero JM, Núñez-Mora C. [Vesiculectomy with laparoscopic partial prostatectomy in the treatment of primary adenocarcinoma of the seminal vesicle with carcinomatous transformation of the ejaculatory duct]. *Actas Urol Esp* 2011; **35**: 304-309 [PMID: 21388710 DOI: 10.1016/j.acuro.2011.01.007]

16 **Xu X**, Bai Y, Shi Z, Gan H. [A case report of primary adenocarcinoma of the seminal vesicle]. *Chin J Urol* 2020; **41**: 550-551 [DOI: 10.3760/cma.j.cn112330-20200118-00038]

17 **Dell'Atti L**. Importance of an Early Diagnosis in Primary Adenocarcinoma of the Seminal Vesicle. *Rare Tumors* 2016; **8**: 6187 [PMID: 27134716 DOI: 10.4081/rt.2016.6187]

18 **Möhring C**, Bach P, Koscicsza S, Goepel M. [A primary adenocarcinoma of the seminal vesicles. Case report of a rare malignancy]. *Urologe A* 2008; **47**: 616-619 [PMID: 18231770 DOI: 10.1007/s00120-008-1625-5]

19 **Smith BA Jr**, Webb EA, Price WE. Carcinoma of the seminal vesicle. *J Urol* 1967; **97**: 743-750 [PMID: 6067120 DOI: 10.1016/s0022-5347(17)63110-0]

20 **Benson RC Jr**, Clark WR, Farrow GM. Carcinoma of the seminal vesicle. *J Urol* 1984; **132**: 483-485 [PMID: 6471181 DOI: 10.1016/s0022-5347(17)49700-x]

21 **Lal H**, Yadav P, Jena R, Jain M. Metastatic primary seminal vesicle adenocarcinoma: management of a rare tumour with multiagent chemotherapy and hormonal therapy. *BMJ Case Rep* 2017; **2017** [PMID: 29021144 DOI: 10.1136/bcr-2017-221896]

22 **Rodriguezkees OS**. Clinical improvement following estrogenic therapy in a case of primary adenocarcinoma of the seminal vesicle. *J Urol* 1964; **91**: 665-670 [PMID: 14172256 DOI: 10.1016/s0022-5347(17)64198-3]

23 **Terrisse S**, Camblor ME, Vérine J, Gauthier H, Mongiat-Artus P, Culine S. Primary adenocarcinoma of the seminal vesicle. *Rare Tumors* 2017; **9**: 7074 [PMID: 29081928 DOI: 10.4081/rt.2017.7074]

24 **Katafigiotis I**, Sfoungaristos S, Duvdevani M, Mitsos P, Roumelioti E, Stravodimos K, Anastasiou I, Constantinides CA. Primary adenocarcinoma of the seminal vesicles. A review of the literature. *Arch Ital Urol Androl* 2016; **88**: 47-51 [PMID: 27072175 DOI: 10.4081/aiua.2016.1.47]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3267-3274

DOI: 10.12998/wjcc.v11.i14.3267

ISSN 2307-8960 (online)

CASE REPORT

Immune checkpoint inhibitor therapy-induced autoimmune polyendocrine syndrome type II and Crohn's disease: A case report

Mei-Juan Gao, Yan Xu, Wen-Bo Wang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sitkin S, Russia; Souza JLS, Brazil

Received: December 4, 2022
Peer-review started: December 4, 2022
First decision: February 7, 2023
Revised: February 17, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Mei-Juan Gao, Yan Xu, Wen-Bo Wang, Department of Endocrinology, Peking University Shougang Hospital, Beijing 100041, China

Corresponding author: Mei-Juan Gao, MD, Chief Physician, Department of Endocrinology, Peking University Shougang Hospital, No. 9 Jinyuanzhuang Road, Beijing 100041, China. gmjluhe@163.com

Abstract

BACKGROUND

The development of immune checkpoint inhibitors (ICIs) has heralded a new era in cancer treatment, enabling the possibility of long-term survival in patients with metastatic disease. Unfortunately, ICIs are increasingly implicated in the development of autoimmune diseases.

CASE SUMMARY

We present a man with squamous cell carcinoma of the oropharynx on a combination of teriprizumab, docetaxel, and cisplatin therapy who developed autoimmune polyendocrine syndrome type II (APS-2) including thyroiditis and type 1 diabetes mellitus and Crohn's disease (CD). He developed thirst, abdominal pain, and fatigue after two-week treatment with the protein 1 ligand inhibitor teriprizumab. Biochemistry confirmed APS-2 and thyrotoxicosis. He was commenced on an insulin infusion. However, his abdominal pain persisted. Follow-up surgery confirmed CD and his abdominal pain was relieved by mesalazine. He was continued on insulin and mesalazine therapy.

CONCLUSION

Immunotherapy can affect all kinds of organs. When clinical symptoms cannot be explained by a single disease, clinicians should consider the possibility of multisystem damage.

Key Words: Immune checkpoint inhibitor; Programmed cell death protein 1 ligand; Autoimmune polyendocrine syndrome type II; Type 1 diabetes mellitus; Thyroiditis; Crohn's disease; Case report

Core Tip: We report a rare case of multi-system damage induced by cancer therapy with protein 1 ligand inhibitor teriprizumab. A man with squamous cell carcinoma of oropharynx on a combination regimen of teriprizumab, docetaxel, and cisplatin developed autoimmune polyendocrine syndrome type II (APS-2) including thyroiditis and type 1 diabetes mellitus (T1DM) and Crohn's disease (CD). This case report highlights the possibility of chronic immune toxicities and the long-term implications of cancer immunotherapy. To the best of our knowledge, this is the first reported case of concurrent atypical APS-2 (including T1DM and thyrotoxicosis) and CD in a patient receiving immunotherapy for metastatic nasopharyngeal carcinoma.

Citation: Gao MJ, Xu Y, Wang WB. Immune checkpoint inhibitor therapy-induced autoimmune polyendocrine syndrome type II and Crohn's disease: A case report. *World J Clin Cases* 2023; 11(14): 3267-3274
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3267.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3267

INTRODUCTION

Immune checkpoint inhibitors (ICIs) such as programmed cell death protein 1 (PD1) or its ligand (PDL1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) have revolutionized the treatment of many malignancies, such as melanoma, non-small cell lung cancer, and renal cell carcinoma. ICI therapy enhances the immune system and has been shown to improve survival in some cancer patients. However, ICIs occasionally induce immune-related adverse events (irAEs), which commonly affect the gastrointestinal tract, liver, skin, and endocrine system, but can affect virtually any organ system[1,2]. Thyroid disorders are common endocrinopathies associated with irAEs[3]. Hypophysitis is another well-recognized endocrine side effect[4]. Autoimmune diabetes mellitus especially type 1 diabetes mellitus (T1DM) has occasionally been reported[5], while adrenal insufficiency is observed even less frequently[6]. However, to the best of our knowledge, ICI-induced autoimmune polyendocrine syndrome type II (APS-2) including T1DM combined with Crohn's disease (CD), has not yet been reported.

Here we report an elderly man who developed partial features of APS-2 combined with CD shortly after initiation of treatment with PDL1 antibody teriprizumab for squamous cell carcinoma of the oropharynx. This patient had an acute onset of T1DM with diabetic ketoacidosis (DKA), short-term thyrotoxicosis, and typical CD. This case report is supplemented by a literature review of PD1/PD-L1 inhibitor-associated APS-2 and CD. Our study may help improve the understanding of endocrinologists, oncologists, and gastroenterologists about rare irAEs.

CASE PRESENTATION

Chief complaints

A 61-year-old man presented to the emergency department of Shougang Hospital with fatigue, vomiting, polyuria, polydipsia, and abdominal pain for a few days.

History of present illness

The patient had earlier received treatment for squamous cell carcinoma of the oropharynx at the Peking University Tumor Hospital. About two weeks after discharge from that hospital, he developed thirst, fatigue, and abdominal pain. Five days later (September 21, 2021), he presented to the emergency department with abrupt onset of extreme fatigue, vomiting, polyuria, polydipsia, bellyache, hyperglycemia, severe acidosis, and the presence of ketones bodies in urine. DKA was diagnosed by an emergency medicine specialist. Treatment protocol for DKA with continuous intravenous insulin was initiated with good response within 8 h. Plasma amylase level was substantially increased. According to the Common Terminology Criteria for Adverse Events of the National Institute of Health, ICI-induced pancreatic injury was suspected although abdominal computed tomography (CT)-scan was unremarkable. After comprehensive treatment, his blood biochemical indicators and blood glucose returned to normal, but abdominal pain persisted. He was admitted to the inpatient department for further evaluation.

His biochemical parameters confirmed recovery, but abdominal pain persisted along with persistent positive stool occult blood and elevated C-reactive protein (CRP). The abdominal pain was mostly around umbilicus, sometimes in the right abdomen, and typically occurred approximately 30 to 45 min after meals; there was no rectal urgency. Sometimes, the pain was relieved after defecation. His dietary intake was reduced due to the pain.

History of past illness

He had been diagnosed with squamous cell carcinoma of the oropharynx which invaded the right medial pterygoid and right-sided neck lymph nodes. The carcinoma was surgically excised along with associated lymph nodes clearance (confirming T4N2M0) on July 22, 2021. One month later (2021-8-31), he received the first cycle of a three-drug chemotherapy regimen (docetaxel, cisplatin, and tigisay) combined with PDL1 targeted antibody (teriprizumab) therapy. The dosing regimen was: Docetaxel 120 mg qd, one day; cisplatin 120 mg qd, one day; tigisay 40 mg bid, two weeks; and teriprizumab 240 mg qd one day, three weekly. Full blood counts, biochemistry, and thyroid function tests were within normal limits prior to the initiation of therapy.

Personal and family history

He had a history of hypertension and cerebral infarction, but there was no past or family history of autoimmune or endocrine disease.

Physical examination

On examination, he was conscious and oriented but looked unwell and was clinically dehydrated. Body temperature was normal. Heart rate was regular at 82 per minute, respiratory rate was 19 per minute with oxygen saturation of 97% on ambient air, and blood pressure was 118/76 mmHg. His body mass index was 20.9 kg/m^2 (height 168 cm, weight 59 kg). He had hoarseness of voice and complained of abdominal pain. Abdominal examination revealed tenderness and active bowel sounds. Other systemic examination was unremarkable.

Laboratory examinations

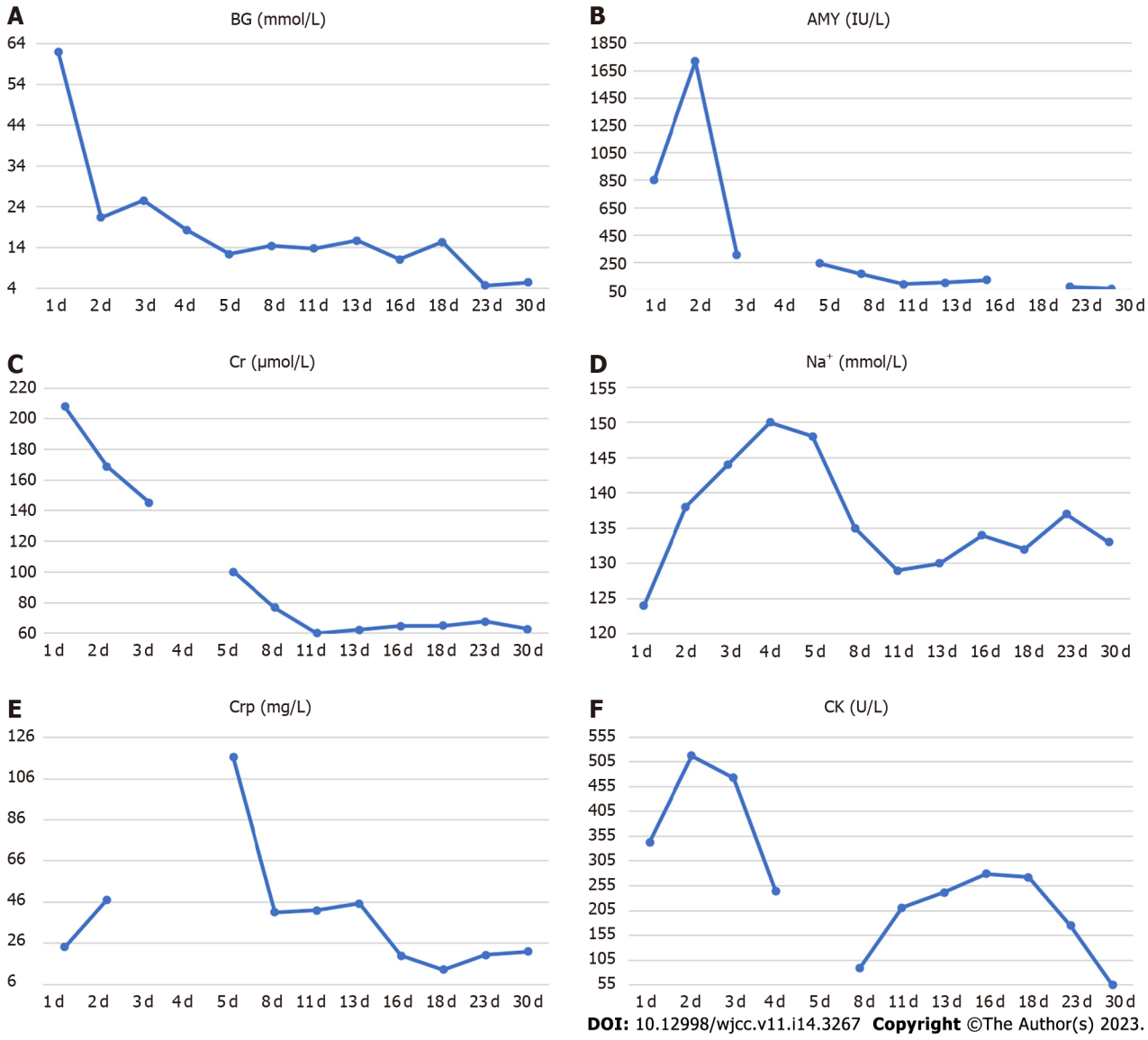
His blood parameters on admission in the emergency room were: Blood glucose 62.09 mmol/L; pH 7.008; urinary ketone body 4+; serum amylase 854 U/L; serum creatinine 207.8 μmol/L; and creatine kinase 343 U/L (Table 1). After following comprehensive treatment, his blood biochemical indicators returned to normal. He was administered multiple daily insulin injections and blood glucose was in an ideal range (Figure 1). Further workup revealed positive glutamic acid decarboxylase antibody insulin autoantibody and low C-peptide level (< 0.01 nmol/L), which was consistent with autoimmune T1DM (Table 2). His glycated hemoglobin (HbA1c) and glycated albumin were 8.3% and 36%, respectively. There were no signs of diabetes-related complications or microangiopathy; the urinary albumin-to-creatinine ratio and fundus retinal examination were all normal. The pituitary function, gonadal function, and adrenal function were within the normal range (Supplementary Table 1). Thyroid function tests showed overt thyrotoxicosis [Thyroid stimulating hormone < 0.01 mU/L, FT4 24.1 pmol/L, FT3 5.27 pmol/L, Thyroglobulin (TG)-Ab > 1000 IU/mL, TG-Ab 226.08 IU/mL, normal thyrotropin receptor antibody (TRAb)] but there were no symptoms of hyperthyroidism. The clinical picture was consistent with thyroiditis, deemed to be an irAE related to the medication teriprizumab (Table 3).

Imaging examinations

Owing to the recovery of biochemical indices, the persistent abdominal pain could not be attributed to DKA; therefore, the possibility of ICI-related gastrointestinal irAEs was considered. Moreover, due to persistent positive stool occult blood and mildly elevated CRP, endoscopy and imaging (electronic colonoscopy) were performed to directly visualize and inspect the bowel lumen. There were no remarkable findings apart from a single colon polyp (Figure 2A), which could not explain the abdominal pain, CRP and hematochezia. Consequently, abdominal CT-scan was performed which showed blurring and thickened of the wall of distal ileum which was presumed to be inflammatory (Figure 2B). He was scheduled for enteroscopy. Unfortunately, one month later, he had to undergo surgical treatment for intestinal obstruction (abdominal pain and distension, no passage of feces or flatus). The resected terminal ileum (about 5 cm) was sent for pathological examination, and there was transmural inflammation at the stenosis of intestinal canal. Postoperative histopathological staining showed extensive infiltration of lymphocytes, plasma cells, and neutrophils, along with simple ulcers in the affected bowel loops. There was destruction of crypt structure along with atrophy of intestinal villi in surrounding bowel loops and no lesion in upper or lower intestine, immunohistochemistry: CD3 (+), CD4 (+), CD5 (+), CD8 (+), CD10 (+++), CD79a (+++), MUM1 (+++), ki-67 (20%+), in situ hybridization: EBER (+), all of which were consistent with inflammatory bowel disease (IBD), especially CD (Figure 3).

FINAL DIAGNOSIS

The patient was diagnosed with APS 2 and CD.



DOI: 10.12998/wjcc.v11.i14.3267

Figure 1 Temporal changes in laboratory parameters during treatment and follow-up. A: Blood glucose; B: Amylase; C: Serum creatinine; D: Serum sodium; E: C-reactive protein; F: Creatine kinase.

TREATMENT

Postoperatively, his blood glucose was difficult to control, then he was suggested to use immune modulators such as methotrexate or biological agents such as adalimumab for his CD, according to the serious adverse reactions induced by earlier treatment of nasopharyngeal carcinoma, he refused these medications. At last, he was administered mesalazine 4 g/d. The patient was discharged on oral mesalazine sustained-release granules with a dosage of 1 g quarter in die for 8 wk and then maintained at 1 g twice daily and daily insulin dosage of 36-42 IU administered *via* four injections per day.

OUTCOME AND FOLLOW-UP

After about two weeks of mesalazine treatment, there was complete remission of abdominal pain and the stool occult blood test was negative. Three months after withdrawal of teriprizumab, his thyroid hormone levels had returned to normal (Table 3). He received more than 20 sessions of local radiotherapy (nasopharyngeal) and cisplatin chemotherapy after his discharge from Shougang Hospital. In the first one-year follow-up, he showed good recovery with disappearance of hoarseness of voice and nasopharyngeal carcinoma. He was taking mesalazine and insulin intensive therapy, with CRP of 6.73 mg/L, negative stool occult blood and HbA1c of 7.8%.

Table 1 Results of laboratory investigations in the emergency room

Investigation	Value	Reference range
Blood gas analysis		
pH	7.008	7.35 to 7.45
base excess (mmol/L)	-26.2	-3 to 3
lactic acid (mmol/L)	3.7	0.4 to 2.2
Blood biochemical analysis		
Blood glucose (mmol/L)	62.09	3.89 to 6.11
Blood potassium (K^+, mmol/L)	5.58	3.5 to 5.5
Blood sodium (Na^+, mmol/L)	124	137 to 147
Serum creatinine (μmol/L)	207.8	20.0 to 98.0
Urea nitrogen (BUN, mmol/L)	18.03	1.7 to 7.5
Creatine kinase (U/L)	343	24 to 195
Amylase (IU/L)	854	40 to 132
C-reactive protein (mg/L)	24.24	0.00 to 6.00
Routine blood test		
White blood cell count (10^9/L)	6.7	3.5 to 9.5
Neutrophils (10^9/L)	3.7	1.8 to 6.3
Red blood cell count (10^{12}/L)	5.23	4.3 to 5.8
Platelet count (10^9/L)	255	125 to 350
Urinalysis		
Urine gravity	1.015	1.006 to 1.030
pH	5	5.5 to 8
Protein	1+	Negative
Urine sugar	4+	Negative
Urinary ketone body	4+	Negative

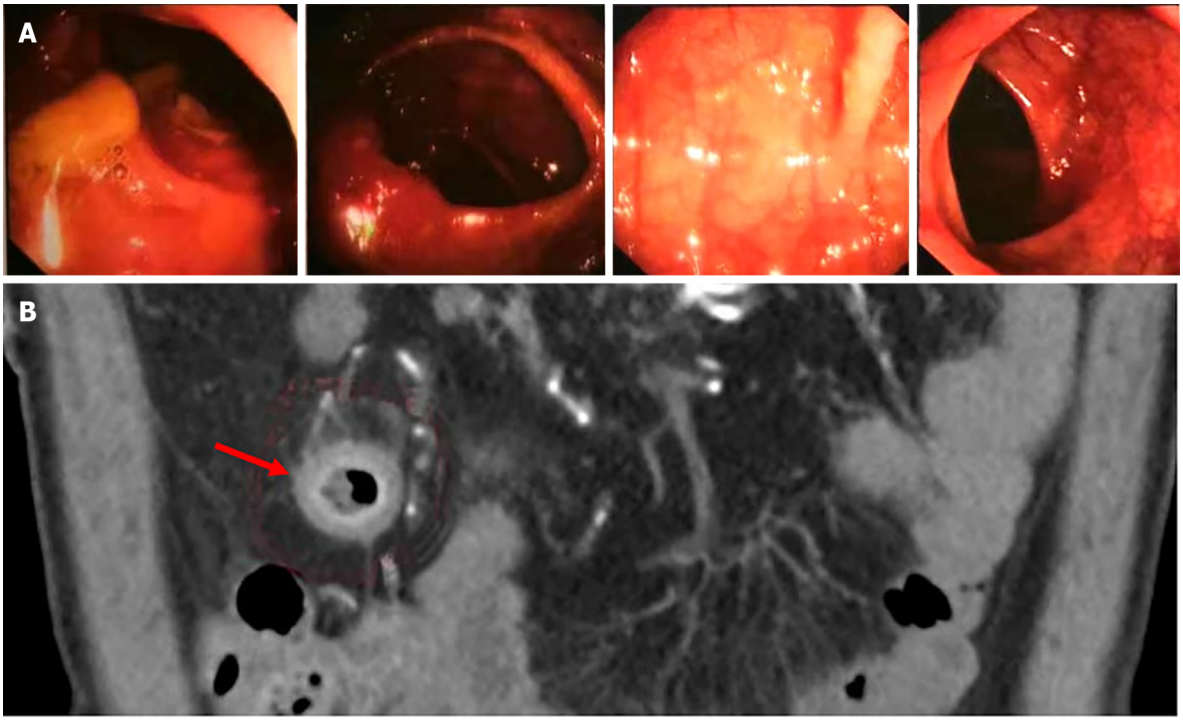
Table 2 Mixed meal test

Time (min)	BG (mmol/L)	Insulin (μIU/mL)	C-peptide (0.78-5.19 ng/mL)	3 mo later C-peptide
0	15.36	10.9 (2.5 to 9.4)	< 0.01	< 0.01
60	25.89	6.6 (11.9 to 43.5)	< 0.01	< 0.01
120	26.99	5.6 (8.7 to 29.7)	< 0.01	< 0.01

BG: Blood glucose.

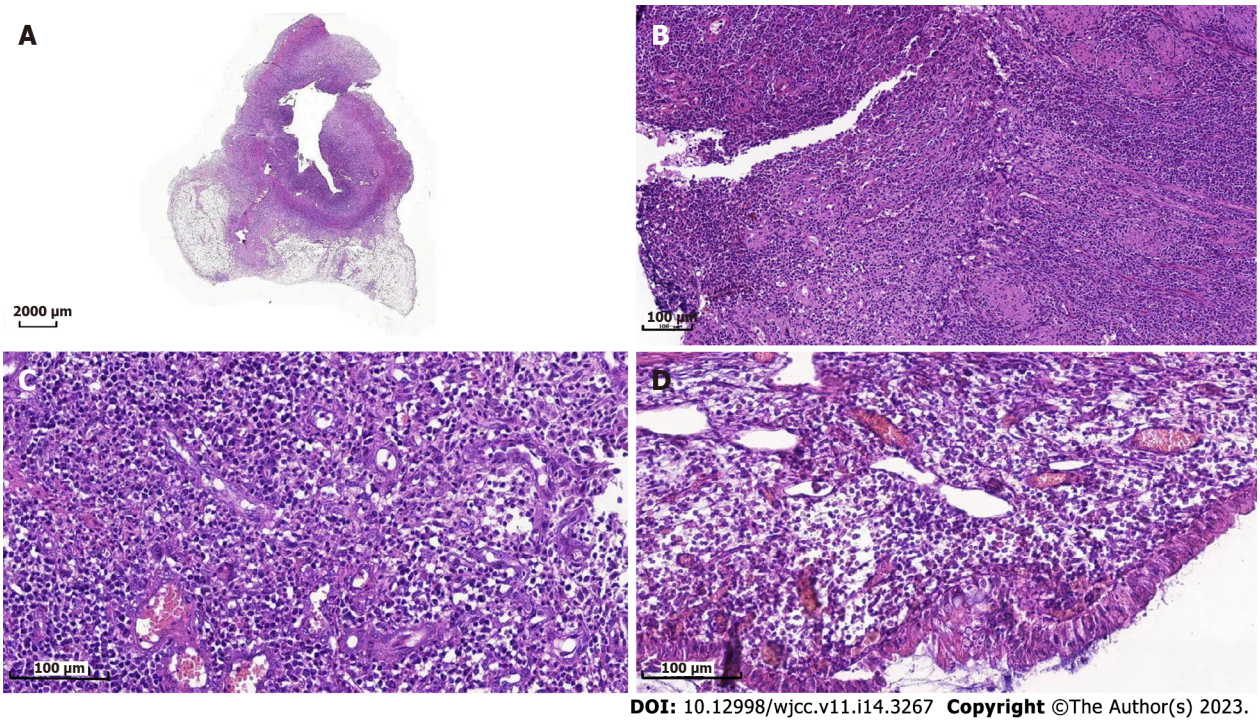
DISCUSSION

Our patient developed low C-peptide level and modestly elevated HbA1c with positive T1DM autoantibody two weeks after initiation of PDL1 antibody therapy pointing to acute, rapid destruction of -islets in pancreas. Increased amylase level indicated damage to the pancreatic exocrine gland. After admission, he was found to have thyroiditis and thyrotoxicosis. In addition, the increase in creatine kinase level was suggestive the possibility of rheumatic immune system damage. During following treatment, the patient developed IBD, especially CD. The overall clinical picture was suggestive of multi-system damage caused by teriprizumab. To the best of our knowledge, this is the first reported case of concurrent atypical APS-2 (including T1DM and thyrotoxicosis) and CD in a patient on immunotherapy for metastatic nasopharyngeal carcinoma.



DOI: 10.12998/wjcc.v11.i14.3267

Figure 2 Colonoscopy and abdominal computed tomography examination. A: Electronic colonoscopy image; B: Abdominal computed tomography scan.



DOI: 10.12998/wjcc.v11.i14.3267

Figure 3 Hematoxylin and eosin-stained sections of terminal ileum. A: 5 times amplification by microscope of the lesions in intestine; B: 50 times amplification by microscope of the lesions in intestine; C: 100 times amplification by microscope of the lesions in intestine; D: 200 times amplification by microscope of the lesions in intestine.

The discovery of Checkpoint inhibitors has changed the landscape of cancer therapeutics. With the growing use of ICIs, the frequency of autoimmune complications has become increasingly apparent. The most common ICI-associated endocrinopathies are thyroid disorders and hypophysitis[7], but hypophysitis is nearly unique to patients receiving CTLA-4, which occurs more often (5% to 10%) and with an earlier onset (median 9 to 12 wk) in patients receiving ipilimumab-based regimens compared to

Table 3 Thyroid function tests

Investigation	On admission	2 wk later	3 mo later	Reference range
T3 (nmol/L)	1.57	1.14	2.25	0.89 to 2.45
T4 (nmol/L)	191.37	128.27	132.69	62.68 to 150.84
TSH (μIU/mL)	< 0.01	0.01	3.84	0.35 to 4.94
FT3 (pmol/L))	5.27	3.87	4.71	2.63 to 5.71
FT4 (pmol/L)	24.1	16.27	10.91	9.1 to 19.24
TPO-Ab (IU/mL)	> 1000.00	> 1000.00	363	0 to 5.61
TG-Ab (IU/mL)	226.08	140.84	218	0 to 4.11

TSH: Thyroid stimulating hormone; TPO: Thyroid peroxidase; TG: Thyroglobulin.

those receiving anti-PD1/PD-L1 antibodies[8]. ICI-induced T1DM is uncommon, with a reported frequency ranging from 0.2% in randomized clinical studies[9] to 1.27% in real-life setting[5]. Primary adrenal insufficiency is less common, albeit with a similar presentation with hypophysitis, although this endocrinopathy may also involve mineralocorticoid deficiency and present with hypotension[10].

There are two definitions of APS-2, with some defining it as occurrence of any two of the three conditions, *i.e.*, T1DM, autoimmune thyroiditis, and primary hypoadrenalism, while others specify that hypoadrenalism must exist, with at least one of the other two conditions. Spontaneous APS-2 is very rare, and anti-PD1/PDL1 antibodies-induced APS-2 has occasionally been reported. Out of the 14 cases reported in literature, three cases experienced primary hypoadrenalism and only one had all three features of APS-2[6]. Our case only presented T1DM and autoimmune thyroiditis, and his adrenocortical function needs further observation.

Regarding gastrointestinal irAEs, colitis occurs in up to 5% of patients receiving anti-PD-1/PD-L1 antibodies, and generally presents as diarrhea and less often as abdominal pain and hematochezia[11, 12]. In addition, these irAEs-related chronic sequelae can also affect the rheumatological, pulmonary, neurological, and other organ systems[6]. These damages typically occur in one system and do not involve several systems at the same time. In our case, the damage involved the endocrine system and gastrointestinal system including T1DM, thyroiditis, and CD.

Abdominal pain was the chief complaint of our patient during treatment and the pain did not correlate with the severity of hyperglycemia. While DKA was cured, abdominal pain persisted. The pain aggravated after meals and was associated with increased CRP and positive occult blood in stool. These symptoms were suspicious of teriprizumab-induced gastrointestinal irAEs, especially IBD. However, no obvious lesions were observed on colonoscopy. Abdominal CT showed edema and thickening of small intestinal wall, and the subsequent pathological examination of the small intestine was consistent with CD, which made the case unique.

CONCLUSION

In conclusion, our patient had a few irAEs associated with PDL1 antibody teriprizumab treatment, especially APS-2 and CD. To the best of our knowledge, this is the first reported case of multi-organ damage associated with teriprizumab. Physicians should be aware of the chronic immune toxicities and the long-term implications of immunotherapy for cancer; especially, when clinical symptoms are not explained by a single disease, the possibility of multisystem damage should be considered.

FOOTNOTES

Author contributions: Gao MJ and Xu Y provided clinical care for the patient; Gao MJ wrote the manuscript; Wang WB was the attending consultant, and he reviewed the final draft of the manuscript; All authors contributed to the writing, editing, and review of the manuscript.

Informed consent statement: The patient and his family signed a letter of consent to the summary of the case report and the publication of the informed notice.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared

and revised according to CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Mei-Juan Gao 0000-0002-8324-9877.

S-Editor: Li L
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Spain L**, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev* 2016; **44**: 51-60 [PMID: 26874776 DOI: 10.1016/j.ctrv.2016.02.001]
2 **Johnson DB**, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022; **19**: 254-267 [PMID: 35082367 DOI: 10.1038/s41571-022-00600-w]
3 **Barroso-Sousa R**, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, Tolaney SM. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. *JAMA Oncol* 2018; **4**: 173-182 [PMID: 28973656 DOI: 10.1001/jamaoncol.2017.3064]
4 **Di Dalmazi G**, Ippolito S, Lupi I, Caturegli P. Hypophysitis induced by immune checkpoint inhibitors: a 10-year assessment. *Expert Rev Endocrinol Metab* 2019; **14**: 381-398 [PMID: 31842671 DOI: 10.1080/17446651.2019.1701434]
5 **Liu J**, Zhou H, Zhang Y, Fang W, Yang Y, Huang Y, Zhang L. Reporting of Immune Checkpoint Inhibitor Therapy-Associated Diabetes, 2015-2019. *Diabetes Care* 2020; **43**: e79-e80 [PMID: 32393586 DOI: 10.2337/dc20-0459]
6 **Gunjur A**, Klein O, Kee D, Cebon J. Anti-programmed cell death protein 1 (anti-PD1) immunotherapy induced autoimmune polyendocrine syndrome type II (APS-2): a case report and review of the literature. *J Immunother Cancer* 2019; **7**: 241 [PMID: 31488221 DOI: 10.1186/s40425-019-0713-y]
7 **Muir CA**, Clifton-Bligh RJ, Long GV, Scolyer RA, Lo SN, Carlino MS, Tsang VHM, Menzies AM. Thyroid Immune-related Adverse Events Following Immune Checkpoint Inhibitor Treatment. *J Clin Endocrinol Metab* 2021; **106**: e3704-e3713 [PMID: 33878162 DOI: 10.1210/clinem/dgab263]
8 **Faje A**, Reynolds K, Zubiri L, Lawrence D, Cohen JV, Sullivan RJ, Nachtigall L, Tritos N. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. *Eur J Endocrinol* 2019; **181**: 211-219 [PMID: 31176301 DOI: 10.1530/EJE-19-0238]
9 **Tsang VHM**, McGrath RT, Clifton-Bligh RJ, Scolyer RA, Jakrot V, Guminski AD, Long GV, Menzies AM. Checkpoint Inhibitor-Associated Autoimmune Diabetes Is Distinct From Type 1 Diabetes. *J Clin Endocrinol Metab* 2019; **104**: 5499-5506 [PMID: 31265074 DOI: 10.1210/jc.2019-00423]
10 **Grouthier V**, Lebrun-Vignes B, Moey M, Johnson DB, Moslehi JJ, Salem JE, Bachelot A. Immune Checkpoint Inhibitor-Associated Primary Adrenal Insufficiency: WHO VigiBase Report Analysis. *Oncologist* 2020; **25**: 696-701 [PMID: 32390168 DOI: 10.1634/theoncologist.2019-0555]
11 **Nishijima TF**, Shachar SS, Nyrop KA, Muss HB. Safety and Tolerability of PD-1/PD-L1 Inhibitors Compared with Chemotherapy in Patients with Advanced Cancer: A Meta-Analysis. *Oncologist* 2017; **22**: 470-479 [PMID: 28275115 DOI: 10.1634/theoncologist.2016-0419]
12 **Wang DY**, Mooradian MJ, Kim D, Shah NJ, Fenton SE, Conry RM, Mehta R, Silk AW, Zhou A, Compton ML, Al-Rohil RN, Lee S, Voorhees AL, Ha L, McKee S, Norrell JT, Mehnert J, Puzanov I, Sosman JA, Chandra S, Gibney GT, Rapisuwon S, Eroglu Z, Sullivan R, Johnson DB. Clinical characterization of colitis arising from anti-PD-1 based therapy. *Oncoimmunology* 2019; **8**: e1524695 [PMID: 30546965 DOI: 10.1080/2162402X.2018.1524695]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3275-3281

DOI: 10.12998/wjcc.v11.i14.3275

ISSN 2307-8960 (online)

CASE REPORT

Late-onset mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome with mitochondrial DNA 3243A>G mutation masquerading as autoimmune encephalitis: A case report

Jian-Wei Wang, Xiao-Bo Yuan, Hong-Fang Chen

Specialty type: Clinical neurology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Mathieu C, France; Sijens PE, Netherlands; Vyshka G, Albania

Received: January 3, 2023
Peer-review started: January 3, 2023
First decision: January 30, 2023
Revised: February 27, 2023
Accepted: April 7, 2023
Article in press: April 7, 2023
Published online: May 16, 2023

Jian-Wei Wang, Hong-Fang Chen, Department of Neurology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, Zhejiang Province, China

Xiao-Bo Yuan, Department of Neurology, The First People's Hospital of Yongkang, Jinhua 321300, Zhejiang Province, China

Corresponding author: Hong-Fang Chen, MM, Chief Physician, Director, Department of Neurology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, No. 356 Renmin East Road, Jinhua 321000, Zhejiang Province, China. jhchf894@163.com

Abstract

BACKGROUND

Here, we present a unique case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, which initially appeared to be autoimmune encephalitis and was ultimately confirmed as MELAS with the mitochondrial DNA 3243A>G mutation.

CASE SUMMARY

A 58-year-old female presented with acute-onset speech impediment and auditory hallucinations, symmetrical bitemporal lobe abnormalities, clinical and laboratory findings, and a lack of relevant prodromal history, which suggested diagnosis of autoimmune encephalitis. Further work-up, in conjunction with the patient's medical history, family history, and lactate peak on brain lesions on magnetic resonance imaging, suggested a mitochondrial disorder. Mitochondrial genome analysis revealed the m.3243A>G variant in the *MT-TL1* gene, which led to a diagnosis of MELAS syndrome.

CONCLUSION

This case underscores the importance of considering MELAS as a potential cause of autoimmune encephalitis even if patients are over 40 years of age, as the symptoms and signs are atypical for MELAS syndrome.

Key Words: MELAS; Mitochondrial DNA mutation; Encephalitis; Case report

Core Tip: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is a multimitochondrial disease caused by DNA mutations and respiratory chain defects that is frequently misdiagnosed. Here, we describe a 58-year-old patient with MELAS syndrome who initially presented with acute cognitive impairment, tinnitus, and headache and was subsequently misdiagnosed with autoimmune encephalitis. The final diagnosis was based on MELAS mutation blood tests and magnetic resonance imaging results. The patient was treated with appropriate medication and gradually improved. This case shows that MELAS syndrome should be diagnosed only after other causes, including autoimmune encephalitis, have been ruled out and the atypical clinical features of MELAS syndrome, such as older age of onset, have been considered.

Citation: Wang JW, Yuan XB, Chen HF. Late-onset mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome with mitochondrial DNA 3243A>G mutation masquerading as autoimmune encephalitis: A case report. *World J Clin Cases* 2023; 11(14): 3275-3281
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3275.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3275

INTRODUCTION

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a multisystemic mitochondrial disorder[1]. MELAS is caused by mutations in mitochondrial DNA and subsequent respiratory chain deficiency[2]. In most cases, MELAS syndrome is characterized by severe aches, stroke-like episodes, short stature, sensorineural deafness, cognitive decline, and exercise intolerance. Conversely, hypertrophic cardiomyopathy, ataxia, ophthalmoplegia, and diabetes mellitus are rare features of MELAS[3,4]. MELAS syndrome presenting with the features of acute encephalitis is rare and has been described in only a few case reports[5,6]. Among these few cases, nonviral encephalitis is even rarer and may therefore pose a diagnostic challenge. Of note, the above clinical manifestations generally occur before the age of 40[5].

Here, we report the unique case of a 58-year-old female whose condition initially appeared to be autoimmune encephalitis and who was ultimately diagnosed with MELAS syndrome in the presence of the m.3243A>G mutation.

CASE PRESENTATION

Chief complaints

Speech impediment and auditory hallucination, accompanied by tinnitus and headache for 3 d.

History of present illness

A 58-year-old female presented with sudden cognitive dysfunction, auditory hallucinations, nonsensical behavior, inability to communicate normally with others, and complaints of headache and tinnitus. The patient had no fever, seizures, or consciousness disturbance.

History of past illness

The patient had a history of bilateral hearing loss.

Personal and family history

The patient had no history of mental retardation or cognitive decline up to the time of her acute illness. Moreover, the patient denied a family history of neuromuscular disease, encephalitis, or mitochondrial disease.

Physical examination

On admission, the patient's height was 158 cm, and her weight was 45 kg. On physical examination, her body temperature was 36.5 °C and a history of previous infection and fever were denied. Chest auscultation revealed normal respiratory sounds and a normal heart rate with no murmur. The patient's neurological examination, limited by the above symptoms, was otherwise normal.

Laboratory examinations

Routine laboratory studies, including blood glucose, hepatic and renal function, coagulation testing, glycosylated hemoglobin, autoantibodies, autoantibody spectrum associated with anti-cardiolipin antibodies, thyroid function, homocysteine, serum tumor markers, human immunodeficiency virus antibody test and syphilis spirochete hemagglutination test, were all unremarkable. The patient's serum white cell count was 14.38 × 10^9/L, and her C-reactive protein level was 7 mg/L. It is worth noting that her arterial blood lactate level was 4.7 mmol/L.

Imaging examinations

Magnetic resonance imaging (MRI) revealed high-intensity lesions in the bitemporal lobe on T2-weighted images (Figure 1A), fluid-attenuated inversion recovery (FLAIR) (Figure 1B) images, and diffusion-weighted images (DWI) (Figure 1C and E). The parts of the lesions involving the cortex appeared hyperintense on DWI (Figure 1C) and hypointense on apparent diffusion coefficient (ADC) maps (Figure 1D), features consistent with cytotoxic edema. Follow-up brain MRI obtained on Day 27 showed an extensive reduction in FLAIR/DWI signals in the left temporal lobe (Figure 1F and G), without an apparent reduction in T2 signals.

Electrophysiological detection

The electroencephalogram only indicated a slight increase in fast waves.

Further diagnostic work-up

Magnetic resonance spectroscopy also revealed a prominent doublet and elevated lactate peak with reduced N-acetyl-aspartate levels (Figure 2). Cerebrospinal fluid (CSF) showed a white cell count of 4/μL and a protein level of 0.668 g/L with a CSF pressure of 140 mmH_2O.

FINAL DIAGNOSIS

The mitochondrial DNA (mtDNA) 3243A>G mutation detected in the patient's blood led to the final diagnosis of MELAS syndrome.

TREATMENT

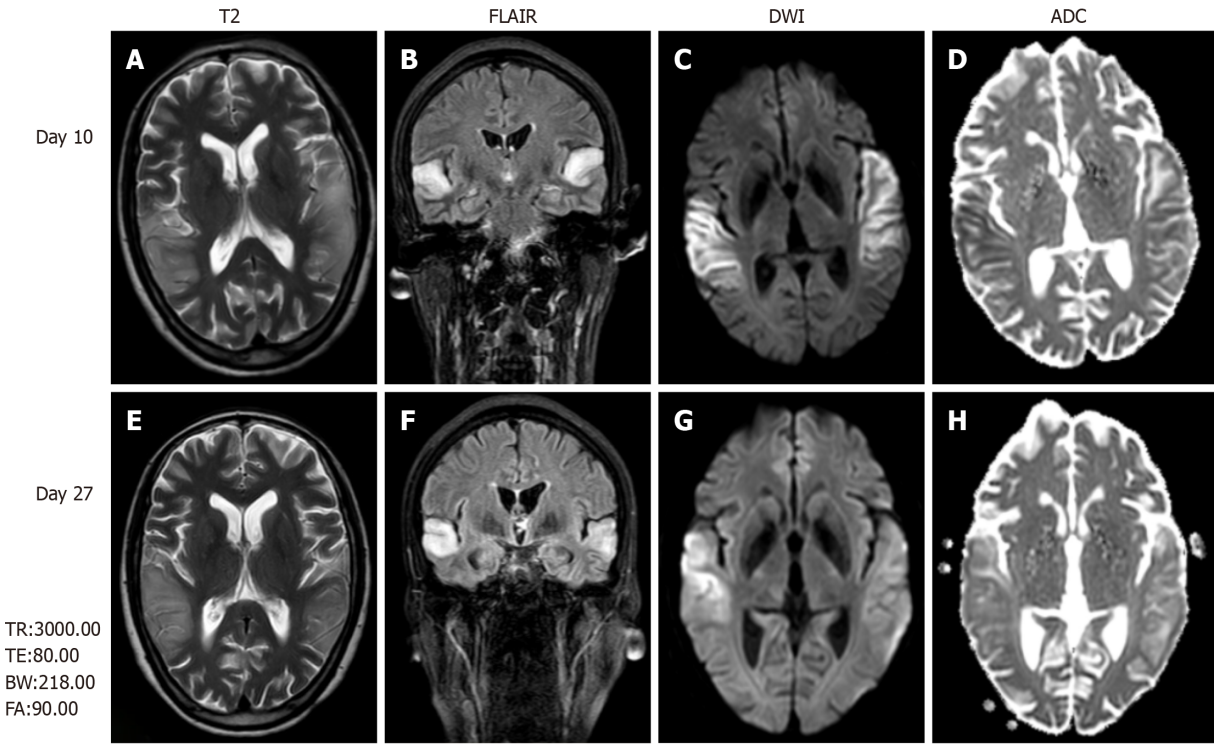
The patient was initially misdiagnosed with autoimmune encephalitis and treated with gamma globulin (18 mg/d × 5 d) therapy and intravenous methylprednisolone (1000 mg/d × 3 d to 500 mg/d × 3 d to 60 mg/d × 9 d). Then, the patient was discharged with slowly tapered oral methylprednisolone (44 mg/d × 2 wk followed by a dosage reduction of 4 mg every 2 wk). When the diagnosis of MELAS was confirmed by the presence of the 3243A>G mutation (Figure 3), we immediately stopped intravenous methylprednisolone and started therapy with L-carnitine (oral 1 g/d × 8 d), L-arginine (oral 4.5 g/d × 8 d), and coenzyme Q10 (oral 60 mg/d × 8 d) (Figure 4).

OUTCOME AND FOLLOW-UP

The patient gradually improved before being discharged from the hospital. At the outpatient follow-up a few months later, the patient's cognitive function had recovered well, and she was basically able to take care of herself.

DISCUSSION

Based on some classic features of MELAS syndrome, such as repeated headaches, previous history of hearing impairment, lactic acidosis, peak lactic acid on brain MRI, and the m.3243A>G mutation detected in serum, the diagnosis of MELAS was clear in our case. The clinical presentation of MELAS depends on the existence of heteroplasmy[6], which refers to the ratio of mutant to normal mtDNA, divided into four different transcription stages of 0%, 20%-30%, 50%-90%, and 100%[7]. It is generally believed that the heteroplasmy rate of typical MELAS is 50%-90%, with higher heterogeneity being associated with earlier onset time. The age of MELAS patients is mostly 10-30 years, and there are few reports of MELAS syndrome onset after 40 years of age[1,8-10]. Our patient's late age of onset and some other atypical symptoms were related to the low heteroplasmy.



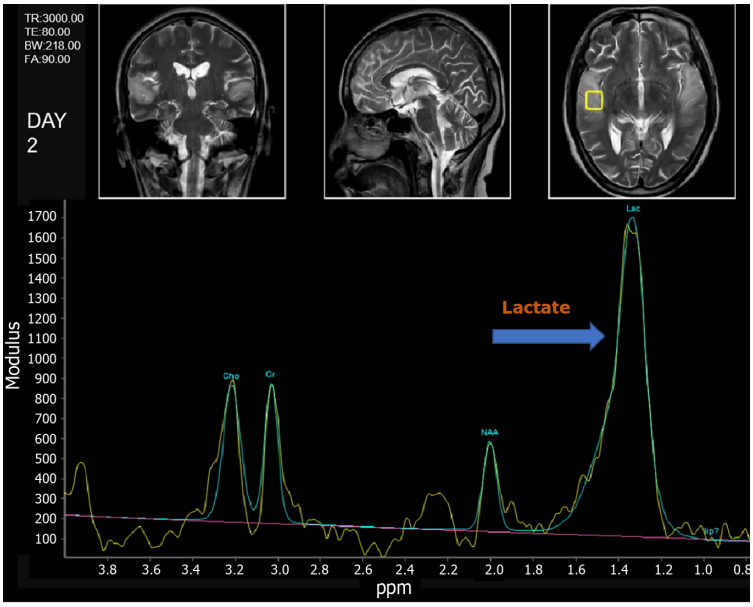
DOI: 10.12998/wjcc.v11.i14.3275

Figure 1 Brain magnetic resonance imaging, fluid-attenuated inversion recovery images, diffusion-weighted images, and apparent diffusion coefficient maps. A and E: Brain magnetic resonance imaging (MRI) revealed high-intensity lesions in the bitemporal lobe on T2-weighted images; B and F: Fluid-attenuated inversion recovery (FLAIR) images; C, D, G and H: Diffusion-weighted images (DWI) (C and G). The parts of the lesions involving the cortex appeared hyperintense on DWI (C and G) and hypointense on apparent diffusion coefficient maps (D and H), which is consistent with cytotoxic edema. The follow-up brain MRI obtained on day 27 showed extensive reduction FLAIR/DWI signals in the left temporal lobe, without an apparent reduction in T2 signals. T2: T2-weighted images; FLAIR: Fluid-attenuated inversion recovery images; DWI: Diffusion-weighted images; ADC: Apparent diffusion coefficient.

This case initially appeared to be autoimmune encephalitis. Few cases of MELAS appearing as acute encephalitis have been reported[11-15]. Most of these cases appear to be herpes simplex encephalitis (HSE). Johns *et al*[11] described three cases with different onset symptoms, all of which involved 3243A>G mutations and increased serum lactic acid levels. The intracranial lesions in all three patients were located in the unilateral temporal or parietal lobes. The case reported by Sharfstein *et al*[12] was characterized by aphasia and delirium; the lesions were located in the left temporal and parietal lobes, and the patient carried the 3243A>G mutation. Hsu *et al*[13] described a patient with acute-onset pyrexia, headache, and seizures who showed aberrant pleocytosis in the CSF but no obvious abnormalities on MRI. The lesions described by both Gieraerts *et al*[14] and Caldarazzo Ienco *et al*[16] were bilateral, but in the study by Gieraerts *et al*[14], the lesions were widely distributed; in the study by Caldarazzo Ienco *et al*[16], they were confined to the bilateral temporal lobes. All of the cases in these abovementioned studies were characterized by the mitochondrial 3243A>G mutation. Of note, 80% of MELAS patients carry the m.3243A>G mutation in the MT-TL1 gene, whereas the frequency of this mutation in the general population is approximately 1:15000[17]. Diseases related to other types of mutations are also misdiagnosed as encephalitis in approximately 20% of MELAS patients. Yokota *et al*[15] described a patient with the mtDNA 14453G→A mutation and acute cognitive impairment, psychosis, headache, and pyrexia who showed mild pleocytosis in the CSF and a lesion in the right temporoparietal lobe.

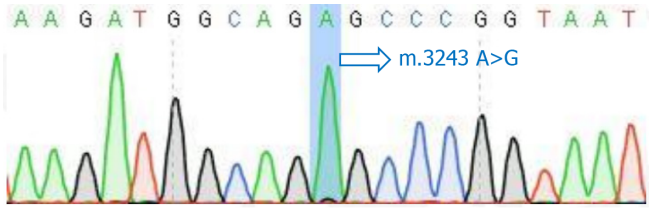
Based on the above cases, the distribution of lesions in MELAS syndrome patients can be diverse, and the symmetry of MELAS lesions is becoming gradually recognized[18,19]. However, the signal distribution of MELAS lesions on DWI and ADC is relatively unique, especially when compared with ischemic stroke lesions. MELAS lesions most often occur due to vasogenic edema; thus, the signal intensity on ADC maps is not or only mildly reduced[20,21]. In contrast, ischemic areas are primarily caused by cytotoxic edema and generally present as restricted diffusion and low signals on ADC maps [22,23]. This phenomenon is consistent with the imaging in our case.

HSE was not the first diagnosis we considered for our patient. First, the patient's CSF was normal, and the gold standard for diagnosing HSE was not detected. Second, the lesions in the bilateral temporal lobes on brain MRI reduced the likelihood of HSE[24,25], though the negative results for the presence of antibodies against neuronal surface antigens in the CSF could not rule out the possibility of autoimmune encephalitis. Graus *et al*[26] reported clinical diagnostic criteria for autoimmune encephalitis and specifically pointed out that mitochondrial diseases can result in a diagnosis different from



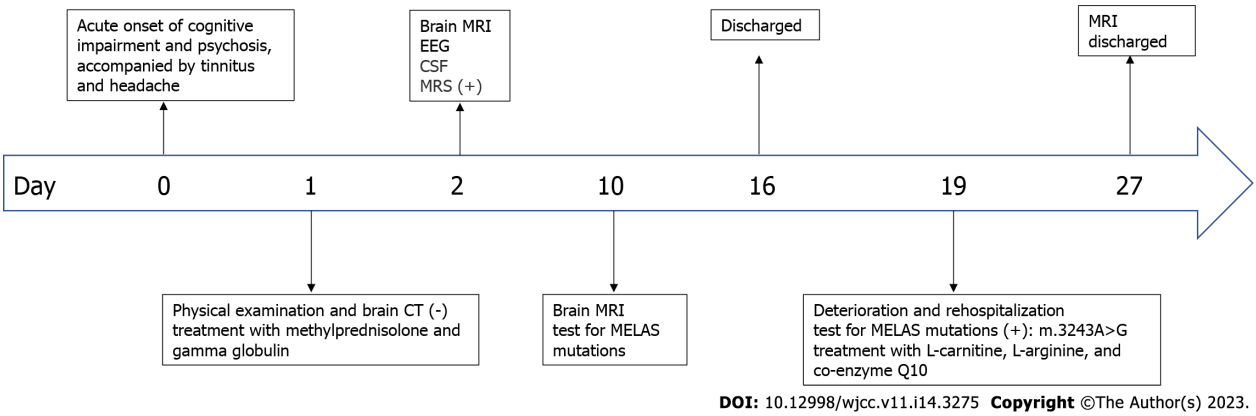
DOI: 10.12998/wjcc.v11.i14.3275

Figure 2 Brain magnetic resonance spectroscopy image, with a visible lip peak in the lesion area, a significantly increased lactate peak, and a decreased NAA peak.



DOI: 10.12998/wjcc.v11.i14.3275

Figure 3 Results of the mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes mutation blood test.



DOI: 10.12998/wjcc.v11.i14.3275

Figure 4 The timeline of the patient's clinical course. CT: Computed tomography; MRI: Magnetic resonance imaging; EEG: Electroencephalogram; CSF: Cerebrospinal fluid; MRS: Magnetic resonance spectroscopy; MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.

autoimmune encephalitis. When the present patient visited one of our physicians, we accepted the original diagnosis of autoimmune encephalitis and discharged her. When she subsequently developed deteriorated mental status under normal medication, combined with the findings of magnetic resonance spectroscopy and serum lactic acid, we then considered the possibility of metabolic disorders, especially MELAS. The final diagnosis of our patient was confirmed by molecular genetic testing of mitochondrial DNA. This case highlights the importance of deferring a diagnosis of autoimmune encephalitis until alternative causes, including MELAS syndrome, have been excluded, especially in antibody-negative encephalitis. It should be recognized that some atypical clinical symptoms of MELAS, such as onset at

an advanced age, and deviation from the classic brain MRI features, including symmetry of the lesion location, are being increasingly reported. In particular, when a disease cannot be clearly diagnosed, we should decisively turn our attention to patient characteristics that do not conform to "classic" features.

CONCLUSION

This case shows that late-onset MELAS syndrome is rare but should be carefully considered in patients presenting with relevant symptoms as a crucial step in the diagnosis and treatment of such patients.

ACKNOWLEDGEMENTS

The authors acknowledge the medical staff at Affiliated Jinhua Hospital, Zhejiang University School of Medicine for their dedicated care of the patient and the cooperation. We sincerely thank the patient.

FOOTNOTES

Author contributions: Chen HF and Yuan XB played a major role in the acquisition of data; Chen HF and Wang JW analyzed and interpreted the patient data regarding a series of MRI images; Chen HF and Yuan XB were major contributors in writing the manuscript; all authors have read and approved the final manuscript.

Supported by the Science and Technology Plan of Jinhua City, No. 2020-3-026.

Informed consent statement: The written informed consent has been obtained from the patient for publication of this case report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Jian-Wei Wang 0000-0001-6453-574X; Xiao-Bo Yuan 0000-0001-7338-2917; Hong-Fang Chen 0000-0002-0706-9559.

S-Editor: Yan JP
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **Sproule DM**, Kaufmann P. Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. *Ann N Y Acad Sci* 2008; **1142**: 133-158 [PMID: 18990125 DOI: 10.1196/annals.1444.011]

2 **Deschauer M**, Tennant S, Rokicka A, He L, Kraya T, Turnbull DM, Zierz S, Taylor RW. MELAS associated with mutations in the POLG1 gene. *Neurology* 2007; **68**: 1741-1742 [PMID: 17502560 DOI: 10.1212/01.wnl.0000261929.92478.3e]

3 **Goto Y**, Horai S, Matsuoka T, Koga Y, Nihei K, Kobayashi M, Nonaka I. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): a correlative study of the clinical features and mitochondrial DNA mutation. *Neurology* 1992; **42**: 545-550 [PMID: 1549215 DOI: 10.1212/wnl.42.3.545]

4 **McFarland R**, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. *Lancet Neurol* 2010; **9**: 829-840 [PMID: 20650404 DOI: 10.1016/S1474-4422(10)70116-2]

5 **Hirano M**, Pavlakis SG. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): current concepts. *J Child Neurol* 1994; **9**: 4-13 [PMID: 8151079 DOI: 10.1177/088307389400900102]

6 **Crimmins D**, Morris JG, Walker GL, Sue CM, Byrne E, Stevens S, Jean-Francis B, Yiannikas C, Pamphlett R.

Mitochondrial encephalomyopathy: variable clinical expression within a single kindred. *J Neurol Neurosurg Psychiatry* 1993; **56**: 900-905 [PMID: 8350109 DOI: 10.1136/jnnp.56.8.900]

7 **Picard M**, Zhang J, Hancock S, Derbeneva O, Golhar R, Golik P, O'Hearn S, Levy S, Potluri P, Lvova M, Davila A, Lin CS, Perin JC, Rappaport EF, Hakonarson H, Trounce IA, Procaccio V, Wallace DC. Progressive increase in mtDNA 3243A>G heteroplasmy causes abrupt transcriptional reprogramming. *Proc Natl Acad Sci U S A* 2014; **111**: E4033-E4042 [PMID: 25192935 DOI: 10.1073/pnas.1414028111]

8 **Zhang Z**, Zhao D, Zhang X, Xiong H, Bao X, Yuan Y, Wang Z. Survival analysis of a cohort of Chinese patients with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) based on clinical features. *J Neurol Sci* 2018; **385**: 151-155 [PMID: 29406897 DOI: 10.1016/j.jns.2017.12.033]

9 **Kaufmann P**, Engelstad K, Wei Y, Kulikova R, Oskoui M, Sproule DM, Battista V, Koenigsberger DY, Pascual JM, Shanske S, Sano M, Mao X, Hirano M, Shungu DC, Dimauro S, De Vivo DC. Natural history of MELAS associated with mitochondrial DNA m.3243A>G genotype. *Neurology* 2011; **77**: 1965-1971 [PMID: 22094475 DOI: 10.1212/WNL.0b013e31823a0c7f]

10 **Yatsuga S**, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, Kakuma T, Koga Y; Taro Matsuoka for MELAS Study Group in Japan. MELAS: a nationwide prospective cohort study of 96 patients in Japan. *Biochim Biophys Acta* 2012; **1820**: 619-624 [PMID: 21443929 DOI: 10.1016/j.bbagen.2011.03.015]

11 **Johns DR**, Stein AG, Wityk R. MELAS syndrome masquerading as herpes simplex encephalitis. *Neurology* 1993; **43**: 2471-2473 [PMID: 8255441 DOI: 10.1212/wnl.43.12.2471]

12 **Sharfstein SR**, Gordon MF, Libman RB, Malkin ES. Adult-onset MELAS presenting as herpes encephalitis. *Arch Neurol* 1999; **56**: 241-243 [PMID: 10025431 DOI: 10.1001/archneur.56.2.241]

13 **Hsu YC**, Yang FC, Perng CL, Tso AC, Wong LJ, Hsu CH. Adult-onset of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome presenting as acute meningoencephalitis: a case report. *J Emerg Med* 2012; **43**: e163-e166 [PMID: 20036095 DOI: 10.1016/j.jemermed.2009.10.021]

14 **Gieraerts C**, Demaerel P, Van Damme P, Wilms G. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome mimicking herpes simplex encephalitis on imaging studies. *J Comput Assist Tomogr* 2013; **37**: 279-281 [PMID: 23493219 DOI: 10.1097/RCT.0b013e3182811170]

15 **Yokota Y**, Hara M, Akimoto T, Mizoguchi T, Goto YI, Nishino I, Kamei S, Nakajima H. Late-onset MELAS syndrome with mtDNA 14453G→A mutation masquerading as an acute encephalitis: a case report. *BMC Neurol* 2020; **20**: 247 [PMID: 32552696 DOI: 10.1186/s12883-020-01818-w]

16 **Caldarazzo Ienco E**, Orsucci D, Simoncini C, Montano V, LoGerfo A, Siciliano G, Bonuccelli U, Mancuso M. Acute encephalopathy of the temporal lobes leading to m.3243A>G. When MELAS is not always MELAS. *Mitochondrion* 2016; **30**: 148-150 [PMID: 27453332 DOI: 10.1016/j.mito.2016.07.008]

17 **Goodfellow JA**, Dani K, Stewart W, Santosh C, McLean J, Mulhern S, Razvi S. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: an important cause of stroke in young people. *Postgrad Med J* 2012; **88**: 326-334 [PMID: 22328278 DOI: 10.1136/postgradmedj-2011-130326]

18 **Miyahara H**, Matsumoto S, Mokuno K, Dei R, Akagi A, Mimuro M, Iwasaki Y, Yoshida M. Autopsied case with MERRF/MELAS overlap syndrome accompanied by stroke-like episodes localized to the precentral gyrus. *Neuropathology* 2019; **39**: 212-217 [PMID: 30972844 DOI: 10.1111/neup.12551]

19 **Bhatia KD**, Krishnan P, Kortman H, Klostranec J, Krings T. Acute Cortical Lesions in MELAS Syndrome: Anatomic Distribution, Symmetry, and Evolution. *AJNR Am J Neuroradiol* 2020; **41**: 167-173 [PMID: 31806591 DOI: 10.3174/ajnr.A6325]

20 **Geberhiwot T**, Chakrapani A, Hendriksz C. Case 36-2005: a woman with seizure, disturbed gait, and altered mental status. *N Engl J Med* 2006; **354**: 1096-7; author reply 1096 [PMID: 16525154 DOI: 10.1056/NEJMc053506]

21 **Farrar MA**, Lin CS, Krishnan AV, Park SB, Andrews PI, Kiernan MC. Acute, reversible axonal energy failure during stroke-like episodes in MELAS. *Pediatrics* 2010; **126**: e734-e739 [PMID: 20679297 DOI: 10.1542/peds.2009-2930]

22 **Tzoulis C**, Bindoff LA. Serial diffusion imaging in a case of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. *Stroke* 2009; **40**: e15-e17 [PMID: 19095975 DOI: 10.1161/STROKEAHA.108.523118]

23 **Xu W**, Wen J, Sun C, Cao J, Li Y, Geng D. Conventional and Diffusional Magnetic Resonance Imaging Features of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes in Chinese Patients: A Study of 40 Cases. *J Comput Assist Tomogr* 2018; **42**: 510-516 [PMID: 29369945 DOI: 10.1097/RCT.0000000000000712]

24 **Pauli W**, Zarzycki A, Krzyształowski A, Walecka A. CT and MRI imaging of the brain in MELAS syndrome. *Pol J Radiol* 2013; **78**: 61-65 [PMID: 24115962 DOI: 10.12659/PJR.884010]

25 **Chow FC**, Glaser CA, Sheriff H, Xia D, Messenger S, Whitley R, Venkatesan A. Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. *Clin Infect Dis* 2015; **60**: 1377-1383 [PMID: 25637586 DOI: 10.1093/cid/civ051]

26 **Graus F**, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; **15**: 391-404 [PMID: 26906964 DOI: 10.1016/S1474-4422(15)00401-9]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3282-3287

DOI: 10.12998/wjcc.v11.i14.3282

ISSN 2307-8960 (online)

CASE REPORT

Metastatic gastric cancer from breast carcinoma presenting with paraneoplastic rheumatic syndrome: A case report

Marília Bortoluz Rech, Eduarda Renz da-Cruz, Karina Salgado, Raul Angelo Balbinot, Silvana Sartori Balbinot, Jonathan Soldera

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hou L, China; Qin Y, China; Wang Z, China

Received: December 21, 2022
Peer-review started: December 21, 2022
First decision: January 20, 2023
Revised: February 2, 2023
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: May 16, 2023

Marília Bortoluz Rech, Eduarda Renz da-Cruz, School of Medicine, Universidade de Caxias do Sul, Caxias do Sul 95070-560, Rio Grande do Sul, Brazil

Karina Salgado, Department of Pathology, ICAP Pathology, Caxias do Sul 95020-002, Rio Grande do Sul, Brazil

Raul Angelo Balbinot, Silvana Sartori Balbinot, Jonathan Soldera, Department of Clinical Gastroenterology, Universidade de Caxias do Sul, Caxias do Sul 95070-560, Rio Grande do Sul, Brazil

Corresponding author: Jonathan Soldera, MD, MSc, Associate Professor, Staff Physician, Department of Clinical Gastroenterology, Universidade de Caxias do Sul, Rua Francisco Getúlio Vargas, 1130, Caxias do Sul 95070-560, Rio Grande do Sul, Brazil.
jonathansoldera@gmail.com

Abstract

BACKGROUND

Breast cancer is the most frequently diagnosed cancer worldwide. It is the leading cause of death by malignant disease in women.

CASE SUMMARY

A female patient, 73 years of age, sought care due to weakness, mild abdominal pain, arthralgia, and weight loss. She was taking anastrazole as maintenance therapy for localized breast cancer and had moderate anemia and elevated acute-phase markers. Upper digestive endoscopy showed isolated erosion in the gastric corpus. This lesion was compatible with signet-ring cell adenocarcinoma in anatomopathological study and was confirmed as metastasis of a breast carcinoma in immunohistochemistry, which was positive for estrogen antibody. Further imaging studies determined numerous proximal bone metastases. The patient was treated with prednisone for paraneoplastic syndrome, which improved the anemia and rheumatic disease, and with chemotherapy, which greatly improved the symptoms. She has been followed-up for 6 mo, and her anemia, arthralgias, and acute phase markers have normalized.

CONCLUSION

Systemic treatment strategies seem to be the best choice for gastric metastasis from breast cancer, resulting in disease control and relapse-free survival. Prospective studies with longer follow-up are needed to better understand the

biological, pathological, and clinicopathological characteristics and outcomes of the endoscopic features associated with metastatic gastric cancer from breast carcinoma.

Key Words: Breast cancer; Gastric metastasis; Anemia; Paraneoplastic syndrome; Case report

Core Tip: Breast cancer, the most frequently diagnosed type of cancer worldwide, is the leading cause of death due to malignant disease in women. We present the case of a female patient, 73 years of age, who sought care due to weakness, mild abdominal pain, arthralgia, and weight loss. She was taking anastrazole as a maintenance therapy for a localized breast cancer. She presented with moderate anemia and elevated acute phase markers. Upper digestive endoscopy showed isolated erosion in the gastric corpus. In anatomopathological study, the lesion was found to be compatible with signet-ring cell adenocarcinoma, while in in immunohistochemistry it was confirmed to be a metastasis of breast carcinoma, being positive for estrogen antibody. Further imaging studies determined numerous proximal bone metastases. The patient has been treated and followed up for 6 mo, and her anemia, arthralgias and acute phase markers have normalized. Systemic treatment strategies appear to be the best choice for gastric metastasis from breast cancer, providing disease control and relapse-free survival. Prospective studies with longer follow up are needed to better understand the biological, pathological, and clinicopathological characteristics and outcomes of the endoscopic features associated with metastatic gastric cancer from breast carcinoma.

Citation: Rech MB, da-Cruz ER, Salgado K, Balbinot RA, Balbinot SS, Soldera J. Metastatic gastric cancer from breast carcinoma presenting with paraneoplastic rheumatic syndrome: A case report. *World J Clin Cases* 2023; 11(14): 3282-3287
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3282.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3282

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer worldwide. It is the leading cause of death due to malignant disease in women. Nevertheless, the lethality of this disease has been subsiding in recent decades due to the advancement of screening protocols and treatment options. It must be pointed out that breast carcinoma commonly metastasizes, generally to the lungs, bones, liver, or brain.

The aim of this report was to describe the case of a woman with metastatic gastric cancer from breast carcinoma who presented with rheumatic paraneoplastic syndrome, which responded well to steroids and chemotherapy.

CASE PRESENTATION

Chief complaints

A female patient, 73 years of age, sought care due to weakness, mild abdominal pain, arthralgia, and weight loss.

History of present illness

The patient presented moderate anemia, with a hemoglobin level of 9.9 g/dL, and elevated acute phase markers (ferritin 1657 ng/mL, C-reactive protein 16.9 mg/L, hem sedimentation rate 30 mm, and transferrin saturation 42%).

History of past illness

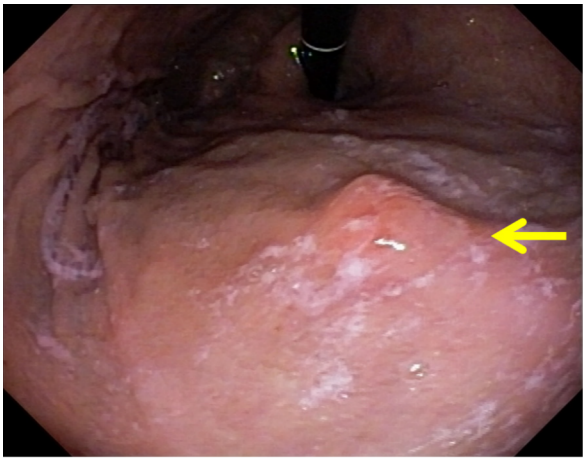
The patient was taking anastrazole as a maintenance therapy for localized breast cancer, which had been resected 4 years previously.

Personal and family history

No previous evidence suggested that her breast cancer had metastasized.

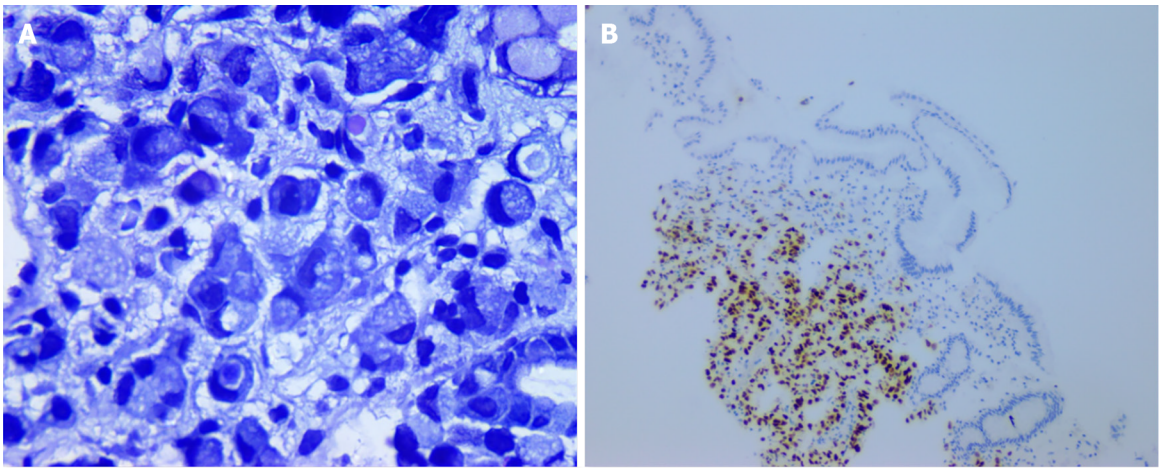
Physical examination

Physical examination showed malnourishment and mild abdominal pain.



DOI: 10.12998/wjcc.v11.i14.3282

Figure 1 Upper digestive endoscopy, gastric corpus: Isolated erosion (arrow).



DOI: 10.12998/wjcc.v11.i14.3282

Figure 2 Biopsy and immunohistochemistry of gastric mucosa. A: Gastric mucosa, biopsy (Giemsa, 40 ×). Diffuse tumor infiltrate with signet ring cells. B: Gastric mucosa, immunohistochemistry (estrogen antibody): Positive for estrogen, suggestive of metastatic gastric cancer from breast carcinoma.

Laboratory examinations

Colonoscopy revealed no remarkable findings, although upper digestive endoscopy showed isolated erosion in the gastric corpus (Figure 1). Anatomopathological study showed that the lesion was compatible with signet-ring cell adenocarcinoma, while and immunohistochemistry confirmed metastasis of the breast carcinoma, which was positive for estrogen antibody clone EP1 (Figure 2), GATA3 monoclonal antibody (L50-823), mammaglobin (23A3 + 304-1A5&31A5), equivocally positive for ERBB2/HER2 membrane receptor (Sp3), and negative for GCDFP-15 (EP1582Y).

Imaging examinations

Endoscopic ultrasound showed that the lesion was ineligible for endoscopic resection. Further imaging studies revealed numerous proximal bone metastases.

FINAL DIAGNOSIS

The patient was treated for paraneoplastic syndrome emulating polymyalgia rheumatica with prednisone at an initial dose of 1 mg/kg, with further tittering and reduction of the dose; the anemia and rheumatic disease improved.

TREATMENT

The patient's disease was treated with paclitaxel, pertuzumab, and trastuzumab. As it progressed, she was switched to trastuzumab deruxtecan, which greatly reduced the symptoms.

OUTCOME AND FOLLOW-UP

The patient has been followed up for over 6 mo, and her anemia, arthralgias, and acute phase markers have normalized (hemoglobin 11 g/dL, C-reactive protein < 5 mg/L, and hem sedimentation rate 23 mm).

DISCUSSION

We describe the case of a woman with rheumatic paraneoplastic syndrome and metastatic gastric cancer from breast carcinoma, which responded well to steroids and chemotherapy. The histological appearance was of signet-cell adenocarcinoma, like another case reported in 2015[1].

Metastatic gastric cancer is very rare, and treatment for a lesion secondary to breast carcinoma differs significantly from an adenocarcinoma of the stomach[2,3]. The prevalence of metastatic gastric cancer from breast carcinoma has been reported to be as low as 0.1%-0.5%[2,4]. Nevertheless, the prevalence in autopsies has been reported at approximately 1.7%[5]. This suggests that the prevalence of metastatic gastric cancer from breast carcinoma has been underestimated[6].

Since the most common symptoms of this metastasis are mild abdominal pain, weight loss, abdominal mass, nausea, early satiety, and melena, it is rather challenging to diagnose. Moreover, the radiological and endoscopic findings are non-specific, as was the isolated gastric erosion in the present case[7-9]. In addition, there is generally a long period of disease-free survival prior to diagnosis, which further delays diagnosis[8,10]. In a series of 37 metastatic gastric cancer cases, breast cancer was the third most common lesion (13.5%): The most common primary malignancy was melanoma (27.0%), followed by lung cancer (18.9%)[11].

In the present case, no symptoms of systemic metastasis were observed prior to those of paraneoplastic syndrome. This is not very rare: In a series of 7 patients, 6 with metastatic gastric cancer and 1 with metastatic colonic cancer from breast carcinoma, none had known systemic disease[12]. Concomitant metastasis to other organs is also possible, as in the bone metastases in the present case [13].

The largest series on metastatic gastric cancer from breast carcinoma was published in 2017 by Xu *et al*[14], comprising 78 cases, none with rheumatic paraneoplastic syndrome. However, after diagnosis of gastric metastasis, other organs were found to be affected in 27 patients. Correct diagnosis of these lesions requires endoscopic examination followed by biopsy and immunohistochemistry[14] for cytokeratin 20, cytokeratin 7, and estrogen receptors[15]. Although primary and metastatic gastrointestinal signet-ring cell carcinomas are generally cytokeratin 20-positive, very few metastatic lobular carcinomas are. Gastrointestinal carcinomas express estrogen receptors, as does almost every lobular breast carcinoma[15].

Early diagnosis allows early treatment of systemic disease, which generally involves hormone therapy. Surgical treatment should only be considered in cases of acute complications, such as gastrointestinal bleeding, obstruction, large lesions, or perforation[3,14,16]. In a case series of 35 patients, the chosen treatment was chemotherapy (37%), hormonotherapy (6%) or both (37%), with a 53% 2-year survival rate after diagnosis of gastric metastasis[3]. In a series of 78 patients, 56.4% received salvage chemotherapy and 51.3% received salvage hormone therapy; 41% underwent surgery, such as total gastrectomy, subtotal gastrectomy, or wedge resection; and 7.7% received radiotherapy[14]. The median survival was 10.5 mo. The best treatment choices seem to be chemotherapy or hormone therapy, both of which lead to increased survival and quality of life, as in the present case.

CONCLUSION

In conclusion, systemic treatment strategies appear to be the best choice for gastric metastasis from breast cancer, providing control of the disease and relapse-free survival. Prospective studies with longer follow-up are needed to better understand the biological, pathological, and clinicopathological characteristics and outcomes of the endoscopic features associated with metastatic gastric cancer from breast carcinoma.

FOOTNOTES

Author contributions: Rech MB, da-Cruz ER, Salgado K, Balbinot RA, Balbinot SS and Soldera J equally contributed to the writing and reviewing of the manuscript; Soldera J contributed as supervisor of the manuscript; All authors have read and approve the final manuscript.

Informed consent statement: The patient has verbally agreed to the reporting of the case.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: Brazil

ORCID number: Karina Salgado 0000-0003-2867-3808; Raul Angelo Balbinot 0000-0003-4705-0702; Silvana Sartori Balbinot 0000-0002-5026-1028; Jonathan Soldera 0000-0001-6055-4783.

Corresponding Author's Membership in Professional Societies: Federação Brasileira De Gastroenterologia; Sociedade Brasileira de Hepatologia; Sociedade Brasileira de Endoscopia Digestiva; Grupo de Estudos de Doença Inflamatória Intestinal do Brasil.

S-Editor: Li L
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **He CL**, Chen P, Xia BL, Xiao Q, Cai FL. Breast metastasis of gastric signet-ring cell carcinoma: a case report and literature review. *World J Surg Oncol* 2015; **13**: 120 [PMID: 25890325 DOI: 10.1186/s12957-015-0538-1]
2 **Abid A**, Moffa C, Monga DK. Breast cancer metastasis to the GI tract may mimic primary gastric cancer. *J Clin Oncol* 2013; **31**: e106-e107 [PMID: 23319694 DOI: 10.1200/JCO.2012.44.6393]
3 **Almubarak MM**, Laé M, Cacheux W, de Cremoux P, Pierga JY, Reyal F, Bennett SP, Falcou MC, Salmon RJ, Baranger B, Mariani P. Gastric metastasis of breast cancer: a single centre retrospective study. *Dig Liver Dis* 2011; **43**: 823-827 [PMID: 21616731 DOI: 10.1016/j.dld.2011.04.009]
4 **Ambroggi M**, Stroppa EM, Mordenti P, Biasini C, Zangrandi A, Michieletti E, Belloni E, Cavanna L. Metastatic breast cancer to the gastrointestinal tract: report of five cases and review of the literature. *Int J Breast Cancer* 2012; **2012**: 439023 [PMID: 23091732 DOI: 10.1155/2012/439023]
5 **Taal BG**, Boot H, van Heerde P, de Jong D, Hart AA, Burgers JM. Primary non-Hodgkin lymphoma of the stomach: endoscopic pattern and prognosis in low *vs* high grade malignancy in relation to the MALT concept. *Gut* 1996; **39**: 556-561 [PMID: 8944565 DOI: 10.1136/gut.39.4.556]
6 **Zelek L**, Cottu PH, Mignot L, de Roquancourt A, Fizazi K, Cojean-Zelek I, Espie M, Marty M. Gastric metastases from breast cancer: a retrospective series of 12 patients. *Am J Clin Oncol* 2001; **24**: 363-365 [PMID: 11474262 DOI: 10.1097/00000421-200108000-00009]
7 **Taal BG**, Peterse H, Boot H. Clinical presentation, endoscopic features, and treatment of gastric metastases from breast carcinoma. *Cancer* 2000; **89**: 2214-2221 [PMID: 11147591]
8 **Takeuchi H**, Hiroshige S, Yoshikawa Y, Kusumoto T, Muto Y. A case of synchronous metastasis of breast cancer to stomach and colon. *Anticancer Res* 2012; **32**: 4051-4055 [PMID: 22993359]
9 **Sataloff DM**, Dentchev D, Henry DH, Weese JL. Isolated Breast Metastases from Primary Gastric Adenocarcinoma. *Breast J* 2000; **6**: 62 [PMID: 11348336 DOI: 10.1046/j.1524-4741.2000.98072.x]
10 **Koike K**, Kitahara K, Higaki M, Urata M, Yamazaki F, Noshiro H. Clinicopathological features of gastric metastasis from breast cancer in three cases. *Breast Cancer* 2014; **21**: 629-634 [PMID: 21779814 DOI: 10.1007/s12282-011-0284-3]
11 **Kim GH**, Ahn JY, Jung HY, Park YS, Kim MJ, Choi KD, Lee JH, Choi KS, Kim DH, Lim H, Song HJ, Lee GH, Kim JH. Clinical and Endoscopic Features of Metastatic Tumors in the Stomach. *Gut Liver* 2015; **9**: 615-622 [PMID: 25473071 DOI: 10.5009/gnl14032]
12 **Schwarz RE**, Klimstra DS, Turnbull AD. Metastatic breast cancer masquerading as gastrointestinal primary. *Am J Gastroenterol* 1998; **93**: 111-114 [PMID: 9448188 DOI: 10.1111/j.1572-0241.1998.111_c.x]
13 **Fernandes GS**, Corrêa TS, Carvalho EP, Katz A, Hoff PM. Gastric and endobronchial metastases in a case of lobular breast cancer. *Case Rep Oncol* 2013; **6**: 555-560 [PMID: 24348393 DOI: 10.1159/000356564]
14 **Xu L**, Liang S, Yan N, Zhang L, Gu H, Fei X, Xu Y, Zhang F. Metastatic gastric cancer from breast carcinoma: A report

of 78 cases. *Oncol Lett* 2017; **14**: 4069-4077 [PMID: 28943914 DOI: 10.3892/ol.2017.6703]

15 **Tot T**. The role of cytokeratins 20 and 7 and estrogen receptor analysis in separation of metastatic lobular carcinoma of the breast and metastatic signet ring cell carcinoma of the gastrointestinal tract. *APMIS* 2000; **108**: 467-472 [PMID: 11028811 DOI: 10.1034/j.1600-0463.2000.d01-84.x]

16 **Gadde R**, Tamariz L, Hanna M, Avisar E, Livingstone A, Franceschi D, Yakoub D. Metastatic gastric cancer (MGC) patients: Can we improve survival by metastasectomy? *J Surg Oncol* 2015; **112**: 38-45 [PMID: 26074130 DOI: 10.1002/jso.23945]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3288-3294

DOI: 10.12998/wjcc.v11.i14.3288

ISSN 2307-8960 (online)

CASE REPORT

Novel mutation of *SPG4* gene in a Chinese family with hereditary spastic paraplegia: A case report

Jie Wang, Wei-Ting Bu, Mei-Jia Zhu, Ji-You Tang, Xiao-Min Liu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Orlacchio A, Italy; Yahya FS, Iraq

Received: January 6, 2023
Peer-review started: January 6, 2023
First decision: February 8, 2023
Revised: March 15, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Jie Wang, Department of Neurology, Shandong Provincial Qianfoshan Hospital, Shandong University of Traditional Chinese Medicine, Jinan 250014, Shandong Province, China

Wei-Ting Bu, Department of Neurology, Shandong Provincial Qianfoshan Hospital, Weifang Medical University, Jinan 250014, Shandong Province, China

Mei-Jia Zhu, Ji-You Tang, Xiao-Min Liu, Department of Neurology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan 250014, Shandong Province, China

Corresponding author: Xiao-Min Liu, PhD, Department of Neurology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, No. 16766 Jingshi Road, Jinan 250014, Shandong Province, China. lxmywc@163.com

Abstract

BACKGROUND

Hereditary spastic paraplegia (HSP) is a group of neurogenetic diseases of the corticospinal tract, accompanied by distinct spasticity and weakness of the lower extremities. Mutations in the spastic paraplegia type 4 (*SPG4*) gene, encoding the spastin protein, are the major cause of the disease. This study reported a Chinese family with HSP caused by a novel mutation of the *SPG4* gene.

CASE SUMMARY

A 44-year-old male was admitted to our hospital for long-term right lower limb weakness, leg stiffness, and unstable walking. His symptoms gradually worsened, while no obvious muscle atrophy in the lower limbs was found. Neurological examinations revealed that the muscle strength of the lower limbs was normal, and knee reflex hyperreflexia and bilateral positive Babinski signs were detected. Members of his family also had the same symptoms. Using mutation analysis, a novel heterozygous duplication mutation, c.1053dupA, p. (Gln352Thrfs*15), was identified in the *SPG4* gene in this family.

CONCLUSION

A Chinese family with HSP had a novel mutation of the *SPG4* gene, which is autosomal dominant and inherited as pure HSP. The age of onset, sex distribution, and clinical manifestations of all existing living patients in this family were analyzed. The findings may extend the current knowledge on the existing mutations in the *SPG4* gene.

Key Words: Hereditary spastic paraplegia; *SPG4* gene; Mutation; Genetic testing; Autosomal dominant HSP; Adenosine triphosphatases associated with diverse cellular activities; Case report

Core Tip: It is difficult to distinguish hereditary spastic paraplegia (HSP) from other spasticity-related genetic diseases because the different affected genes lead to large differences in the pathogenic mechanisms, clinical features, and imaging abnormalities of HSP. Therefore, genetic testing is important for the diagnosis and typing of HSP. A Chinese HSP male patient was identified, and pedigree surveys of his relatives were performed. Furthermore, genomic DNA was extracted for whole-exome sequencing, and pathogenic variants were screened by bioinformatics methods and verified using Sanger sequencing. A novel heterozygous duplication mutation, c.1053dupA, p. (Gln352Thrfs*15), was identified in the *SPG4* gene in this family.

Citation: Wang J, Bu WT, Zhu MJ, Tang JY, Liu XM. Novel mutation of *SPG4* gene in a Chinese family with hereditary spastic paraplegia: A case report. *World J Clin Cases* 2023; 11(14): 3288-3294
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3288.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3288

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of neurogenetic diseases caused by degeneration of the corticospinal tract, which is characterized by slow progressive spasms and weakness of the lower limbs. The disease has obvious clinical and genetic heterogeneity[1]. According to their clinical manifestations, HSP is divided into pure and complex types. The pure type presents with slowly progressive lower extremity weakness and spasticity, corticospinal tract signs, disturbance in the vibration sense and proprioception, and possible sphincter disturbances. Complex HSP is characterized by leg spasticity and other complications, such as ataxia, a thin corpus callosum, extrapyramidal signs, chorioretinal dystrophy, peripheral neuropathy, and mental retardation[2,3]. HSP can be inherited by autosomal dominant (AD), autosomal recessive, X-linked, and mitochondrial maternal patterns. More than 80 genes or loci involved in the inheritance of this disease have been identified. Spastic paraplegia type 4 (*SPG4*) is the most common cause of pure HSP, accounting for 45% of pure HSP cases. It is inherited by AD mode and is caused by the mutation of the *SPAST* gene[1,4,5].

CASE PRESENTATION

Chief complaints

Seven years before his admission to our hospital, a 44-year-old male (patient V: 4) experienced right lower limb weakness, leg stiffness, and unstable walking. The symptoms appeared without obvious inducement. The patient was from the Han Chinese population in Shandong Province, China.

History of present illness

Initially, he felt that his symptoms were mild. He was never treated, and his symptoms gradually worsened over time. In the 4th year after onset, he began to experience hotness in his right knee joint, his gait became increasingly slow, his legs felt stiff, and lumbago appeared. The patient's lumbago symptoms were most severe at night during sleep and in the morning. Meanwhile, the patient felt that the range of motion of both knees was limited, which aggravated when he was tired. He could not run and had difficulty climbing stairs.

History of past illness

The patient was healthy before. The patient denied a history of surgery and trauma, diabetes mellitus, cardiac disease, or infectious diseases.

Personal and family history

His family history revealed that he was born to non-consanguineous parents, but similar symptoms were found in several of his relatives.

Physical examination

Neurological examination showed that the cranial nerves of the proband were not abnormal. The proximal and distal muscle strength and muscle tone of double upper extremities were normal. Biceps reflexes, triceps reflexes, and radial reflexes were normal, and bilateral Hoffman signs were negative. The proximal and distal muscle strength of both lower limbs was normal. Lower limb hypermyotonia and bilateral knee reflex were enhanced. Bilateral Chaddock's sign, Oppenheim sign, and Gordon sign were negative, while Babinski sign was positive. There was no muscle atrophy or abnormal involuntary movement.

Laboratory examinations

The proband was initially suspected of having myelopathy. Further laboratory examinations, such as cerebrospinal fluid sample analysis and determination of the serum vitamin B12 level, were conducted. No inflammatory or immune lesions were detected. Neuro-electrophysiological examination suggested normal motor nerve conduction, sensory nerve conduction, and needle electromyography.

Imaging examinations

The magnetic resonance imaging of the cervical spinal cord, thoracic spinal cord, and lumbar spinal cord revealed only intervertebral disc herniation of the cervical and lumbar spine. No obvious swelling, atrophy, or compression of the spinal cord was found.

Family structure and description of deceased and living patients

After obtaining written informed consent from the proband and his relatives, a detailed investigation of this Han Chinese family from Shandong Province, China was conducted. This family was traced back to the sixth generation, with a total of 11 people suffering from the disease, with an AD genetic pattern (Figure 1A). Five deceased individuals had spastic paraplegia in their lifetime, including four males (patients I: 1, II: 1, II: 2, and IV: 6) and one female (patient III: 2). Of the six living patients, five were male (patients IV: 2, IV: 4, V: 4, VI: 1, and VI: 3), and one was female (patient V: 3).

Other living and symptomatic patients initially showed weak legs or unstable walking. They developed different clinical symptoms as they grew older and the course of the disease progressed. The proband's father (patient IV: 4) and uncle (patient IV: 2) were affected by the illness in middle age, with a long course of disease, severe symptoms, difficulty in lifting the legs, and a scissor gait. Neurological examination revealed the increased lower limb hypermyotonia and tendon hyperreflexia, and bilateral Babinski signs were positive. They started using crutches to assist walking approximately 20 years and 10 years after onset, respectively. The proband's nephew (VI: 1), now 20 years old, developed a gait disturbance at the age of 10-years-old. Although there was obvious difficulty in walking, he did not need the assistance of appliances. The proband's cousin (V: 3) was a female patient with an onset age of 46-years-old and a disease course of 2 years who presented with mild weakness of both lower limbs. The son (VI: 3) of the proband, aged 19-years-old, was an asymptomatic mutation carrier. The mean age of onset of symptoms was 36.6 ± 14.1-years-old. The disease course was 14.8 ± 10.9 years. All the surviving patients were intellectually normal with no cognitive impairment, peripheral neuropathy, bladder dysfunction, and claw-feet. No scoliosis was detected. Their age of onset, course of disease, sex, spastic paraplegia rating scale[6], and disability stage were recorded and evaluated. The spastic paraplegia rating scale is a composite measurement modality. It includes walking distance without pause, gait speed, quality of gait, climbing stairs, arising from chair, spasticity quality, weakness and contractures, pain caused by spastic paraplegia-related symptoms, and bladder dysfunction. The score for each item ranged from 0 (no dysfunction) to 4 (the most severe dysfunction), and the highest total score of all items is 52. Thus, higher spastic paraplegia rating scale scores represent heavier dysfunction. Additional data are presented in Table 1.

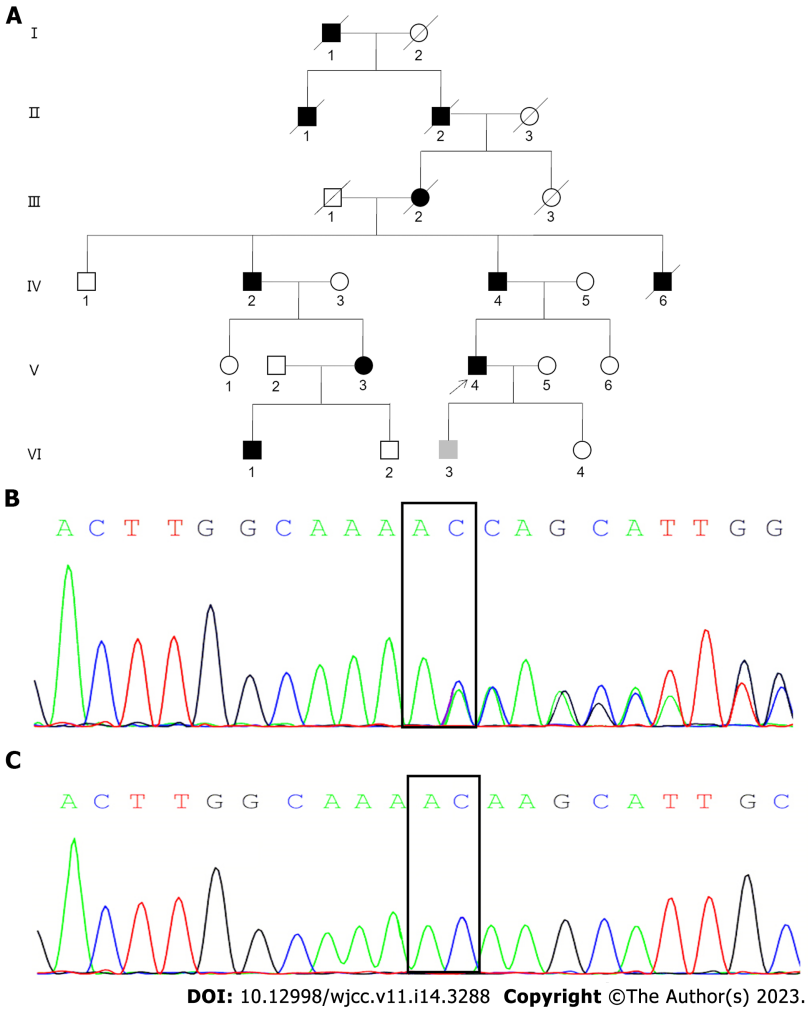
GENETIC TESTING

After obtaining written informed consent from participants, DNA was extracted from seven peripheral blood samples, including the proband (V: 4), his father (IV: 4), his mother (IV: 5), his wife (V: 5), his sister (V: 6), his son (VI: 3), and his daughter (VI: 4). Whole-exome sequencing was first performed, pathogenic variants were analyzed by bioinformatics methods, and were then verified using Sanger sequencing. It was found that the proband (V: 4) and the patient (IV: 4, VI: 3) carried a pathogenic heterozygous variant of the *SPG4* gene, namely c.1053dupA, p. (Gln352Thrfs*15), located at the shear site of the *SPG4* exon 7 (Figures 1B and C). This mutation has not previously been reported. It was also not registered in the Clinvar, dbSNP, and HGMD databases.

Table 1 Clinical features of patients with a c.1053dupA mutation of the *SPG4* gene

Patient	Sex	Age at onset, yr	Duration of the disease, yr	Hyperreflexia	Spasticity	Decreased vibration sense	Sensory impairment	Stages[a]	SPRS
IV: 2	Male	50	24	+	+	-	N	4	28
IV: 4	Male	40	31	+	+	-	N	4	30
V: 3	Female	46	2	-	-	-	N	1	3
V: 4	Male	37	7	+	+	-	N	3	20
VI: 1	Male	10	10	+	+	-	N	2	16
VI: 3	Male	-	-	-	-	-	N	1	0

[a]The following stages were defined: (1) Normal or very slight stiffness in the legs; (2) Moderate gait stiffness; (3) Unable to run while able to walk alone; (4) Able to walk on crutches or with help; and (5) Wheelchair-bound. -: Absent; +: Present; N: Normal; SPRS: Spastic paraplegia rating scale.



DOI: 10.12998/wjcc.v11.i14.3288

Figure 1 Pedigree of the patient and mutation analysis of the *SPG4* gene. A: The family with hereditary spastic paraplegia (HSP). The proband is indicated by an arrow. A square indicates male, a circle for female, a shadow symbol for an HSP individual, including a black shadow for a symptomatic patient and a gray shadow for an asymptomatic patient, a non-shadowing symbol for a non-HSP individual, and a slash symbol for a deceased individual; B: Sequence analysis identified a c. 1053dupA mutation in the *SPG4* gene in this family. Black frames delineate the C. 1053dupA nucleotides; and C: Wild-type sequence.

FINAL DIAGNOSIS

Referring to the Harding diagnostic criteria[7] and based on genetic testing, the proband and other related relatives were finally diagnosed with SPG4 HSP.

TREATMENT

The proband was given an intravenous injection of methylcobalamin (500 μg/d) for 2 wk; then the route was changed to oral administration (1.5 mg/d) for 3 mo. He also took baclofen orally (15 mg/d at the initial stage, which then increased to 30 mg/d) for 6 wk.

OUTCOME AND FOLLOW-UP

Although his low back pain was resolved somewhat, his slow walking and stiffness in both lower limbs were not significantly improved. He still could not run, and he had difficulty climbing the stairs.

DISCUSSION

HSP is a nervous system disease, accompanied by diverse clinical manifestations and complex genetic etiology and pathogenesis. The onset age ranges from infancy to senility, and the functional impairment is highly variable[4]. The onset age span of patients in the present study was large, in which the largest age span between two relatives was 40 years. The majority of patients developed the disease in middle age.

According to the clinical symptoms, it was revealed that the pure HSP type was dominant in the proband's family, including progressive weakness of the lower extremities and spasticity[1-4]. Notably, in this family, male patients were more affected by the disease than female patients, with a male to female ratio of 9:2, which is consistent with the findings of another study[8]. Earlier reports have also confirmed that patients with *SPG4* gene mutation-related diseases were mostly male, suggesting that in some cases sex is a stronger contributing factor to the time of onset of disease symptoms than age[9]. This may be associated with the higher levels of estrogen and progesterone in female patients[10,11]. Due to the genetic and clinical heterogeneity of HSP, its phenotype is complex, and the diagnosis is difficult, which may be attributed to the effects of genetic factors, environmental modifiers, penetrance, and sex[8,12,13].

In the present study, a novel mutation, c.1053dupA, p. (Gln352Thrfs*15), was detected in the *SPG4* gene in the family with HSP. This variant is a frameshift mutation that results in a Gln 352-to-Thr substitution and a new reading frame and is terminated at codon 15 downstream of the amino acid at position 352, causing early translation termination compared with the wild-type protein. This may lead to truncation of the coding protein synthesis, thereby losing its normal function. This novel variant was predicted to be deleterious by Mutation Taster analysis (http://www.mutationtaster.org/MT69/MutationTaster69.cgi?bases_inserted=A&end_insdel=1054&start_insdel=1053&transcript_stable_id_text=ENST00000315285&sequence_type=CDS&gene=spast). The DNA sequence variants were named following the guidelines of the Human Genome Variation Society (https://varnomen.hgvs.org/recommendations/general/).

In 2009 and 2010, two mutations of the *SPG4* gene were reported in two families, including c.1055A > C, p. (Gln352Pro) and c.1054C > T, p. (Gln352X), respectively[14,15]. Both are mutations caused by a single-base substitution, one being a missense mutation and the other being a nonsense mutation. These two previously detected mutations and our newly identified mutation are located within the conserved adenosine triphosphatases associated with diverse cellular activities cassette, resulting in changes in activity of the spastin protein and loss of function. The findings of the present study suggest that mutations in this region are not uncommon. To date, at least 80 genes and several variants have been found to be associated with HSP, of which those of *SPG4* cause the most common type of HSP[9,16,17]. Most of the mutations of the *SPG4* gene are missense (33%), frameshift (24%), splice-site (16%), nonsense variants, and deletions (12%)[4].

The *SPG4* gene encodes a microtubule (MT)-severing protein, namely spastin, which is an MT-severing enzyme containing an MTbinding domain and adenosine triphosphatases associated with diverse cellular activity domains with adequate severing activity, playing an important role in axon development, synaptic formation, and spinal cord maturation[18-20]. A number of factors lead to mutations in the *SPG4* gene and the onset of related disease symptoms, of which the main factor is a decrease in the level of the functional spastin protein, resulting in insufficient MT cutting[18-21]. Another study found that aggregation of the mutant spastin protein caused toxicity, while it could not explain the underlying mechanisms and possible consequences[21]. Qiang *et al*[22] demonstrated that the function acquisition mechanism of *SPG4* gene is more meaningful than its function loss mechanism.

Only symptomatic treatment of HSP is currently available. In the present study, the proband was treated with methylcobalamin and baclofen, which only relieved his low back pain, while the other symptoms were not improved significantly. Therefore, it is critically important to find an effective treatment for this disease. A recent study proposed a new direction of targeted therapeutic application [23]. The results of this investigation showed that the mutation of the *SPG4* gene was not only associated with haploinsufficiency causing decreased spastin function but also could be one of the important

pathogenic factors of spastin function dysregulation. The phosphorylation of S268 mediated by HIPK2 may contribute to the stability of the spastin protein and rescue HSP neurite defects.

CONCLUSION

In conclusion, a newly pathogenic mutation was proposed, expanding the existing knowledge of the spectrum of mutations of the *SPG4* gene. The findings may provide a reliable basis for further research on the genetic etiology and pathogenesis of HSP. The diagnosis and typing of HSP through genetic analysis can control and treat the disease as well as avoid the transmission of pathogenic genes in the family.

ACKNOWLEDGEMENTS

The authors thank all participants for their active contribution to this study. The authors also thank reviewers for their comments and suggestions.

FOOTNOTES

Author contributions: Wang J wrote the manuscript; Liu XM and Zhu MJ performed the neurological examinations; Wang J and Liu XM assessed the mutation and analyzed neuroimages; Liu XM and Tang JY designed the report; Wang J and Bu WT drafted the manuscript; and all authors read and approved the final version of the manuscript.

Supported by The Shandong Provincial Natural Science Foundation, No. ZR2021MH059.

Informed consent statement: This study was approved by the Ethics Committee of Shandong First Medical University. Informed consent was obtained for the publication of relevant clinical information and photographs.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Jie Wang 0000-0003-2052-965X; Wei-Ting Bu 0000-0001-9018-4007; Mei-Jia Zhu 0000-0003-0067-629X; Ji-You Tang 0000-0002-4520-6585; Xiao-Min Liu 0000-0002-5783-1134.

S-Editor: Liu XF
L-Editor: Filipodia
P-Editor: Cai YX

REFERENCES

1 **Murala S**, Nagarajan E, Bollu PC. Hereditary spastic paraplegia. *Neurol Sci* 2021; **42**: 883-894 [PMID: 33439395 DOI: 10.1007/s10072-020-04981-7]
2 **Shribman S**, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol* 2019; **18**: 1136-1146 [PMID: 31377012 DOI: 10.1016/S1474-4422(19)30235-2]
3 **Walusinski O**. A historical approach to hereditary spastic paraplegia. *Rev Neurol (Paris)* 2020; **176**: 225-234 [PMID: 31911003 DOI: 10.1016/j.neurol.2019.11.003]
4 **Lallemant-Dudek P**, Durr A. Clinical and genetic update of hereditary spastic paraparesis. *Rev Neurol (Paris)* 2021; **177**: 550-556 [PMID: 32807405 DOI: 10.1016/j.neurol.2020.07.001]
5 **Meyyazhagan A**, Orlacchio A. Hereditary Spastic Paraplegia: An Update. *Int J Mol Sci* 2022; **23** [PMID: 35163618 DOI: 10.3390/ijms23031697]
6 **Schüle R**, Holland-Letz T, Klimpe S, Kassubek J, Klopstock T, Mall V, Otto S, Winner B, Schöls L. The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology* 2006; **67**: 430-434 [PMID:

16894103 DOI: 10.1212/01.wnl.0000228242.53336.90]
7 **Harding AE**. Classification of the hereditary ataxias and paraplegias. *Lancet* 1983; **1**: 1151-1155 [PMID: 6133167 DOI: 10.1016/S0140-6736(83)92879-9]
8 **Parodi L**, Fenu S, Barbier M, Banneau G, Duyckaerts C, Tezenas du Montcel S, Monin ML, Ait Said S, Guegan J, Tallaksen CME, Sablonniere B, Brice A, Stevanin G, Depienne C, Durr A; SPATAX network. Spastic paraplegia due to SPAST mutations is modified by the underlying mutation and sex. *Brain* 2018; **141**: 3331-3342 [PMID: 30476002 DOI: 10.1093/brain/awy285]
9 **Erfanian Omidvar M**, Torkamandi S, Rezaei S, Alipoor B, Omrani MD, Darvish H, Ghaedi H. Genotype-phenotype associations in hereditary spastic paraplegia: a systematic review and meta-analysis on 13,570 patients. *J Neurol* 2021; **268**: 2065-2082 [PMID: 31745725 DOI: 10.1007/s00415-019-09633-1]
10 **Orlacchio A**, Kawarai T, Gaudiello F, Totaro A, Schillaci O, Stefani A, Floris R, St George-Hyslop PH, Sorbi S, Bernardi G. Clinical and genetic study of a large SPG4 Italian family. *Mov Disord* 2005; **20**: 1055-1059 [PMID: 15858810 DOI: 10.1002/mds.20494]
11 **Hu R**, Sun H, Zhang Q, Chen J, Wu N, Meng H, Cui G, Hu S, Li F, Lin J, Wan Q, Feng H. G-protein coupled estrogen receptor 1 mediated estrogenic neuroprotection against spinal cord injury. *Crit Care Med* 2012; **40**: 3230-3237 [PMID: 22975889 DOI: 10.1097/CCM.0b013e3182657560]
12 **Boutry M**, Morais S, Stevanin G. Update on the Genetics of Spastic Paraplegias. *Curr Neurol Neurosci Rep* 2019; **19**: 18 [PMID: 30820684 DOI: 10.1007/s11910-019-0930-2]
13 **Rodrigues R**, Silva R, Branco M, Brandão E, Alonso I, Ruano L, Loureiro JL. Determinants of age at onset in a Portuguese cohort of autosomal dominant spastic paraplegia. *J Neurol Sci* 2020; **410**: 116646 [PMID: 31887672 DOI: 10.1016/j.jns.2019.116646]
14 **Loureiro JL**, Miller-Fleming L, Thieleke-Matos C, Magalhães P, Cruz VT, Coutinho P, Sequeiros J, Silveira I. Novel SPG3A and SPG4 mutations in dominant spastic paraplegia families. *Acta Neurol Scand* 2009; **119**: 113-118 [PMID: 18664244 DOI: 10.1111/j.1600-0404.2008.01074.x]
15 **Alvarez V**, Sánchez-Ferrero E, Beetz C, Díaz M, Alonso B, Corao AI, Gámez J, Esteban J, Gonzalo JF, Pascual-Pascual SI, López de Munain A, Moris G, Ribacoba R, Márquez C, Rosell J, Marín R, García-Barcina MJ, Del Castillo E, Benito C, Coto E; Group for the Study of the Genetics of Spastic Paraplegia. Mutational spectrum of the SPG4 (SPAST) and SPG3A (ATL1) genes in Spanish patients with hereditary spastic paraplegia. *BMC Neurol* 2010; **10**: 89 [PMID: 20932283 DOI: 10.1186/1471-2377-10-89]
16 **Yang JO**, Yoon JY, Sung DH, Yun S, Lee JJ, Jun SY, Halder D, Jeon SJ, Woo EJ, Seok JM, Cho JW, Jang JH, Choi JK, Kim BJ, Kim NS. The emerging genetic diversity of hereditary spastic paraplegia in Korean patients. *Genomics* 2021; **113**: 4136-4148 [PMID: 34715294 DOI: 10.1016/j.ygeno.2021.10.014]
17 **McDermott C**, White K, Bushby K, Shaw P. Hereditary spastic paraparesis: a review of new developments. *J Neurol Neurosurg Psychiatry* 2000; **69**: 150-160 [PMID: 10896685 DOI: 10.1136/jnnp.69.2.150]
18 **Liu Q**, Zhang G, Ji Z, Lin H. Molecular and cellular mechanisms of spastin in neural development and disease (Review). *Int J Mol Med* 2021; **48** [PMID: 34664680 DOI: 10.3892/ijmm.2021.5051]
19 **Sandate CR**, Szyk A, Zehr EA, Lander GC, Roll-Mecak A. Author Correction: An allosteric network in spastin couples multiple activities required for microtubule severing. *Nat Struct Mol Biol* 2020; **27**: 400 [PMID: 32203494 DOI: 10.1038/s41594-020-0414-8]
20 **Kelliher MT**, Saunders HA, Wildonger J. Microtubule control of functional architecture in neurons. *Curr Opin Neurobiol* 2019; **57**: 39-45 [PMID: 30738328 DOI: 10.1016/j.conb.2019.01.003]
21 **Rehbach K**, Kesavan J, Hauser S, Ritzenhofen S, Jungverdorben J, Schüle R, Schöls L, Peitz M, Brüstle O. Multiparametric rapid screening of neuronal process pathology for drug target identification in HSP patient-specific neurons. *Sci Rep* 2019; **9**: 9615 [PMID: 31270336 DOI: 10.1038/s41598-019-45246-4]
22 **Qiang L**, Piermarini E, Baas PW. New hypothesis for the etiology of SPAST-based hereditary spastic paraplegia. *Cytoskeleton (Hoboken)* 2019; **76**: 289-297 [PMID: 31108029 DOI: 10.1002/cm.21528]
23 **Sardina F**, Pisciottani A, Ferrara M, Valente D, Casella M, Crescenzi M, Peschiaroli A, Casali C, Soddu S, Grierson AJ, Rinaldo C. Spastin recovery in hereditary spastic paraplegia by preventing neddylation-dependent degradation. *Life Sci Alliance* 2020; **3** [PMID: 33106322 DOI: 10.26508/lsa.202000799]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3295-3303

DOI: 10.12998/wjcc.v11.i14.3295

ISSN 2307-8960 (online)

CASE REPORT

Chronic pulmonary mucormycosis caused by rhizopus microsporus mimics lung carcinoma in an immunocompetent adult: A case report

Xing-Zi Guo, Liang-Hui Gong, Wen-Xiang Wang, De-Song Yang, Bai-Hua Zhang, Ze-Tao Zhou, Xiao-Hui Yu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Nasa P, United Arab Emirates; Rotondo JC, Italy

Received: January 7, 2023
Peer-review started: January 7, 2023
First decision: March 24, 2023
Revised: April 2, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Xing-Zi Guo, Department of Gynecologic Oncology, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410031, Hunan Province, China

Liang-Hui Gong, Wen-Xiang Wang, De-Song Yang, Bai-Hua Zhang, The Second Department of Thoracic Surgery, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410031, Hunan Province, China

Ze-Tao Zhou, GZMU-GIBH School of Life Sciences, Guangzhou Medical University, Guangzhou 511436, Guangdong Province, China

Xiao-Hui Yu, Department of Pathology, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410031, Hunan Province, China

Corresponding author: Xiao-Hui Yu, MD, PhD, Doctor, Department of Pathology, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Tongzipo Road, Yuelu District, Changsha 410031, Hunan Province, China. yuxiaohui@hnca.org.cn

Abstract

BACKGROUND

Pulmonary mucormycosis is a rare but life-threatening invasive fungal infection that mostly affects immunocompromised patients. This disease usually develops acutely and progresses rapidly, often leading to a poor clinical prognosis. Chronic pulmonary mucormycosis is highly unusual in immunocompetent patients.

CASE SUMMARY

A 43-year-old man, who was a house improvement worker with a long history of occupational dust exposure, presented with an irritating cough that had lasted for two months. The patient was previously in good health, without dysglycemia or any known immunodeficiencies. Chest computed tomography revealed a mass in the left lower lobe, measuring approximately 6 cm in diameter, which was suspected to be primary lung carcinoma complicated with obstructive pneumonia. Thoracoscopic-assisted left lower lobectomy was performed, and metagenomic next-generation sequencing detection, along with special pathological staining of surgical specimens, suggested Rhizopus microsporus infection. Postoperatively, the patient's respiratory symptoms were relieved, and no signs of recurrence were found during the six-month follow-up.

CONCLUSION
This article reports a rare case of chronic pulmonary mucormycosis caused by Rhizopus microsporus in a middle-aged male without dysglycemia or immunodeficiency. The patient's surgical outcome was excellent, reaffirming that surgery remains the cornerstone of pulmonary mucormycosis treatment.

Key Words: Rhizopus microsporus; Pulmonary mucormycosis; Immunocompetent patient; Surgical resection; Case report

Core Tip: Pulmonary mucormycosis is a rare yet life-threatening invasive fungal infection that typically affects immunocompromised patients. In this report, we present a case of chronic pulmonary mucormycosis in a 43-year-old immunocompetent house improvement worker. The patient initially presented with an irritating cough and a solitary mass in the left lower lobe, which raised concerns of primary lung carcinoma. A successful thoracoscopic-assisted left lower lobectomy was performed, and subsequent metagenomic next-generation sequencing analysis and specialized pathological staining of surgical specimens suggested Rhizopus microsporus as the causative agent of the infection. During a six-month postoperative follow-up, no signs of recurrence were observed.

Citation: Guo XZ, Gong LH, Wang WX, Yang DS, Zhang BH, Zhou ZT, Yu XH. Chronic pulmonary mucormycosis caused by rhizopus microsporus mimics lung carcinoma in an immunocompetent adult: A case report. *World J Clin Cases* 2023; 11(14): 3295-3303
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3295.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3295

INTRODUCTION

Pulmonary mucormycosis is a rare but aggressive and life-threatening fungal infection that mainly affects immunocompromised individuals[1]. The most common causative agents are Rhizopus species, particularly Rhizopus microsporus, which belong to the class Zygomycetes[2]. The infection typically occurs in patients with underlying conditions such as diabetes mellitus, hematologic malignancy, and solid organ or stem cell transplant[3]. Pulmonary mucormycosis is an aggressive and rapidly progressive infection that carries a poor clinical prognosis, with a mortality rate as high as 50%-60% worldwide[4,5]. Chronic pulmonary mucormycosis, lasting more than one month, is extremely rare, with most reported cases occurring in patients with diabetes[6-10]. In this case report, we present a rare case of chronic pulmonary mucormycosis caused by Rhizopus microsporus, which mimicked lung carcinoma in an immunocompetent middle-aged male. The patient underwent aggressive surgical resection, and achieved an excellent therapeutic response.

CASE PRESENTATION

Chief complaints

A 43-year-old man from China presented at the hospital with a history of coughing and sputum production for the past two months.

History of present illness

Two months prior to admission to our hospital, the patient visited a local hospital due to an irritative cough with a small amount of white, foamy sputum that lasted for two wk. The patient did not exhibit any obvious indications of accompanying symptoms such as blood in the sputum, fever, night sweats, weight loss, hoarseness, dyspnea, or discomforts. A chest computed tomography (CT) scan revealed a soft tissue mass, approximately 57 mm x 51 mm in size, in the left lower lobe that was suspected to be a fungal infection or tumor. Electronic bronchoscopy showed that the basal branch mucosa of the left lower lobe was swollen and hypertrophic, and the surface was not smooth. No active bleeding or new organisms were found. Bronchial mucosal biopsy revealed chronic inflammatory changes. Acid-fast stains of bronchoalveolar lavage fluid, as well as bacterial and fungal cultures, were negative. Since the specific cause of the symptoms could not be clarified, the patient was treated with empirical anti-

infection medication, specifically cephalosporins, in the local hospital for two wk. However, the patient's cough symptoms did not improve significantly. As a result, the patient was admitted to our thoracic medicine department as an outpatient for further diagnosis and treatment.

History of past illness

The patient did not report any prior history of surgeries, trauma, severe infections, or significant medical conditions. Additionally, the patient denied any previous infection with coronavirus disease 2019.

Personal and family history

The patient reported no significant family history of related illnesses. However, it was observed that the patient had been working as a house improvement worker and had a prolonged history of occupational dust exposure.

Physical examination

On physical examination, the patient's height was 176 cm, weight 70 kg, body temperature 36.2 °C, heart rate 94 beats per minute, respiratory rate 20 breaths per minute, and blood pressure 132/87 mmHg. The superficial lymph nodes in the supraclavicular and neck regions were non-palpable, and the chest wall was symmetrical with no deformities. The patient's breathing was regular, and apart from decreased breath sounds in the lower left lung, no other significant abnormalities were noted.

Laboratory examinations

The laboratory test results were as follows: White blood cell count was 9.54 × 10^9/L, neutrophil percentage was 52%, hemoglobin was 151 g/L, hematocrit was 47.1%, fasting blood glucose was 5.5 mmol/L, total protein level was 81 g/L, and globulin level was 37 g/L. Additionally, twelve tumor markers including AFP, CEA, NSE, CA125, CA15-3, CA242, CA19-9, PSA, f-PSA, FER, β-HCG, and HGH were measured by protein biochip detection in the serum and found to be within the normal range. Pulmonary function test results showed forced vital capacity of 5.18 L (110% predicted) and forced expiratory volume in 1 s of 3.79 L (98% predicted). Other results of routine laboratory examinations were within normal limits, including urine and stool routine, liver and kidney function, and electrolytes. The patient's infectious disease screening, which included hepatitis B, hepatitis C, syphilis, and human immunodeficiencyvirus tests, also showed no abnormalities.

Imaging examinations

The contrast-enhanced chest CT taken at our hospital revealed a 6 cm mass in the left lower lobe, primarily located in the lateral segment (S9) and posterior segment (S10). The mass showed slight enhancement and obstructed the bronchi of the affected lung segments, with the pulmonary vasculature faintly visible within it (Figures 1 and 2). Bronchoscopy revealed narrowed lumens of the left lower lobe's lateral and posterior segmental bronchi, along with congested and swollen mucosa, without any detection of new organisms in the lumen (Figure 3). Magnetic resonance imaging of the head and CT scans of the neck and abdomen showed no abnormalities. The bone scan also had negative results.

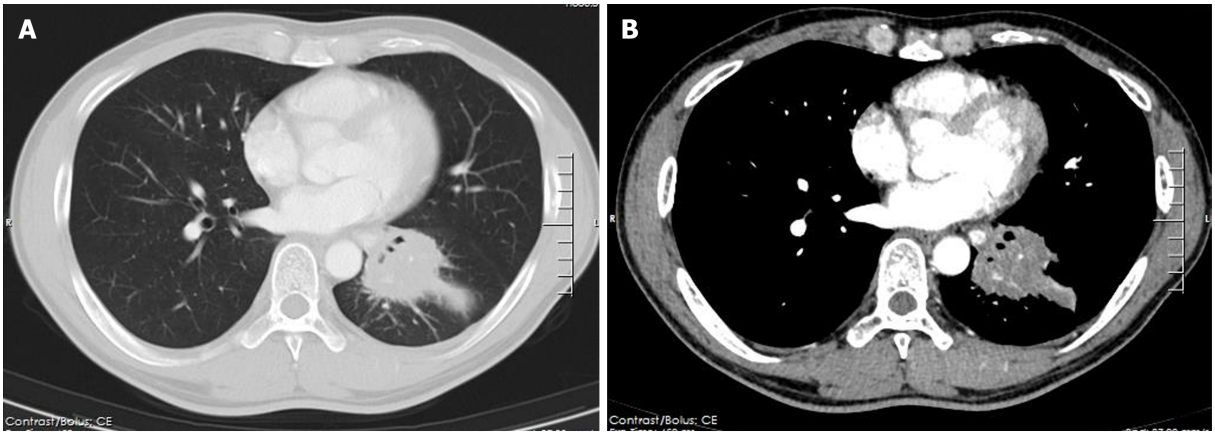
MULTIDISCIPLINARY EXPERT CONSULTATION

The patient had undergone bronchoscopy twice at different hospitals, but both procedures failed to confirm the pathological diagnosis by forceps biopsy. The patient declined further biopsies, including percutaneous lung biopsy or endobronchial ultrasound-guided transbronchial needle aspiration (ebus tbna). However, the patient expressed a strong desire for surgery and was willing to accept the risks associated with surgical treatment.

Thoracic medical oncologists organized a multidisciplinary consultation. The experts unanimously recommended respecting the patient's wishes and scheduling a surgical operation to remove the left lower lung within a specific time frame. The mass tissue obtained during the operation would then be used to make a diagnosis and guide subsequent treatment steps. Following the experts' advice, the patient was transferred to Department of Thoracic Surgery for surgical treatment.

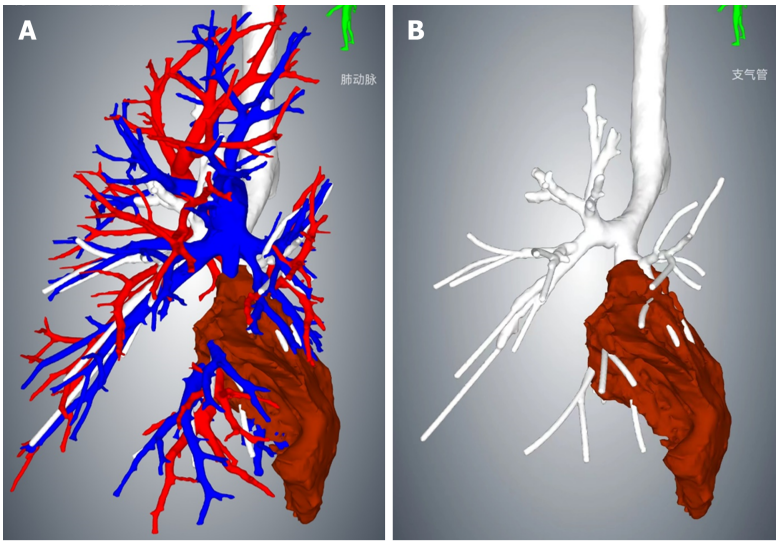
FINAL DIAGNOSIS

Based on the patient's two-month medical history and imaging signs, primary bronchial lung cancer combined with obstructive pneumonia was suspected, and specific infectious lesions could not be entirely ruled out. No sign of distant metastasis of a malignant tumor was detected during the patient's systemic examination. If the mass in the patient's left lower lobe was malignant, the current clinical stage would be cT3N1M0, stage IIIA.



DOI: 10.12998/wjcc.v11.i14.3295

Figure 1 High-resolution chest contrast-enhanced computed tomography. A: Lung window; and B: Mediastinal window. A mass in the left lower lobe with a diameter of approximately 6 cm. It was slightly enhanced and mainly located in the lateral segment (S9) and posterior segment (S10). The pulmonary vasculature was still looming in this mass, but there was bronchial occlusion of the affected lung segments.



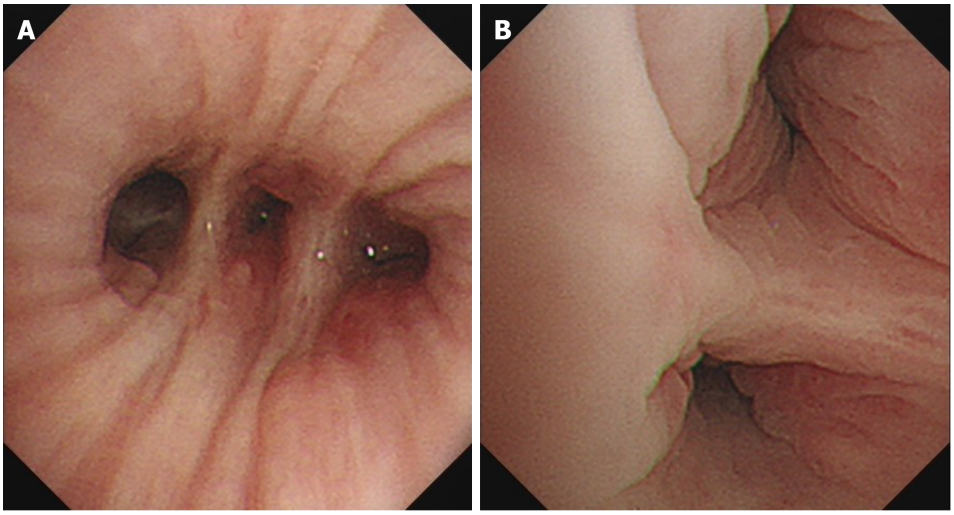
DOI: 10.12998/wjcc.v11.i14.3295

Figure 2 Three-dimensional reconstruction of the chest based on computed tomography images. A: The pulmonary vasculature is visible; and B: The pulmonary vasculature is hidden. The mass volume calculated by 3D reconstruction was 136 mL.

TREATMENT

Due to the large size of the mass, we performed a thoracoscopic-assisted left lower lobectomy through an anterolateral incision approximately 10 cm long in the fourth intercostal space. The thoracoscopic hole was located in the seventh intercostal space on the posterior axillary line. Intraoperative exploration revealed that the visceral and parietal pleura were smooth without nodules, the oblique fissure was well developed, and the mass in the left lower lobe was hard, with the basal segment densely adhered to the lateral chest wall. After separating the adherent tissues, the pulmonary artery, vein, and bronchi belonging to the left lower lobe were exposed sequentially and then closed and separated using the endoscopic linear cutting stapler. During this surgical procedure, we found that the lymph nodes in the lung mass's drainage area were significantly enlarged and hardened, but their adventitia remained intact. Interestingly, these lymph nodes appeared purulent white instead of the conventional carbon black.

The resected left lower lobe was removed from the incision. The mass was firm, approximately 6 cm in diameter, and pale in color when sectioned. Subsequent intraoperative frozen rapid pathological examination results indicated that the mass was a granulomatous inflammatory lesion with no malignant components. It was suspected that this may have been a particular type of infection which needed to be further confirmed by routine pathological examination and special staining. To determine the cause of the granuloma, we excised the clean granuloma tissue approximately 0.5 cm^3 in size and



DOI: 10.12998/wjcc.v11.i14.3295

Figure 3 Images during electronic bronchoscopy. A: Bronchoscopy revealed that the lumen of the left lower lobe's lateral and posterior segmental bronchi was narrowed; and B: The mucosa was congested and swollen, and no new organisms were found in the lumen.

sent it for clinical metagenomic next-generation sequencing (mNGS). The 3-h operation went smoothly, and the blood loss was 100 mL. There were no postoperative complications. The drainage tube was removed on the fifth day after the operation, and the patient was discharged one day later.

OUTCOME AND FOLLOW-UP

The results of mNGS analysis for the left lower lobe granuloma were obtained on the second day after the operation. The analysis suggested an infection caused by Rhizopus microsporus, and no other pathogenic microorganisms, including bacteria, viruses, parasites, mycobacteria, mycoplasma, or chlamydia, were detected. The analysis was performed by Precision Genes Technology, Inc. on August 25, 2022.

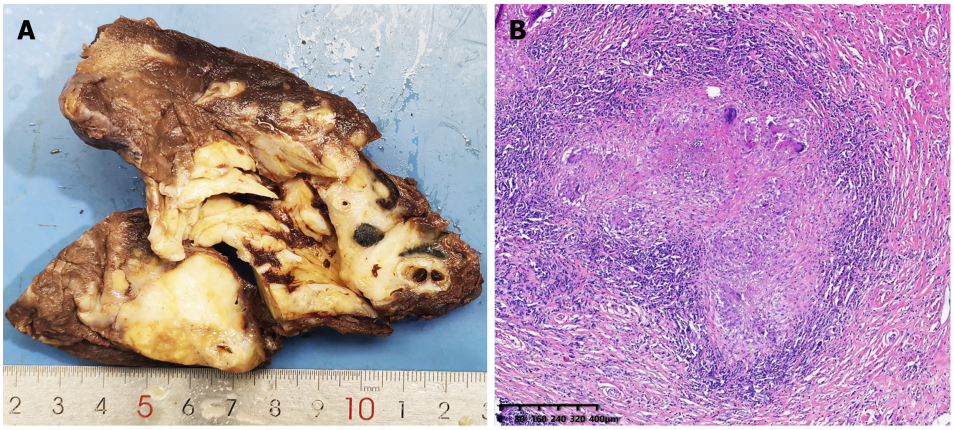
The postoperative routine pathological examination revealed that the left lower lobe mass was an inflammatory granuloma (Figure 4). Interstitial fibrous tissue hyperplasia, inflammatory cell infiltration, and multinucleated giant cell reaction were all observed under the microscope. In addition, hexamine silver staining of its histological sections revealed broad, right-angled branched aseptate hyphae, strongly suggesting the possibility of pulmonary mucormycosis (Figure 5).

Considering the patient's clinical manifestations, as well as the laboratory, imaging, mNGS, and histopathological examinations, the patient was finally diagnosed with chronic pulmonary mucormycosis caused by Rhizopus microsporus infection, which is very rare in immunocompetent nondiabetic patients.

After surgery, the patient's respiratory symptoms were relieved, and a CT re-examination three and six months after the operation showed that the lungs were in good condition, with no signs of recurrence (Figure 6).

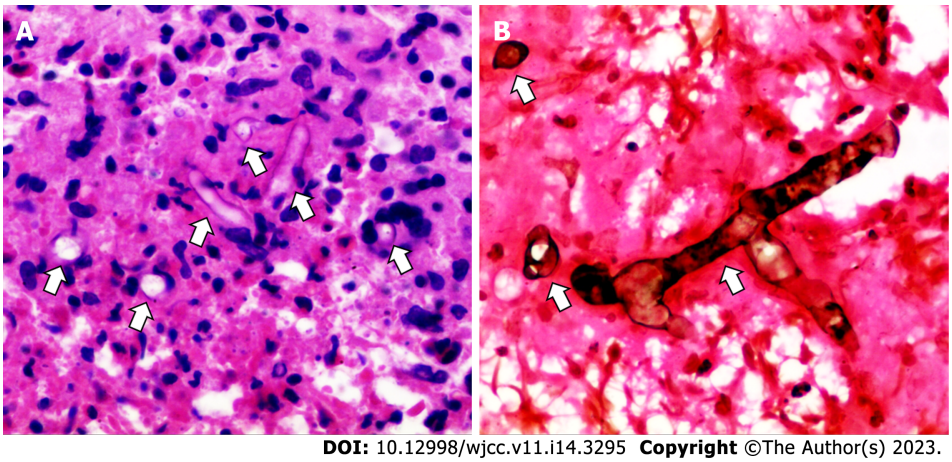
DISCUSSION

Pulmonary mucormycosis represents a group of invasive fungal infections in the lungs caused by members of the order Mucorales, and it has a high mortality rate[1,5]. The causative fungal agent is commonly found on decaying food, soil, and animal excrement. During its asexual reproduction, its hyphae develop sporangium and release spores. Patients often become infected by inhaling these spores into the bronchioles and alveoli[1,11]. Pulmonary mucormycosis is a relatively uncommon opportunistic infection that primarily occurs in immunocompromised populations, with risk factors including diabetes mellitus, hematologic malignancy, neutropenia, or transplantation[12,13]. Very rarely, pulmonary mucormycosis also occurs in immunocompetent individuals and should not be entirely ignored[5,11,14,15]. In our report, we present a case of a 43-year-old Chinese man who developed pulmonary mucormycosis without dysglycemia or any known immunodeficiency. We learned from the consultation that the patient did not wear a mask at work to reduce dust inhalation. Therefore, as a house improvement worker, he may have inhaled mucormycosis spores during his occupational work, which may have induced this pulmonary mucormycosis infection.



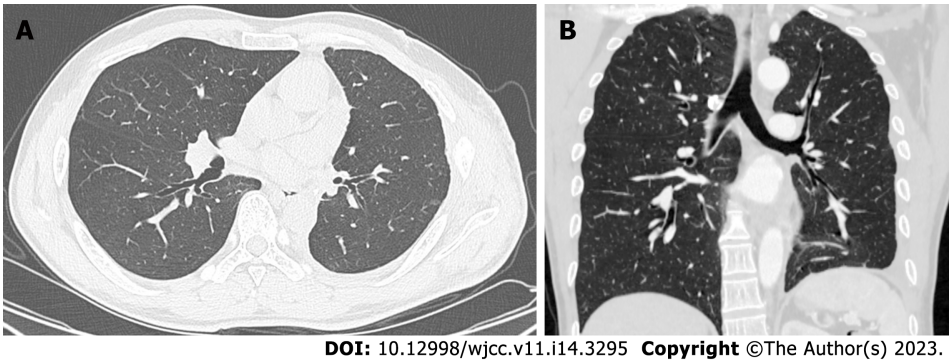
DOI: 10.12998/wjcc.v11.i14.3295

Figure 4 Macroscopic and microscopic features of the left lower lobe mass. A: The mass was firm, approximately 6 cm in diameter, and pale in color when sectioned; and B: Hematoxylin and eosin stained section revealed that the left lower lobe mass was an inflammatory granuloma. Interstitial fibrous tissue hyperplasia, inflammatory cell infiltration, and multinucleated giant cell reaction were all observed under the microscope.



DOI: 10.12998/wjcc.v11.i14.3295

Figure 5 Postoperative histopathological results of the left lower lobe mass. A: Hematoxylin and eosin staining (400 ×); and B: Hexamine silver staining (400 ×), showed broad, right-angled branched aseptate hyphae indicating mucormycosis (marked with white arrows).



DOI: 10.12998/wjcc.v11.i14.3295

Figure 6 High-resolution chest contrast-enhanced computed tomography. A: Transverse plane; and B: Coronal plane. A re-examination of computed tomography three months after the operation showed that the lungs were in good condition, and no recurrence was found.

The clinical and imaging manifestations of pulmonary mucormycosis are not specific[16]. Most patients present with an acute respiratory infection and have typical symptoms such as fever, cough, chest pain, dyspnea, and hemoptysis. Additionally, a few patients suffer a longer course of the disease and manifest as chronic lung lesions, which need to be differentiated from lung carcinoma[17]. In our case, the patient had a persistent left lower lung mass and mild clinical symptoms characterized by an irritating cough for at least two months. These chronic symptoms led us to consider lung cancer

initially, but it was eventually ruled out by thoracoscopic excisional biopsy.

The definitive diagnosis of pulmonary mucormycosis relies on the histopathological finding of mucoraceous hyphae in affected tissues. Its pathological characteristics include broad, aseptate, and ribbon-like hyaline hyphae with wide-angle branching[18]. Although specimen fungal culture allows for species identification, it is time-consuming and has a low positive rate[5,19]. In recent years, polymerase chain reaction and mNGS, especially the latter, have become relatively precise and convenient methods for finding pathogens[3,20,21]. In our case, we first identified the only suspected pathogenic microorganism, Rhizopus microsporus, by mNGS detection of sterile surgical specimens, although its sequence number was only two. Then, the pathologist identified mucoraceous hyphae by special stains. Interestingly, corresponding to the low sequence number of mNGS results, the hyphae in the specimen were sparse, which may also be associated with chronic infection and a good prognosis.

Due to the high mortality rate associated with pulmonary mucormycosis, early identification and treatment of the disease are critical for an improved likelihood of survival. Surgical resection is the cornerstone treatment for pulmonary mucormycosis[22], and it should be strongly considered when feasible[23]. In addition, timely antifungal therapy with amphotericin B or posaconazole has also been shown to improve outcomes[1,24]. Despite our repeated insistence on the necessity of antifungal therapy, the patient refused any further antifungal treatment postoperatively. The patient cited mild preoperative infection symptoms, satisfactory postoperative recovery, concerns about potential drug side effects, and high follow-up treatment costs as reasons for declining the treatment. Nevertheless, follow-up CT scans of the patient's chest at three and six months after surgery showed satisfactory results without any signs of recurrence.

CONCLUSION

This article reports a rare case of chronic pulmonary mucormycosis caused by Rhizopus microsporus in a middle-aged male without dysglycemia or immunodeficiency. The patient presented with an irritating cough and a solitary left lower lobe mass that lasted for two months, similar to that of lung carcinoma. We performed a lobectomy, and the surgical specimen was subjected to mNGS detection and special pathological staining, which suggested rhizopus microsporus infection. The surgical outcome for the patient was excellent, reaffirming that surgery remains the cornerstone of treatment for pulmonary mucormycosis.

ACKNOWLEDGEMENTS

We would like to thank the patient for his participation and cooperation in this case report.

FOOTNOTES

Author contributions: Guo XZ, Gong LH, Wang WX, Yang DS, Zhang BH, and Zhou ZT contributed to manuscript writing and editing; Yu XH contributed to conceptualization and supervision; and all authors have read and approved the final manuscript.

Supported by Hunan Provincial Natural Science Foundation of China, No. 2022JJ40247 and No. 2022JJ40256.

Informed consent statement: We obtained informed written consent from the patient to publish this case report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Xing-Zi Guo 0000-0002-7585-9595; Liang-Hui Gong 0000-0002-7272-1160; Wen-Xiang Wang 0000-0003-3209-5211; De-Song Yang 0000-0003-4108-8312; Bai-Hua Zhang 0000-0002-7941-9052; Ze-Tao Zhou 0009-0003-9157-9993;

Xiao-Hui Yu 0000-0001-6046-7188.

S-Editor: Liu XF
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Agrawal R**, Yeldandi A, Savas H, Parekh ND, Lombardi PJ, Hart EM. Pulmonary Mucormycosis: Risk Factors, Radiologic Findings, and Pathologic Correlation. *Radiographics* 2020; **40**: 656-666 [PMID: 32196429 DOI: 10.1148/rg.2020190156]
2 **Jeong W**, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SC. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clin Microbiol Infect* 2019; **25**: 26-34 [PMID: 30036666 DOI: 10.1016/j.cmi.2018.07.011]
3 **Chen L**, Su Y, Xiong XZ. Rhizopus microsporus lung infection in an immunocompetent patient successfully treated with amphotericin B: A case report. *World J Clin Cases* 2021; **9**: 11108-11114 [PMID: 35047625 DOI: 10.12998/wjcc.v9.i35.11108]
4 **Muthu V**, Agarwal R, Dhooria S, Sehgal IS, Prasad KT, Aggarwal AN, Chakrabarti A. Has the mortality from pulmonary mucormycosis changed over time? *Clin Microbiol Infect* 2021; **27**: 538-549 [PMID: 33418022 DOI: 10.1016/j.cmi.2020.12.035]
5 **Lee FY**, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. *Arch Intern Med* 1999; **159**: 1301-1309 [PMID: 10386506 DOI: 10.1001/archinte.159.12.1301]
6 **Tojima H**, Tokudome T, Otsuka T. [Chronic pulmonary mucormycosis that developed in preexisting cavities caused by tuberculosis in a patient with diabetes mellitus and liver cirrhosis]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1997; **35**: 100-105 [PMID: 9071165]
7 **Soltani A**, Torabizadeh Z, Akha O, Godazandeh G, Mohammad G. A case of chronic pulmonary mucormycosis with indolent course complicating diabetic ketoacidosis. *Respiratory Medicine Extra* 2006; **2**: 105-107 [DOI: 10.1016/j.rmedx.2006.08.001]
8 **Matsumura Y**, Shibuya J, Kobayashi S, Handa M, Kondo T, Fujimura S. [Chronic pulmonary mucormycosis diagnosed by bronchoscopy: a case report]. *Kyobu Geka* 1993; **46**: 891-894 [PMID: 8377321]
9 **Iqbal N**, Irfan M, Jabeen K, Kazmi MM, Tariq MU. Chronic pulmonary mucormycosis: an emerging fungal infection in diabetes mellitus. *J Thorac Dis* 2017; **9**: E121-E125 [PMID: 28275494 DOI: 10.21037/jtd.2017.02.31]
10 **Agarwal R**, Kumar V, Gupta D. Pulmonary mucormycosis: two of a kind. *Eur J Intern Med* 2006; **17**: 63-65 [PMID: 16378892 DOI: 10.1016/j.ejim.2005.08.009]
11 **Yang J**, Zhang J, Feng Y, Peng F, Fu F. A case of pulmonary mucormycosis presented as Pancoast syndrome and bone destruction in an immunocompetent adult mimicking lung carcinoma. *J Mycol Med* 2019; **29**: 80-83 [PMID: 30553628 DOI: 10.1016/j.mycmed.2018.10.005]
12 **Roden MM**, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; **41**: 634-653 [PMID: 16080086 DOI: 10.1086/432579]
13 **Petrikkos G**, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis* 2012; **54** Suppl 1: S23-S34 [PMID: 22247442 DOI: 10.1093/cid/cir866]
14 **Ng KL**, Huan NC, Nasaruddin MZ, Muhammad NA, Daut UN, Abdul Rahaman JA. Pulmonary mucormycosis masquerading as endobronchial tumour in an immunocompetent pregnant young lady. *Respirol Case Rep* 2021; **9**: e00704 [PMID: 33364028 DOI: 10.1002/rcr2.704]
15 **He J**, Sheng G, Yue H, Zhang F, Zhang HL. Isolated pulmonary mucormycosis in an immunocompetent patient: a case report and systematic review of the literature. *BMC Pulm Med* 2021; **21**: 138 [PMID: 33906622 DOI: 10.1186/s12890-021-01504-8]
16 **Tsyrkunou AV**, Ellison RT 3rd, Akalin A, Wiederhold N, Sutton DA, Lindner J, Fan H, Levitz SM, Zivna I. Multifocal Rhizopus microsporus lung infection following brush clearing. *Med Mycol Case Rep* 2014; **6**: 14-17 [PMID: 25379391 DOI: 10.1016/j.mmcr.2014.08.001]
17 **Peng M**, Meng H, Sun Y, Xiao Y, Zhang H, Lv K, Cai B. Clinical features of pulmonary mucormycosis in patients with different immune status. *J Thorac Dis* 2019; **11**: 5042-5052 [PMID: 32030220 DOI: 10.21037/jtd.2019.12.53]
18 **Kantarcioğlu AS**, Yücel A, Nagao K, Sato T, Inci E, Ogreden S, Kaytaz A, Alan S, Bozdağ Z, Edali N, Sar M, Kepil N, Oz B, Altas K. A Rhizopus oryzae strain isolated from resected bone and soft tissue specimens from a sinonasal and palatal mucormycosis case. Report of a case and *in vitro* experiments of yeastlike cell development. *Med Mycol* 2006; **44**: 515-521 [PMID: 16966168 DOI: 10.1080/13693780600764973]
19 **Leung CCD**, Chan YH, Ho MY, Chan MC, Chen CH, Kwok CT, Yeung YC. First reported case of late recurrence of pulmonary mucormycosis in a renal transplant recipient with poorly controlled diabetes mellitus. *Respirol Case Rep* 2021; **9**: e0877 [PMID: 34795903 DOI: 10.1002/rcr2.877]
20 **Sun Y**, Li H, Chen J, Ma Z, Han P, Liu Y, Wen J, Ren F, Ma X. Case Report: Metagenomics Next-Generation Sequencing Can Be Performed for the Diagnosis of Disseminated Mucormycosis. *Front Med (Lausanne)* 2021; **8**: 675030 [PMID: 34746163 DOI: 10.3389/fmed.2021.675030]
21 **Gu Z**, Buelow DR, Petraitiene R, Petraitis V, Walsh TJ, Hayden RT. Quantitative multiplexed detection of common pulmonary fungal pathogens by labeled primer polymerase chain reaction. *Arch Pathol Lab Med* 2014; **138**: 1474-1480 [PMID: 25357108 DOI: 10.5858/arpa.2013-0592-OA]

22 **Choi H**, Lee H, Jeon K, Suh GY, Shin S, Kim HK, Kim K, Jeong D, Kim H. Factors affecting surgical resection and treatment outcomes in patients with pulmonary mucormycosis. *J Thorac Dis* 2019; **11**: 892-900 [PMID: 31019778 DOI: 10.21037/jtd.2019.01.75]

23 **Multani A**, Reveron-Thornton R, Garvert DW, Gomez CA, Montoya JG, Lui NS. Cut it out! *Mycoses* 2019; **62**: 893-907 [PMID: 31173415 DOI: 10.1111/myc.12954]

24 **Yuan F**, Chen J, Liu F, Dang YC, Kong QT, Sang H. Successful treatment of pulmonary mucormycosis caused by Rhizopus microsporus with posaconazole. *Eur J Med Res* 2021; **26**: 131 [PMID: 34775981 DOI: 10.1186/s40001-021-00602-x]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3304-3310

DOI: 10.12998/wjcc.v11.i14.3304

ISSN 2307-8960 (online)

CASE REPORT

Idiopathic sclerosing mesenteritis presenting with small bowel volvulus in a patient with antiphospholipid syndrome: A case report

Papawee Chennavasin, Montri Gururatsakul

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Gu GL, China; Zharikov YO, Russia

Received: January 16, 2023
Peer-review started: January 16, 2023
First decision: March 13, 2023
Revised: March 16, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: May 16, 2023

Papawee Chennavasin, Department of Surgery, Chulabhorn Hospital, Princess Srisavangavadhana College of Medicine, Chulabhorn Royal Academy, Bangkok 10210, Thailand

Montri Gururatsakul, Department of Gastroenterology and Hepatology, Chulabhorn Hospital, Princess Srisavangavadhana College of Medicine, Chulabhorn Royal Academy, Bangkok 10210, Thailand

Corresponding author: Papawee Chennavasin, MD, Surgeon, Department of Surgery, Chulabhorn Hospital, Princess Srisavangavadhana College of Medicine, Chulabhorn Royal Academy, 906 Kamphaeng Phet 6 Road Talat Bang Khen, Lak Si, Bangkok 10210, Thailand. papawee.che@cra.ac.th

Abstract

BACKGROUND

Sclerosing mesenteritis is a rare disorder involving inflammation of the mesentery. Its etiology remains unclear, but it is believed to be associated with previous abdominal surgery, trauma, autoimmune disorders, infection, or malignancy. Clinical manifestations of sclerosing mesenteritis are varied and include chronic abdominal pain, bloating, diarrhea, weight loss, formation of an intra-abdominal mass, bowel obstruction, and chylous ascites. Here, we present a case of idiopathic sclerosing mesenteritis with small bowel volvulus in a patient with antiphospholipid syndrome.

CASE SUMMARY

A 68-year-old female presented with recurrent small bowel obstruction. Imaging and pathological findings were consistent with sclerosing mesenteritis causing mesenteric and small bowel volvulus. Computed tomography scans also revealed pulmonary embolism, and the patient was started on a high dose of corticosteroid and a therapeutic dose of anticoagulants. The patient subsequently improved clinically and was discharged. The patient was also diagnosed with antiphospholipid syndrome after a hematological workup.

CONCLUSION

Sclerosing mesenteritis is a rare condition, and patients with no clear etiology should be considered for treatment with immunosuppressive therapy.

Key Words: Sclerosing mesenteritis; Mesenteric panniculitis; Small bowel obstruction; Antiphospholipid syndrome; Small bowel volvulus; Case report

Core Tip: In patients with sclerosing mesenteritis, any condition that causes chronic inflammation of mesenteric tissue should be investigated. Antiphospholipid syndrome may be linked with chronic thrombotic activity that can contribute to chronic ischemia of the mesentery. Patients with uncertain etiology should be considered for treatment with immunosuppressive therapy.

Citation: Chennavasin P, Gururatsakul M. Idiopathic sclerosing mesenteritis presenting with small bowel volvulus in a patient with antiphospholipid syndrome: A case report. *World J Clin Cases* 2023; 11(14): 3304-3310
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3304.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3304

INTRODUCTION

Sclerosing mesenteritis is a condition of mesenteric inflammation that causes thickening and fibrosis in the bowel mesentery. The disease is frequently limited to the adipose tissue of the small bowel mesentery and is unlikely to involve the omentum, peritoneum, or mesocolon[1]. Sclerosing mesenteritis was first reported in 1924 as "retractile mesenteritis and/or mesenteric panniculitis"[2]. The incidence of this condition is 0.16%–3.30%[3]. The etiology is still unclear; however, it may be associated with various conditions that cause chronic inflammation, such as previous abdominal surgery, trauma, mesenteric ischemia, cancer, infection, and autoimmune conditions. Sclerosing mesenteritis is more common in Caucasians, with a male-to-female ratio of 2-3:1[3,4]. The characteristics of sclerosing mesenteritis may differ in Asian populations since a previous study showed that 58% of Japanese patients also had mesocolon involvement[5].

Clinical manifestations of sclerosing mesenteritis can vary from asymptomatic to severe abdominal pain. It can cause small bowel obstruction, significant weight loss, and chylothorax in severe cases[6,7]. Computed tomography (CT) scans are the investigation of choice, and clinical diagnosis is made using the Coulier criteria, which are: (1) Presence of a well-defined "mass effect" on neighboring structures; (2) Inhomogeneous higher attenuation of mesenteric fat tissue than adjacent retroperitoneal or mesocolonic fat; (3) Small soft tissue nodes; (4) A hypoattenuated fatty "halo sign"; and (5) The presence of a hyperattenuating pseudocapsule, which may also surround the entire entity[8]. Tissue biopsy is recommended to exclude malignancy and confirm the diagnosis of mesenteric fibrosis, chronic inflammation, and fat necrosis[9].

We present the case of a 68-year-old female with recurrent small bowel volvulus caused by sclerosing mesenteritis who responded well to treatment with a corticosteroid. When further investigations were performed to find the cause of the sclerosing mesenteritis, the patient was also found to have antiphospholipid syndrome (APS).

CASE PRESENTATION

Chief complaints

A 68-year-old female presented at the hospital with acute abdominal pain and vomiting that had persisted for 1 d.

History of present illness

The patient developed colicky pain with bilious vomiting 1 d prior to visiting the emergency department. Her abdomen was distended, but there was no fever.

History of past illness

The patient's medical history showed only hypertension, and there was no previous abdominal surgery or abdominal trauma.

Personal and family history

There was no significant personal or family history.

Physical examination

Physical examination revealed generalized abdominal tenderness; however, there was no evidence of peritonitis.

Laboratory examinations

Laboratory examination showed that the patient's white blood cell count was 5930 cells/μL, and creatinine levels had risen from 0.83 mg/dL to 1.76 mg/dL.

Imaging examinations

Abdominal X-rays showed generalized small bowel dilatation with air-fluid levels consistent with small bowel obstruction. Therefore, a CT scan of the abdomen was requested. The initial CT scan showed a thickened mesentery around the terminal ileum. At the terminal ileum, there was an abrupt change in caliber caused by rotation with upstream dilatation of the distal jejunum and ileum, consistent with high-grade small bowel obstruction. Misty mesentery and enlargement of mesenteric nodes in the right lower quadrant adjacent to the distal ileum were also observed, possibly secondary to an infection or an inflammatory process (Figure 1).

FINAL DIAGNOSIS

The patient was given the diagnosis of sclerosing mesenteritis with small bowel obstruction.

TREATMENT

An exploratory laparotomy was performed, which revealed diffuse thickening of the small bowel mesentery causing mesenteric distortion and small bowel volvulus at the level of the terminal ileum with upstream dilatation of the entire small bowel that was associated with significant mesenteric lymphadenopathy. The entire small bowel was viable after small bowel devolvulation was performed. Lymph nodes were also excised for histopathological examination, which subsequently revealed reactive lymph nodes with fat necrosis (Figure 2).

After the operation, the patient's bowel movements returned to normal. The patient was able to pass stools and tolerated a soft food diet. Further investigations were indicated to exclude occult malignancy, tuberculosis, and other underlying autoimmune conditions. However, while waiting for the results from these investigations, acute abdominal pain with abdominal distension returned on postoperative day 5. Subsequent abdominal X-ray and CT scans showed recurrent small bowel volvulus with the same misty mesentery. A second laparotomy confirmed recurrent small bowel volvulus due to inflammation, and retraction of the small bowel mesentery was observed.

Serology tests showed a positive result for antinuclear antibodies (1:160), which were homogenous with a fine granular cytoplasmic staining pattern, a normal range of IgG4 (0.285 g/L), and negative results for other autoimmune serology and tumor markers (carbohydrate antigen 19-9, alpha fetoprotein, carcinoembryonic antigen, and cancer antigen 125). Tuberculosis was not found in either tissue histopathology or in the stool. A CT scan of the chest was also performed to exclude tuberculosis or occult malignancy, both of which were negative. However, an incidental small pulmonary embolism was detected. There was no evidence of deep vein thrombosis on Doppler ultrasound of either leg. As a result, further investigation for APS was performed, and tests for anti-beta2-glycoprotein-1 (for all 3 immunoglobulin isotypes: IgA, IgG, and IgM) were found to be positive. Upon a repeat test 3 mo later, the result was still positive (Table 1).

After the second operation, the patient was diagnosed with idiopathic sclerosing mesenteritis, and treatment with high-dose corticosteroids and a therapeutic dose of low molecular weight heparin was commenced. The patient responded well to corticosteroids and did not develop further small bowel obstruction or volvulus. In addition, bowel function was normal, a normal diet was tolerated, and the patient was discharged after 2 wk with a weaning dose of oral corticosteroid over an 8-wk period.

OUTCOME AND FOLLOW-UP

At a follow-up appointment 2 mo after discharge, an upper endoscopy and a colonoscopy were performed; the results of which were unremarkable. A repeat anti-beta2-glycoprotein1 (IgA, IgG, and IgM) test at 3 mo was positive, and the patient was diagnosed with APS. As a result, the patient must continue lifelong anticoagulant therapy.

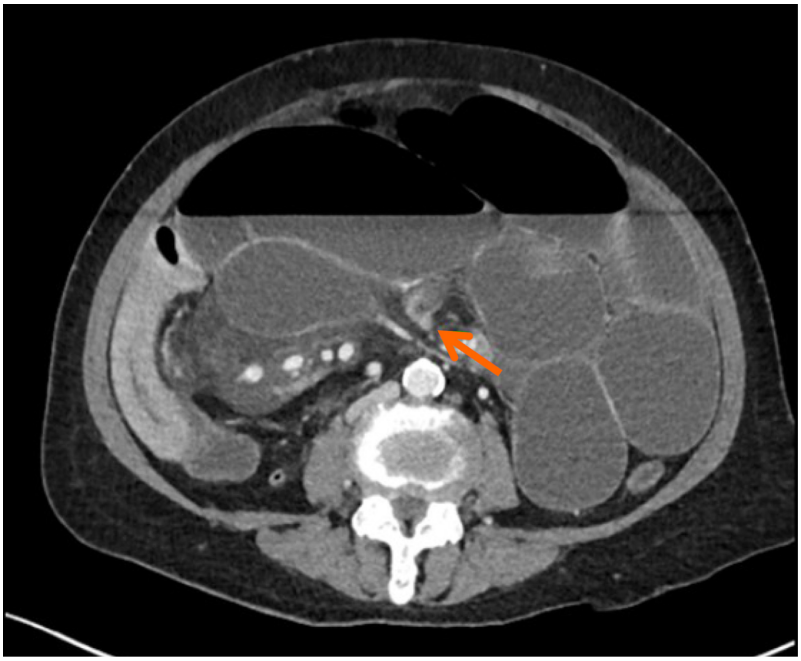
DISCUSSION

Sclerosing mesenteritis refers to chronic inflammation of the mesentery. This condition is rare and is more common in Caucasian males[4]. In the present case report, the patient was an Asian female

Table 1 Blood test results

Blood test	Results
Anti-Beta 2-Glycoprotein-1 IgA/IgG/IgM	38.29 RU/mL
Anti-Beta 2-Glycoprotein-1 IgA/IgG/IgM (3 mo later)	35.69 RU/mL
Anticardiolipin IgG	7.130 U/mL
Anticardiolipin IgM	< 2 U/mL
ANA	1:160
ANA 12 specific antigen profile	Negative
Serum IgG4	0.285 g/L
Tissue IgG4	Negative
Lupus anticoagulant	Negative
C3 compliment	0.79 g/L
C4 compliment	0.14 g/L
Tissue PCR for mycobacterium tuberculosis	Not detected
Stool PCR for mycobacterium tuberculosis	Not detected
CEA	0.9 ng/mL
Alpha fetoprotein	15 ng/mL
CA 125	30 U/mL
CA 19-9	< 2 U/mL

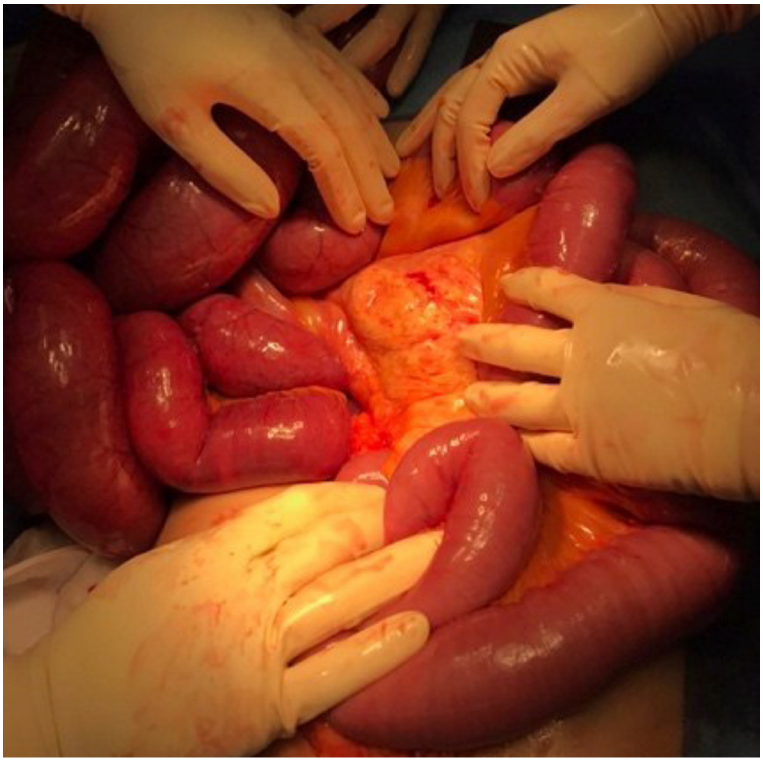
ANA: Antinuclear antibodies; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 125: Cancer antigen 125.



DOI: 10.12998/wjcc.v11.i14.3304

Figure 1 Computed tomography scan showed a dilated small bowel and misty mesentery (orange arrow), consistent with small bowel obstruction.

without any significant underlying disease and no previous abdominal surgery. Sclerosing mesenteritis was considered to be the rare cause of small bowel obstruction. The CT scan revealed inhomogeneous higher attenuation of mesenteric fat tissue and small soft tissue nodes in the mesentery surrounded by hypoattenuated mesenteric fat, which is consistent with the Coulier criteria[8] for sclerosing



DOI: 10.12998/wjcc.v11.i14.3304

Figure 2 Operative findings revealed diffused mesenteric thickening with enlarged mesenteric lymph nodes and viable small bowel after detorsion.

mesenteritis. Pathological features also confirmed chronic inflammation of mesenteric fat without evidence of malignancy.

Several studies have reported patients with sclerosing mesenteritis who have small bowel obstruction, and the majority of these cases required surgical intervention to correct the obstruction followed by treatment with an immunosuppressive medication[10-12]. Surgery may be performed to correct gut obstruction, but it is not a curative treatment[13]. Our patient was diagnosed with idiopathic sclerosing mesenteritis. After the first operation was performed, we did not administer any immunosuppressive medication immediately because we were waiting for all the results to exclude other primary causes, including infection and cancer. Subsequently, the patient developed recurrent small bowel volvulus and required a second exploratory operation. The patient responded well to treatment with corticosteroids.

The etiology of sclerosing mesenteritis is unclear; however, it is generally associated with chronic inflammation of mesenteric tissue. This may be caused by previous abdominal surgery, trauma, mesenteric ischemia, cancer, infection, or autoimmune disease[13]. In this case, the patient was also subsequently diagnosed with APS after an incidental finding of pulmonary embolism during the diagnostic workup. Only a few case reports have shown chronic thrombosis-associated chronic mesenteric ischemia. One case report detailed sclerosing mesenteritis with sacroiliitis[14], and another reported sclerosing mesenteritis with Factor V Leiden[15]. Both cases raise the possibility of a link between mesenteric ischemia and chronic thrombotic activity.

Thrombosis can affect vessels of any size in APS patients; however, a gastrointestinal manifestation in APS is uncommon[16]. To date, there has been no reports of a potential association between APS and sclerosing mesenteritis; however, it is thought that chronic venous thrombosis may cause mesenteric ischemia in APS patients[17]. In the case of our patient, it is possible that the small veins in the small bowel mesentery were affected by chronic venous thrombosis causing chronic inflammation that led to sclerosing mesenteritis. Therefore, it is necessary to investigate hypercoagulable states in patients with sclerosing mesenteritis.

CONCLUSION

Sclerosing mesenteritis is a chronic inflammation of the mesentery that is commonly caused by other medical conditions, including infection, autoimmune conditions, and malignancy. Symptomatic patients with unclear etiology should be considered for treatment with immunosuppressive medications. In

addition, while rare, chronic thrombotic conditions can also cause sclerosing mesenteritis, and they should also be considered.

ACKNOWLEDGEMENTS

We thank Edanz (www.edanz.com/ac) for editing a draft of this manuscript.

FOOTNOTES

Author contributions: Chennavasin P designed the research study and wrote the manuscript; Gururatsakul M revised the manuscript and performed language editing; and all authors read and approved the final manuscript.

Informed consent statement: Inform consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Thailand

ORCID number: Papawee Chennavasin 0000-0002-0466-1610.

S-Editor: Liu XF
L-Editor: Filipodia
P-Editor: Zhang YL

REFERENCES

1 **Buragina G**, Magenta Biasina A, Carrafiello G. Clinical and radiological features of mesenteric panniculitis: a critical overview. *Acta Biomed* 2019; **90**: 411-422 [PMID: 31910164 DOI: 10.23750/abm.v90i4.7696]
2 **Green MS**, Chhabra R, Goyal H. Sclerosing mesenteritis: a comprehensive clinical review. *Ann Transl Med* 2018; **6**: 336 [PMID: 30306075 DOI: 10.21037/atm.2018.07.01]
3 **Protin-Catteau L**, Thiéfin G, Barbe C, Jolly D, Soyer P, Hoeffel C. Mesenteric panniculitis: review of consecutive abdominal MDCT examinations with a matched-pair analysis. *Acta Radiol* 2016; **57**: 1438-1444 [PMID: 26868171 DOI: 10.1177/0284185116629829]
4 **Sharma P**, Yadav S, Needham CM, Feuerstadt P. Sclerosing mesenteritis: a systematic review of 192 cases. *Clin J Gastroenterol* 2017; **10**: 103-111 [PMID: 28197781 DOI: 10.1007/s12328-017-0716-5]
5 **Endo K**, Moroi R, Sugimura M, Fujishima F, Naitoh T, Tanaka N, Shiga H, Kakuta Y, Takahashi S, Kinouchi Y, Shimosegawa T. Refractory sclerosing mesenteritis involving the small intestinal mesentery: a case report and literature review. *Intern Med* 2014; **53**: 1419-1427 [PMID: 24990334 DOI: 10.2169/internalmedicine.53.1813]
6 **Akram S**, Pardi DS, Schaffner JA, Smyrk TC. Sclerosing mesenteritis: clinical features, treatment, and outcome in ninety-two patients. *Clin Gastroenterol Hepatol* 2007; **5**: 589-96; quiz 523 [PMID: 17478346 DOI: 10.1016/j.cgh.2007.02.032]
7 **Nyberg L**, Björk J, Björkdahl P, Ekberg O, Sjöberg K, Vigren L. Sclerosing mesenteritis and mesenteric panniculitis - clinical experience and radiological features. *BMC Gastroenterol* 2017; **17**: 75 [PMID: 28610559 DOI: 10.1186/s12876-017-0632-7]
8 **Coulier B**. Mesenteric panniculitis. Part 1: MDCT--pictorial review. *JBR-BTR* 2011; **94**: 229-240 [PMID: 22191287 DOI: 10.5334/jbr-btr.658]
9 **Emory TS**, Monihan JM, Carr NJ, Sobin LH. Sclerosing mesenteritis, mesenteric panniculitis and mesenteric lipodystrophy: a single entity? *Am J Surg Pathol* 1997; **21**: 392-398 [PMID: 9130985 DOI: 10.1097/00000478-199704000-00004]
10 **Allen PB**, De Cruz P, Efthymiou M, Fox A, Taylor AC, Desmond PV. An Interesting Case of Recurrent Small Bowel Obstruction. *Case Rep Gastroenterol* 2009; **3**: 408-413 [PMID: 21103263 DOI: 10.1159/000254708]
11 **Corado SC**, Almeida H, Baltazar JR. A severe case of sclerosing mesenteritis. *BMJ Case Rep* 2019; **12** [PMID: 31289157 DOI: 10.1136/bcr-2018-229035]
12 **Haikal A**, Thimmanagari K. Colon Perforation As Initial Presentation of Refractory and Complicated Sclerosing

Mesenteritis. *Cureus* 2021; **13**: e17142 [PMID: 34532177 DOI: 10.7759/cureus.17142]

13 **Danford CJ**, Lin SC, Wolf JL. Sclerosing Mesenteritis. *Am J Gastroenterol* 2019; **114**: 867-873 [PMID: 30829677 DOI: 10.14309/ajg.0000000000000167]

14 **Rothlein LR**, Shaheen AW, Vavalle JP, Smith SV, Renner JB, Shaheen NJ, Tarrant TK. Sclerosing mesenteritis successfully treated with a TNF antagonist. *BMJ Case Rep* 2010; **2010** [PMID: 22802373 DOI: 10.1136/bcr.07.2010.3145]

15 **Reddington H**, Ballinger Z, Abghari M, Modukuru V, Wallack M. Sclerosing Mesenteritis in a Patient Heterozygous for Factor V Leiden. *Am J Case Rep* 2020; **21**: e926332 [PMID: 33017382 DOI: 10.12659/AJCR.926332]

16 **Cervera R**, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, Buonaiuto V, Jacobsen S, Zeher MM, Tarr T, Tincani A, Taglietti M, Theodossiades G, Nomikou E, Galeazzi M, Bellisai F, Meroni PL, Derksen RH, de Groot PG, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, Quéré I, Hachulla E, Vasconcelos C, Fernández-Nebro A, Haro M, Amoura Z, Miyara M, Tektonidou M, Espinosa G, Bertolaccini ML, Khamashta MA; Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies). Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015; **74**: 1011-1018 [PMID: 24464962 DOI: 10.1136/annrheumdis-2013-204838]

17 **Zou X**, Fan Z, Zhao L, Xu W, Zhang J, Jiang Z. Gastrointestinal symptoms as the first manifestation of antiphospholipid syndrome. *BMC Gastroenterol* 2021; **21**: 148 [PMID: 33794795 DOI: 10.1186/s12876-021-01736-2]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3311-3316

DOI: 10.12998/wjcc.v11.i14.3311

ISSN 2307-8960 (online)

CASE REPORT

Neisseria mucosa - A rare cause of peritoneal dialysis-related peritonitis: A case report

Jian-Min Ren, Xiao-Yao Zhang, Si-Yu Liu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ferreira GSA, Brazil; Suwanto D, Indonesia

Received: February 2, 2023
Peer-review started: February 2, 2023
First decision: February 17, 2023
Revised: February 23, 2023
Accepted: March 30, 2023
Article in press: March 30, 2023
Published online: May 16, 2023

Jian-Min Ren, Si-Yu Liu, Department of Clinical Laboratory, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui 323000, Zhejiang Province, China

Xiao-Yao Zhang, Department of Rehabilitation, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui 323000, Zhejiang Province, China

Si-Yu Liu, The Key Laboratory of Imaging Diagnosis and Minimally Invasive Interventional Research of Zhejiang Province, Zhejiang University Lishui Hospital, Lishui 323000, Zhejiang Province, China

Corresponding author: Si-Yu Liu, MD, Deputy Director, Department of Clinical Laboratory, The Fifth Affiliated Hospital of Wenzhou Medical University, No. 289 Kuocang Road, Liandu District, Lishui 323000, Zhejiang Province, China. 77744832@qq.com

Abstract

BACKGROUND

Neisseria mucosa is a gram negative diplococcus belonging to the genus Neisseria found commonly in the upper respiratory tract. It is typically a commensal organism when it is parasitic on oral and nasal mucosa. To our knowledge, it does not cause disease in healthy individuals with normal immunity, but can be pathogenic in those with impaired immune function or change in bacterial colonization site. *Neisseria mucosa* has been reported to cause bacterial meningitis, conjunctivitis, pneumonia, endocarditis, peritonitis and urethritis. However, peritoneal dialysis-related peritonitis caused by *Neisseria mucosa* is extremely rare in clinical practice, which has not previously been reported in China.

CASE SUMMARY

A 55-year-old female presented to the nephrology clinic with upper abdominal pain without apparent cause, accompanied by nausea, vomiting and diarrhea for two days. The patient had a history of Stage 5 chronic kidney disease for five years, combined with renal hypertension and renal anemia, and was treated with peritoneal dialysis for renal replacement therapy. The patient was subsequently diagnosed with peritoneal dialysis-related peritonitis. Routine examination of peritoneal dialysis fluid showed abdominal infection, and the results of microbial culture of the peritoneal dialysis fluid confirmed *Neisseria mucosa*. Imi-penem/cilastatin 1.0 g q12h was added to peritoneal dialysis fluid for anti-infection treatment. After 24 d, the patient underwent upper extremity arteriovenous fistulation. One month later, the patient was discharged home in a clinically stable state.

CONCLUSION
Peritonitis caused by *Neisseria mucosa* is rare. Patients with home-based self-dialysis cannot guarantee good medical and health conditions, and require education on self-protection.

Key Words: Peritoneal dialysis; Peritonitis; Neisseria mucosa; Case report

Core Tip: *Neisseria mucosa* is part of the normal human flora when it is parasitic in the oral and nasal mucosa, and rarely causes infection. However, it may be associated with severe disease when patients undergo invasive, instrumented procedures or have underlying conditions, as shown in the present patient who was undergoing continuous ambulatory peritoneal dialysis. In addition, the infection was also closely related to the patient's health behavior and habits during peritoneal dialysis. Treatment should be based on antimicrobial susceptibility testing and a sufficient and full course of antimicrobial therapy should be given.

Citation: Ren JM, Zhang XY, Liu SY. *Neisseria mucosa* - A rare cause of peritoneal dialysis-related peritonitis: A case report. *World J Clin Cases* 2023; 11(14): 3311-3316
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3311.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3311

INTRODUCTION

The Gram-negative diplococci Neisseria are commensal bacteria of mucosal surfaces in humans[1]. Two major subspecies, *Neisseria meningitidis* and *Neisseria gonorrhoeae*, are pathogenic in humans, while most other subspecies such as *Neisseria mucosa* are recognized as non-pathogenic. *Neisseria mucosa* is generally not pathogenic in healthy individuals with normal immunity, but can be pathogenic in those with impaired immune function or changes in bacterial colonization sites.

It has been reported that *Neisseria mucosa* is associated with meningitis, endocarditis, pneumonia, bacteremia, arthritis, peritonitis, endophthalmitis and urethritis[2-7]. We herein report the first case of refractory peritoneal dialysis-related peritonitis caused by *Neisseria mucosa* in mainland China.

CASE PRESENTATION

Chief complaints

A 55-year-old Chinese female presented to the nephrology clinic with the complaint of abdominal pain for 2 d.

History of present illness

Symptoms started 2 d before presentation with no obvious cause of upper abdominal pain (the Visual analogue scale was 2), with nausea, vomiting of gastric contents, and diarrhea, with no chills, fever, chest tightness, shortness of breath, edema, hematemesis, or melena.

History of past illness

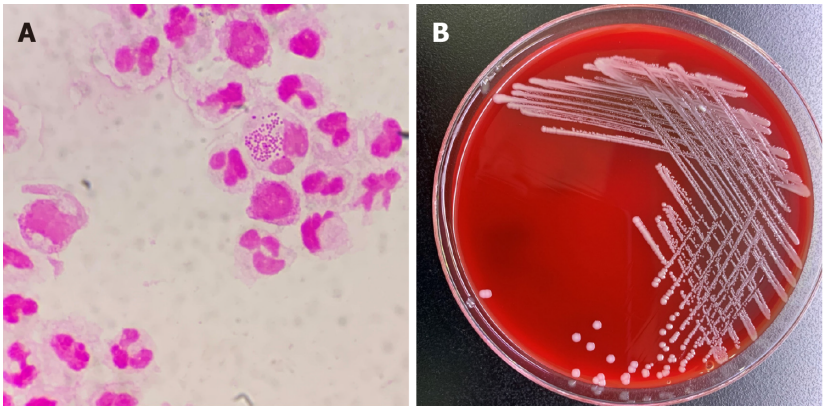
The patient was diagnosed with Stage 5 chronic kidney disease five years ago, combined with renal hypertension and renal anemia. She was treated with peritoneal dialysis for renal replacement therapy, and with compound α-keto acid tablets, amlodipine tablets, and clonidine tablets.

Personal and family history

The patient denied a history of hepatitis, tuberculosis and other infectious diseases, diabetes, cardiovascular and cerebrovascular disease, and had no family history of malignant tumors.

Physical examination

On initial evaluation, vital signs revealed a temperature of 36.5 °C, pulse rate of 98 bpm, blood pressure of 116/77 mmHg and a respiration rate of 19 breaths/min. The patient was conscious and oriented without chills, diarrhea, chest tightness, chest pain or any other discomfort. No yellowing of the skin or eyes was observed. Both lungs were clear, no dry or moist crackles (rales) were heard. Furthermore, the



DOI: 10.12998/wjcc.v11.i14.3311

Figure 1 Smear examination and bacterial culture results of peritoneal dialysis fluid. A: Gram staining of peritoneal dialysate specimens after centrifugation (×1000); B: Colony morphology on a blood agar plate at 35 °C, 5% CO_2 and cultured for 48 h.

abdomen was flat, an abdominal tube was visible on the right lower abdomen, the tunnel had a little exudation, and the tunnel score was 1 point. No tenderness, rebound pain, enlarged liver or spleen, and no tapping pain in both kidneys were observed. No edema was noted in both ankles, limb muscle strength was Grade V, and Babbitt negative.

Laboratory examinations

Routine blood examination showed the following results: Leukocyte count 6.0 × 10^9/L, neutrophil percentage 89.7%, hemoglobin 108 g/L; high sensitivity C reactive protein 244.94 mg/L. On the day of admission, routine examination of peritoneal dialysis fluid was performed after disinfection which showed that the fluid was colorless, turbid, with a white blood cell count of 6000/μL, and neutrophils of 95%. The Lifanta test was positive, and dialysate bacterial smear examination showed Gram-negative cocci identified by Gram staining (Figure 1A).

Blood electrolyte results were: Potassium 3.52 mmol/L, sodium 131.9 mmol/L, and chlorine 89.0 mmol/L. After admission, peritoneal dialysis fluid was collected for bacterial smear examination. The peritoneal dialysis fluid was cultured on a Columbia blood agar plate for 48 h, and 2-4 mm, gray-white, round, moist, and raised colonies were observed (Figure 1B). The pure culture was identified as *Neisseria mucosa/mucosa* by a Vitek MS mass spectrometer. In order to obtain accurate identification results, 16sRNA sequencing was performed. The results showed that the sequence was 99.85% consistent with *Neisseria mucosa* (GenBank No. NR_117696.1). Combined with the colony characteristics, the strain was finally identified as *Neisseria mucosa*.

Imaging examinations

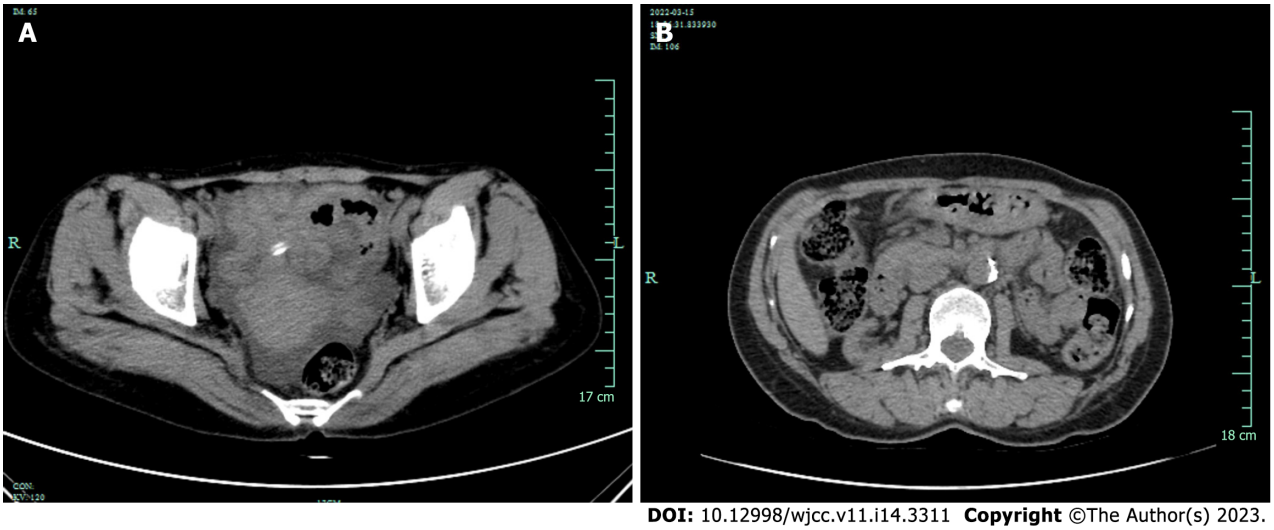
Hepatobiliary system, spleen, pancreas, kidneys and ureters were examined by brightness-mode ultrasound, and the patient was found to have a right kidney cyst and ascites. She was admitted to hospital after an initial diagnosis of peritonitis. Routine enhanced computed tomography (CT) of the abdomen and pelvis showed that the patient had multiple cysts in both kidneys and pelvic effusion. There was no evidence of intra-abdominal abscess or a focus of infection. Two weeks later, reexamination with CT showed that after treatment of peritonitis, peritoneal thickening has not been completely absorbed caused by peritonitis (Figure 2).

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was peritoneal dialysis-related peritonitis caused by *Neisseria mucosa*.

TREATMENT

For adequate coverage of Gram-positive and Gram-negative organisms, the empirical antibiotic therapy given was vancomycin 1000 mg qd combined with imipenem/cilastatin 1.0 g q12h added to peritoneal dialysis fluid. In addition, 2.5% dialysate 2 L + 1.5% dialysate 6 L/d continuous ambulatory peritoneal dialysis was carried out to eliminate toxins and maintain water, electrolyte, and acid-base balance. Vancomycin was discontinued after the pathogen was identified, and imipenem/cilastatin injection 1.0



DOI: 10.12998/wjcc.v11.i14.3311

Figure 2 Computed tomography results before and after treatment. A: Before treatment, computed tomography (CT) showed ascites without obvious thickening of the membrane; B: CT reexamination showed that peritoneal thickening has not been completely absorbed caused by peritonitis after treatment.

g q12h for anti-infection treatment was continued. After 8 d, the patient's dialysate was clear and her condition had improved. Ceftazidime injection 1.0 g qd was added to the dialysate for follow-up anti-inflammatory treatment.

OUTCOME AND FOLLOW-UP

On the 24th day of hospitalization, arteriovenous fistulation of the upper extremity was performed. The purpose of surgical treatment is to change his treatment plan from peritoneal dialysis to hemodialysis three months after the operation. The patient was discharged in a stable condition after one month. Two weeks after discharge, the patient was again hospitalized due to peritoneal dialysis-related peritonitis. The same organism-*Neisseria mucosa* was cultured from the patient's peritoneal dialysis fluid. After a detailed medical history enquiry, it was found that the patient frequently used her mouth to open the cap of the dialysate bottle during peritoneal dialysis at home. During her second hospitalization, the patient was treated with imipenem/cilastatin injection 1.0 g q12h added to peritoneal dialysis fluid for 20 d and was cured. The patient is currently undergoing close follow-up observation.

DISCUSSION

Neisseria species other than *Neisseria meningitidis* and *Neisseria gonorrhoeae*, such as *Neisseria mucosa*, *Neisseria subflava*, *Neisseria lactamica*, *Neisseria cinerea*, and *Neisseria mucosa*, are unusual pathogens in humans[8]. *Neisseria mucosa*, originally described as *Diplococcus mucosus* by von Lingelsheim in 1906, frequently colonizes the nasopharynx and dolphin respiratory tract[9]. It was gram-negative diplococcus, with large colonies and mucus type, often fused together. Most strains do not produce pigment, or light gray to light yellow. It can decompose glucose, maltose, fructose and sucrose. It is difficult to distinguish from *Neisseria mucosa* during mass spectrometry identification. Based on whole genome sequencing analysis, *Neisseria mucosa* is the same species as *Neisseria rhesus* and *Neisseria mucosa*, and *Neisseria mucosa* has priority naming rights. Therefore, we further identified the pathogen of this infection as *Neisseria mucosa* by 16sRNA sequencing, combined with biochemical reaction characteristics and colony morphology. According to the literature, Neisseria can cause meningitis, conjunctivitis, pneumonia, endocarditis, urethritis and peritonitis[2-6]. There are few reports of peritoneal dialysis-related peritonitis caused by *Neisseria mucosa*. To our knowledge, the first case was reported in 1993 and only 5 cases have been reported so far. Patients were aged 17 to 68 years, with no specificity, and ultimately received effective treatment[10-14]. This is the first case report of peritoneal dialysis-associated peritonitis caused by *Neisseria mucosa* in mainland China.

The patient was diagnosed with Stage 5 chronic kidney disease, combined with renal hypertension, renal anemia, and maintenance peritoneal dialysis for more than 5 years. Therefore, the patient's immune function and nutritional status were poor, and the peritoneal self-defense function was impaired. Combined with the significant increase in systemic infection indicators, the leukocytes in peritoneal dialysis fluid were chemotactic and were mainly polymorphonuclear neutrophils. Bacterial smears and culture results confirmed the diagnosis of peritoneal dialysis-associated peritonitis caused

by *Neisseria mucosa*.

The patient was treated with antibiotics added to peritoneal dialysis fluid for anti-inflammatory treatment. According to the Clinical and Laboratory Standards Institute[3], there is no accepted standard for assessing the antimicrobial sensitivity of *Neisseria mucosa*. We provide *in vitro* drug sensitivity test results for reference: Penicillin G (0.125 μg/mL), ceftriaxone (0.25 μg/mL), meropenem (0.125 μg/mL), combined with the International Society of Peritoneal Dialysis (ISPD) guidelines for the treatment of abdominal infection[15], the first treatment with imipenem/cilastatin resulted in significant improvement, and 8 d after treatment with ceftazidime, the clinical symptoms disappeared.

However, the patient was readmitted to hospital due to peritonitis caused by *Neisseria mucosa* two weeks later, according to ISPD peritonitis guideline recommendations in 2022[16]. The patient's second infection was defined as a relapse. The reason for the second infection may be that the first treatment did not involve removal of the peritoneal dialysis tube, resulting in a small amount of bacterial colonization. In addition, after a detailed medical history enquiry, it was found that the patient frequently used her mouth to open the cap of the dialysate bottle during peritoneal dialysis at home. Therefore, it is speculated that the patient's *Neisseria mucosa* was derived from the peritoneal dialysis fluid contaminated by her own saliva and caused repeat peritonitis.

In summary, we report a case of peritoneal dialysis-related peritonitis caused by repeated infection with *Neisseria mucosa*. There are few reports on infections caused by *Neisseria mucosa*. The pathogenic mechanism, infection route and treatment plan of *Neisseria mucosa* require further study. Peritoneal dialysis patients, due to long-term impaired renal function and low immunity, should pay attention to the prevention of peritonitis. In particular, in home-based self-dialysis patients, medical and health conditions are poor; thus, education on relevant protective measures is needed.

CONCLUSION

Peritoneal dialysis patients, due to long-term impaired renal function and low immunity, should pay attention to the prevention of peritonitis. *Neisseria mucosa*, as part of the normal flora of the human oral cavity, rarely causes infection in the body, especially the abdominal cavity. Peritonitis caused by *Neisseria mucosa* is very rare. *Neisseria mucosa* was detected during two hospitalizations for peritonitis in this case, which may have been related to the patient's habit of opening the peritoneal dialysis fluid cap using her mouth. Unfortunately, we were unable to confirm whether *Neisseria mucosa* from the patient's mouth was the same strain as the two isolated strains. However, this case demonstrates that home-based self-dialysis patients, because they cannot guarantee good medical and health conditions, need to be repeatedly educated and protected.

FOOTNOTES

Author contributions: Ren JM contributed to manuscript writing and editing, and data collection; Zhang XY contributed to data analysis; Liu SY contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Jian-Min Ren 0000-0001-6005-0374; Xiao-Yao Zhang 0000-0002-5144-7027; Si-Yu Liu 0000-0001-7475-0267.

S-Editor: Hu YR
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Zapun A**, Morlot C, Taha MK. Resistance to β-Lactams in Neisseria ssp Due to Chromosomally Encoded Penicillin-Binding Proteins. *Antibiotics (Basel)* 2016; **5** [PMID: 27690121 DOI: 10.3390/antibiotics5040035]

2 **Altdorfer A**, Pirotte BF, Gaspard L, Gregoire E, Firre E, Moerman F, Moonen M, Sanoussi A, Van Esbroeck M, Mori M. Infective endocarditis caused by Neisseria mucosa on a prosthetic pulmonary valve with false positive serology for Coxiella burnetii - The first described case. *IDCases* 2021; **24**: e01146 [PMID: 34026536 DOI: 10.1016/j.idcr.2021.e01146]

3 **Khan KN**, Saxena R, Choti M, Ariyamuthu VK. Neisseria mucosa Peritonitis in the Setting of a Migrated Intrauterine Device. *Adv Perit Dial* 2018; **34**: 47-49 [PMID: 30480537]

4 **Osses DF**, Dijkmans AC, van Meurs AH, Froeling FM. Neisseria Mucosa: A New Urinary Tract Pathogen? *Curr Urol* 2017; **10**: 108-110 [PMID: 28785197 DOI: 10.1159/000447161]

5 **Mechergui A**, Achour W, Baaboura R, Ouertani H, Lakhal A, Torjemane L, Othman TB, Hassen AB. Case report of bacteremia due to Neisseria mucosa. *APMIS* 2014; **122**: 359-361 [PMID: 23905778 DOI: 10.1111/apm.12144]

6 **Durán E**, Salvo S, Gil J, Sanjoaquín I. [Pneumonia and bacteremia due to Neisseria mucosa in a human immunodeficient virus seropositive patient parenteral drug abuser]. *Enferm Infecc Microbiol Clin* 2011; **29**: 236-237 [PMID: 21354666 DOI: 10.1016/j.eimc.2010.09.006]

7 **Gini GA**. Ocular infection in a newborn caused by Neisseria mucosa. *J Clin Microbiol* 1987; **25**: 1574-1575 [PMID: 3624452 DOI: 10.1128/jcm.25.8.1574-1575.1987]

8 **John EB**, Raphael D, Martin JB. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 9th ed. Elsevier, 2019: 3049-3135

9 **Jin Y**, Xu H, Yao Q, Gu B, Wang Z, Wang T, Yu X, Lu Y, Zheng B, Zhang Y. Confirmation of the Need for Reclassification of Neisseria mucosa and Neisseria sicca Using Average Nucleotide Identity Blast and Phylogenetic Analysis of Whole-Genome Sequencing: Hinted by Clinical Misclassification of a Neisseria mucosa Strain. *Front Microbiol* 2021; **12**: 780183 [PMID: 35281306 DOI: 10.3389/fmicb.2021.780183]

10 **Arora S**, Chitkara NL. Non-pathogenic neisserian Neisseria catarrhalis--as cause of meningitis. *J Assoc Physicians India* 1973; **21**: 255-257 [PMID: 4792800]

11 **Macia M**, Vega N, Elcuaz R, Aterido T, Palop L. Neisseria mucosa peritonitis in CAPD: another case of the "nonpathogenic" Neisseriae infection. *Perit Dial Int* 1993; **13**: 72-73 [PMID: 8443288 DOI: 10.1177/089686089301300121]

12 **Lee WC**, Yang WC, Chen TW, Huang CH, Lin CC. Unusual presentation of Neisseria mucosa peritonitis with persistent ultrafiltration failure and clear effluent. *Perit Dial Int* 2003; **23**: 198-199 [PMID: 12713091 DOI: 10.1177/089686080302300219]

13 **Shetty AK**, Nagaraj SK, Lorentz WB, Bitzan M. Peritonitis due to Neisseria mucosa in an adolescent receiving peritoneal dialysis. *Infection* 2005; **33**: 390-392 [PMID: 16258875 DOI: 10.1007/s15010-005-5074-4]

14 **Awdisho A**, Bermudez M. A Case Report of Neisseria Mucosa Peritonitis in a Chronic Ambulatory Peritoneal Dialysis Patient. *Infect Dis Rep* 2016; **8**: 6950 [PMID: 28191300 DOI: 10.4081/idr.2016.6950]

15 **Humphries R**, Bobenchik AM, Hindler JA, Schuetz AN. Overview of Changes to the Clinical and Laboratory Standards Institute Performance Standards for Antimicrobial Susceptibility Testing, M100, 31st Edition. *J Clin Microbiol* 2021; **59**: e0021321 [PMID: 34550809 DOI: 10.1128/JCM.00213-21]

16 **Li PK**, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, Kanjanabuch T, Kim YL, Madero M, Malyszko J, Mehrotra R, Okpechi IG, Perl J, Piraino B, Runnegar N, Teitelbaum I, Wong JK, Yu X, Johnson DW. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. *Perit Dial Int* 2022; **42**: 110-153 [PMID: 35264029 DOI: 10.1177/08968608221080586]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3317-3322

DOI: 10.12998/wjcc.v11.i14.3317

ISSN 2307-8960 (online)

CASE REPORT

Rectal prolapse in a 30-year-old bladder stone male patient: A case report

Hong-Xiang Ding, Jia-Guo Huang, Chao Feng, Sheng-Cheng Tai

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cassell III AK, Liberia; Pietroletti R, Italy

Received: February 4, 2023
Peer-review started: February 4, 2023
First decision: March 24, 2023
Revised: March 31, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Hong-Xiang Ding, Jia-Guo Huang, Sheng-Cheng Tai, Department of Urology, Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou 310000, Zhejiang Province, China

Chao Feng, School of Medicine, Hangzhou Normal University, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Sheng-Cheng Tai, MM, Surgeon, Department of Urology, Affiliated Xiaoshan Hospital, Hangzhou Normal University, No. 728 North Yucai Road, Xiaoshan District, Hangzhou 311200, Zhejiang Province, China. tsc13516811191@126.com

Abstract

BACKGROUND

Rectal prolapse occurs most commonly in children and middle-aged and elderly women and is relatively rare in young men and is occasionally caused by bladder stones. Severe rectal prolapse, bilateral hydronephrosis, and renal insufficiency caused by bladder stones are rare in a 30-year-old man.

CASE SUMMARY

We report the case of a 30-year-old male patient with cerebral palsy who presented with a large bladder stone that resulted in severe rectal prolapse, bilateral hydronephrosis, and renal insufficiency. Following a definitive diagnosis, the bladder stone was successfully removed, and his kidney function returned to normal. We assessed the patient's nutritional status and stone composition and concluded that the main cause was malnutrition.

CONCLUSION

Rectal prolapse is a rare clinical manifestation of bladder stones, particularly in young adults. Cerebral palsy patients are a vulnerable group in society because of their intellectual disabilities and communicative impairments. Accordingly, besides taking care of their daily diet, abnormal signs in their bodies should receive the doctors' attention in a timely manner.

Key Words: Bladder stone; Rectal prolapse; Cerebral palsy; Malnutrition; Case report

Core Tip: Bladder stones are generally observed in elderly males and children but are rarely found in young adults. Similarly, rectal prolapse is extremely rare in young men. Clinically, the most common symptoms of bladder stones are urinary frequency, interrupted urine flow, typically terminal hematuria, dysuria, or suprapubic pain, which are worst at the end of urination. Rectal prolapse is a rare clinical manifestation of bladder stones. We report an unusual case of a young man with cerebral palsy who presented with rectal prolapse and finally confirmed a diagnosis of bladder stone. Patients with cerebral palsy are unable to accurately describe physical discomfort due to intellectual disability and communication disabilities. Therefore, the abnormal signs in their body should be given timely attention by doctors, and early diagnosis and provision of appropriate active treatment positively impact on the prognosis of patients.

Citation: Ding HX, Huang JG, Feng C, Tai SC. Rectal prolapse in a 30-year-old bladder stone male patient: A case report. *World J Clin Cases* 2023; 11(14): 3317-3322
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3317.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3317

INTRODUCTION

Bladder stones constitute approximately 5% of all urinary tract stones[1]. They are generally observed in elderly males and children and are rarely found in young adults[2-4]. The most common symptoms of bladder stones are urinary frequency, interrupted urine flow, typically terminal hematuria, dysuria, or suprapubic pain, which are worst at the end of urination. These symptoms may be exacerbated following sudden movement and exercise[5,6]. In addition to dysuria, children may experience pulling of the penis, urinary retention, enuresis, or rectal prolapse. Bladder stones are incidental findings in 10% of cases[7,8]. Bladder stone presentations are often due to interrupted urination, dysuria, or gross hematuria. Rectal prolapse is an extremely rare reason for a doctor's visit for bladder stones in young adults. Here, we report the case of a 30-year-old male patient.

CASE PRESENTATION

Chief complaints

A 30-year-old male patient with cerebral palsy presented to the emergency department with a history of recurrent rectal prolapse for one year and a six-hour failed manual reduction procedure.

History of present illness

The symptoms started one year before presentation with recurrent rectal prolapse. When rectal prolapse had occurred, the patient had shown obvious irritability and painful expressions. The obvious irritability and painful expressions could be relieved after manual reduction. Six hours before admission, the patient developed rectal prolapse. Because of a failed manual reduction procedure, he was brought to the emergency department of our hospital, accompanied by a doctor of his welfare home.

History of past illness

The patient had typical clinical manifestations of cerebral palsy, including central motor disorders, abnormal posture, intellectual disability, communicative impairments, and abnormal mental behavior. He could walk only short distances, spent most of his time sitting or resting in bed, and his emotional changes could only be guessed through facial expressions.

Personal and family history

The patient's family history was unknown because he was abandoned in an orphanage after being diagnosed with cerebral palsy in infancy.

Physical examination

On physical examination, his body mass index (BMI), calculated from 145 cm of height and 35 kg of weight, was 16.6 kg/m^2. A palpable mass in the bladder area of the lower abdomen demonstrated marked tenderness, and the rectum was prolapsed approximately 10 cm from the anus (Figure 1).

DOI: 10.12998/wjcc.v11.i14.3317

Figure 1 Rectal prolapse.

Laboratory examinations

Blood biochemical analysis indicated a potassium level of 2.443 mmol/L, creatinine levels of 381 μmol/L, and blood urea nitrogen of 11.53 mmol/L.

Imaging examinations

Abdominal computed tomography revealed a large bladder stone, bilateral hydronephrosis, and thickening of the bladder wall (Figure 2).

FINAL DIAGNOSIS

Bladder stone, rectal prolapse.

TREATMENT

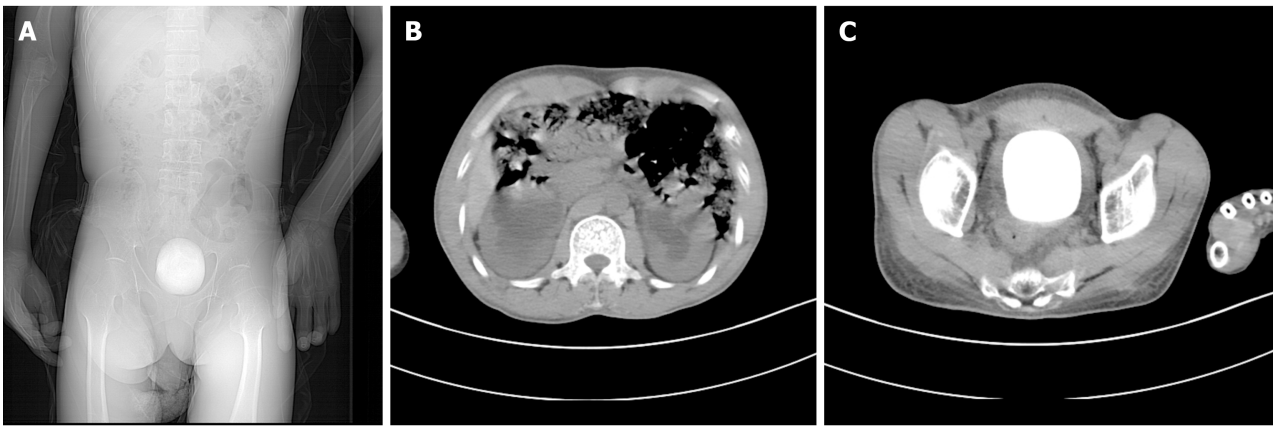
The anorectal surgeon manually reset the prolapsed rectum, and the patient was referred to the urology department for treatment. After the patient's hypokalemia was corrected and nutritional support was provided, we performed a cystotomy and excised the bladder stone. We analyzed the components of the bladder stone and found that the main components were ammonium uric acid and calcium oxalate.

OUTCOME AND FOLLOW-UP

One week after the operation, the patient's catheter was removed, and he returned to normal urination. The renal function and serum potassium were normal upon reexamination. The patient with rectal prolapse underwent surgery in the proctology department.

DISCUSSION

Bladder stones are rare causes of rectal prolapse. In the past few decades, only four papers have reported rectal prolapse caused by bladder stones. Among them, three cases were of primary bladder stones in infants and young children[9-11], and one case was of secondary bladder stones caused by foreign bodies in an adult's bladder[12]. There have been no reports of bladder stones as the primary cause of rectal prolapse in adults. This study reports a patient aged 30 years without prior history of benign prostatic hyperplasia, whose large bladder stone led to severe rectal prolapse, bilateral



DOI: 10.12998/wjcc.v11.i14.3317

Figure 2 Preoperative abdominal computed tomography findings. A: A large bladder stone; B: Bilateral hydronephrosis; and C: A large bladder stone and thickening of the bladder wall.

hydronephrosis, and renal insufficiency.

Rectal prolapse mostly occurs in children, middle-aged, and elderly women and is generally related to an increase in abdominal pressure (such as constipation), chronic cough, difficulty in urinating, or multiple deliveries, which often leads to increased abdominal pressure and pushes the rectum to prolapse downward[13]. Rectal prolapse is rarer in men than it is in women. Some theories suggest that the prostate is a powerful anchor for the pelvic organ and may also be associated with low-frequency constipation[14]. In this patient, dysuria due to bladder stones was a probable cause, accompanied by a persistent increase in the abdominal pressure required to urinate, ultimately leading to rectal prolapse. Additionally, the prolapsed rectum, pulling the floor of the bladder may have caused chronic, incomplete bladder emptying, favoring urine residue and stone formation. They affect each other, leading to a vicious circle.

In recent decades, the incidence of bladder stones has decreased annually[15]. Bladder stones are usually multi-factorial in etiology[3] and are classified as primary, secondary, or migratory[16]. Primary or endemic bladder stones are usually observed in children in areas with poor hydration, recurrent diarrhea, and a diet deficient in animal protein without any other urinary tract pathology[7]. Secondary bladder stones are most commonly caused by bladder outlet obstruction in adults, accounting for 45%–79% of bladder stones. They are also associated with neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies, catheters, bladder diverticula, bladder augmentation, and urinary diversion [3,5,6,17,18]. The term "migratory" refers to stones that have left the upper urinary tract after forming and may serve as a site for bladder stone growth once they have passed[19]. It was necessary to analyze the etiology of the patient's bladder stone; its composition was mainly ammonium acid urate and calcium oxalate, which is consistent with research findings on bladder stones caused by malnutrition [20]. Furthermore, the patient's BMI of 16.6 indicated a poor nutritional state. Thus, the stone formation in the patient was due to malnutrition and low water intake but was also aggravated by secondary urinary tract infection after stone formation.

It is also likely that rectal prolapse and bladder stones are two separate pathologies. The patient had cerebral palsy and could have been prone to chronic constipation as an underlying risk factor for rectal prolapse. However, the outcome of the disease is often not caused by a single factor; therefore it is necessary to consider whether there is an interaction between pathogenic factors when studying the pathogenic mechanism.

The patient was diagnosed with cerebral palsy and was unable to live independently. Residing in a welfare home, he could not express his physical discomfort clearly. In the early stage of rectal prolapse, the patient had abnormal physical signs, but the doctors did not notice them promptly, and he did not receive treatment until severe rectal prolapse occurred one year later. It is possible that the doctors in the welfare home did not conduct a comprehensive evaluation of the patient, which may have accounted for the delayed diagnosis and treatment. However, patients with cerebral palsy are a vulnerable group in society and deserve special attention.

CONCLUSION

Bladder stones are a rare cause of rectal prolapse, particularly in young adults. In this case, the diagnosis and treatment were delayed because of the patient's cerebral palsy, intellectual disability, and communication impairment. Patients with cerebral palsy are a vulnerable group in society and deserve particular attention. Accordingly, besides taking care of their daily diet, clinicians should be keenly

aware of any abnormal signs in the patient's body and make timely diagnoses and treatments.

ACKNOWLEDGEMENTS

We acknowledge the contribution of the participants. We thank Home for Researchers editorial team (www.home-for-researchers.com) for language editing service.

FOOTNOTES

Author contributions: Tai SC contributed to conceptualization, supervision, writing-review and editing; Ding HX contributed to investigation, writing-original draft; Huang JG contributed to investigation; Feng C contributed to case collection, and all authors have read and approved the final manuscript.

Supported by Bureau of Science and Technology in Xiaoshan District, Hangzhou, China, NO. 2020210.

Informed consent statement: Informed consent was obtained from the patients' guardian for publication of this case report details.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Sheng-Cheng Tai 0000-0002-4014-3159.

S-Editor: Liu XF
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Aydogdu O**, Telli O, Burgu B, Beduk Y. Infravesical obstruction results as giant bladder calculi. *Can Urol Assoc J* 2011; **5**: E77-E78 [PMID: 21806900 DOI: 10.5489/cuaj.10130]
2 **Halstead SB**. Epidemiology of bladder stone of children: precipitating events. *Urolithiasis* 2016; **44**: 101-108 [PMID: 26559057 DOI: 10.1007/s00240-015-0835-8]
3 **Takasaki E**, Suzuki T, Honda M, Imai T, Maeda S, Hosoya Y. Chemical compositions of 300 Lower urinary tract calculi and associated disorders in the urinary tract. *Urol Int* 1995; **54**: 89-94 [PMID: 7538235 DOI: 10.1159/000282696]
4 **Naqvi SA**, Rizvi SA, Shahjehan S. Bladder stone disease in children: clinical studies. *J Pak Med Assoc* 1984; **34**: 94-101 [PMID: 6429380]
5 **Smith JM**, O'Flynn JD. Vesical stone: The clinical features of 652 cases. *Ir Med J* 1975; **68**: 85-89 [PMID: 1112692]
6 **Millán-Rodríguez F**, Errando-Smet C, Rousaud-Barón F, Izquierdo-Latorre F, Rousaud-Barón A, Villavicencio-Mavrich H. Urodynamic findings before and after noninvasive management of bladder calculi. *BJU Int* 2004; **93**: 1267-1270 [PMID: 15180620 DOI: 10.1111/j.1464-410X.2004.04815.x]
7 **Lal B**, Paryani JP, Memon SU. Childhood bladder stones-an endemic disease of developing countries. *J Ayub Med Coll Abbottabad* 2015; **27**: 17-21 [PMID: 26182729]
8 **Al-Marhoon MS**, Sarhan OM, Awad BA, Helmy T, Ghali A, Dawaba MS. Comparison of endourological and open cystolithotomy in the management of bladder stones in children. *J Urol* 2009; **181**: 2684-7; discussion 2687 [PMID: 19375100 DOI: 10.1016/j.juro.2009.02.040]
9 **Liu J**. One Case Report of Bladder Stone Complicated with Prolapse of Anus in Children. *Jiangxi Medical Journal* 1982; **6**: 64-64
10 **Munns J**, Amawi F. A large urinary bladder stone: an unusual cause of rectal prolapse. *Arch Dis Child* 2010; **95**: 1026 [PMID: 20870623 DOI: 10.1136/adc.2010.198440]
11 **Lauschke H**. Large urinary bladder stones associated with prolapse of the rectum in children: case report. *Trop Doct* 1989; **19**: 65-66 [PMID: 2734839 DOI: 10.1177/004947558901900207]

12 **Chi J**, Guo Z. [A case report of rectal prolapse caused by bladder stones]. Gong Qi Yi Kan 1995; 2: 87-87

13 **Goldstein SD**, Maxwell PJ 4th. Rectal prolapse. *Clin Colon Rectal Surg* 2011; **24**: 39-45 [PMID: 22379404 DOI: 10.1055/s-0031-1272822]

14 **Church J**. Rectal Prolapse: Diagnosis and Clinical Management. Gastroenterology 2009; 136: 1456-1457 [DOI: 10.1053/j.gastro.2009.02.031]

15 **Ye Z**, Zeng G, Yang H, Li J, Tang K, Wang G, Wang S, Yu Y, Wang Y, Zhang T, Long Y, Li W, Wang C, Wang W, Gao S, Shan Y, Huang X, Bai Z, Lin X, Cheng Y, Wang Q, Xu Z, Xie L, Yuan J, Ren S, Fan Y, Pan T, Wang J, Li X, Chen X, Gu X, Sun Z, Xiao K, Jia J, Zhang Q, Sun T, Xu C, Shi G, He J, Song L, Sun G, Wang D, Liu Y, Han Y, Liang P, Wang Z, He W, Chen Z, Xing J, Xu H. The status and characteristics of urinary stone composition in China. *BJU Int* 2020; **125**: 801-809 [PMID: 30958622 DOI: 10.1111/bju.14765]

16 **Philippou P**, Moraitis K, Masood J, Junaid I, Buchholz N. The management of bladder lithiasis in the modern era of endourology. *Urology* 2012; **79**: 980-986 [PMID: 22119259 DOI: 10.1016/j.urology.2011.09.014]

17 **Douenias R**, Rich M, Badlani G, Mazor D, Smith A. Predisposing factors in bladder calculi. Review of 100 cases. *Urology* 1991; **37**: 240-243 [PMID: 2000681 DOI: 10.1016/0090-4295(91)80293-g]

18 **Yang X**, Wang K, Zhao J, Yu W, Li L. The value of respective urodynamic parameters for evaluating the occurrence of complications linked to benign prostatic enlargement. *Int Urol Nephrol* 2014; **46**: 1761-1768 [PMID: 24811567 DOI: 10.1007/s11255-014-0722-1]

19 **Childs MA**, Mynderse LA, Rangel LJ, Wilson TM, Lingeman JE, Krambeck AE. Pathogenesis of bladder calculi in the presence of urinary stasis. *J Urol* 2013; **189**: 1347-1351 [PMID: 23159588 DOI: 10.1016/j.juro.2012.11.079]

20 **Salah MA**, Holman E, Khan AM, Toth C. Percutaneous cystolithotomy for pediatric endemic bladder stone: experience with 155 cases from 2 developing countries. *J Pediatr Surg* 2005; **40**: 1628-1631 [PMID: 16226996 DOI: 10.1016/j.jpedsurg.2005.06.039]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3323-3329

DOI: 10.12998/wjcc.v11.i14.3323

ISSN 2307-8960 (online)

CASE REPORT

Successful treatment of veno-arterial extracorporeal membrane oxygenation complicated with left ventricular thrombus by intravenous thrombolysis: A case report

Ya-Dong Wang, Jin-Feng Lin, Xiao-Ying Huang, Xu-Dong Han

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Emam AMA, Saudi Arabia; Bonacchi M, Italy

Received: February 13, 2023
Peer-review started: February 13, 2023
First decision: March 14, 2023
Revised: March 22, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 16, 2023

Ya-Dong Wang, Intensive Care Medicine, Nantong Third People's Hospital, Nantong 226000, Jiangsu Province, China

Jin-Feng Lin, Xiao-Ying Huang, Xu-Dong Han, Critical Care Medicine, Nantong Third People's Hospital, Nantong 226000, Jiangsu Province, China

Corresponding author: Xu-Dong Han, MD, Chief Physician, Critical Care Medicine, Nantong Third People's Hospital, No. 60 Qingnian Road, Nantong 226000, Jiangsu Province, China. hanxudong9610@163.com

Abstract

BACKGROUND

Left ventricular thrombus is a rare condition, for which appropriate treatments are not extensively studied. Although it can be treated by thrombectomy, such surgery can be difficult and risky, and not every patient can tolerate the surgery.

CASE SUMMARY

We report a case of a middle-aged man receiving veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for acute myocardial infarction who developed left ventricular thrombus despite systemic anticoagulation. After systemic thrombolysis with urokinase, the left ventricular thrombus disappeared, ECMO was successfully withdrawn 9 days later, and the patient recovered and was discharged from hospital.

CONCLUSION

Systemic thrombolysis is a treatment option for left ventricular thrombus in addition to anticoagulation and thrombectomy.

Key Words: Extracorporeal membrane oxygenation; Left ventricular thrombus; Thrombolysis; Case report

Core Tip: Urokinase is a useful medicine for thrombolysis. This is the first case report of urokinase administration for left ventricular thrombus occurring during veno-arterial extracorporeal membrane oxygenation therapy. Systemic thrombolytic therapy with urokinase can be considered when the effect of anticoagulant therapy is poor or the risk of surgical treatment is high after left ventricular thrombus formation.

Citation: Wang YD, Lin JF, Huang XY, Han XD. Successful treatment of veno-arterial extracorporeal membrane oxygenation complicated with left ventricular thrombus by intravenous thrombolysis: A case report. *World J Clin Cases* 2023; 11(14): 3323-3329
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3323.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3323

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an important treatment for severe cardiopulmonary insufficiency. In recent years, particularly after coronavirus disease 2019, ECMO has rapidly developed in China. Recently, ECMO has become more reliable due to improvements in equipment and increased experience, which is reflected in improved results[1]. However, many complications can occur during ECMO treatment, such as bleeding and thrombosis. Of these complications, intracardiac thrombosis is rare but can be life-threatening. For intracardiac thrombosis, the current guidelines and expert consensus recommend anticoagulation and thrombectomy, but there are no reports on intravenous thrombolysis. We report a case of successful intravenous thrombolysis after left ventricular thrombus which occurred during VA-ECMO therapy.

CASE PRESENTATION

Chief complaints

The patient had undergone cardiopulmonary resuscitation twice in half a day.

History of present illness

A 48-year-old man who suffered from persistent angina pectoris for 2 h was diagnosed with acute extensive anterior wall myocardial infarction in a local hospital on September 19, 2022. Coronary angiography showed total occlusion of the left main ostium. Following implantation of a Medtronic 3.0 mm × 2.6 mm drug-eluting stent (10 atm, 10 s) in the left anterior descending artery, the blood flow returned to TIMI3. The patient was then admitted to the intensive care unit (ICU). Sudden cardiac arrest occurred twice in the ICU, and cardiopulmonary resuscitation was given. The patient required 15 min resuscitation during the first arrest, and 5 min resuscitation during the second arrest. However, his blood pressure was extremely unstable, and the dose of norepinephrine was raised to 120 μg/min. After consultation, VA-ECMO treatment was initiated. The speed of the ECMO centrifugal pump was 3500 rpm, the air flow rate was 2.5 L/min, the oxygen concentration was 100%, and the blood flow rate was approximately 2.4 L/min. His arterial blood pressure increased to 125/114 mmHg, and the dose of norepinephrine was decreased to 40 μg/min. The patient was then transferred to our department.

History of past illness

The patient had no previous medical history.

Personal and family history

All family members were healthy and denied any history of genetic disease and genetic predisposition.

Physical examination

The patient's temperature was 36°C, heart rate was 86 bpm, blood pressure was 125/114 mmHg with norepinephrine 40 μg/min, and respiratory rate was 15 breaths/min. The patient was in a state of subcoma, moist rales were heard in both lungs, arrhythmia was identified, heart sounds were low and weak, and bowel sounds were not heard.

Laboratory examinations

Laboratory examinations indicated leucocytosis (white blood cell count, 15.96 × 10^9/L); glutamic oxaloacetic transaminase 906 U/L; cardiac troponin I 50 ng/mL; N-Terminal pro-brain natriuretic

peptide 2000 pg/mL.

Imaging examinations

Echocardiography revealed segmental wall dyskinesia and hypofunction of the left heart.

FINAL DIAGNOSIS

Acute extensive anterior wall myocardial infarction and cardiogenic shock.

TREATMENT

He was given 100 mg/d aspirin, 180 mg/d ticagrelor and 600 U/h heparin. Bedside echocardiography showed that systolic function of the left ventricle was extremely poor, there was no obvious thrombus in the left ventricle, and the patient's blood was in a turbulent state. The mean arterial pressure was 72 mmHg when the dose of norepinephrine was 20 μg/min and the blood flow rate was 3.2 L/min. The active partial thromboplastin time (APTT) was 54.6 s.

Eight hours later, bedside echocardiography showed a large left ventricular thrombus (Figure 1A). However, the Antithrombin-III was only 46.6%, which did not improve after plasma infusion. We administered argatroban 1 mg/h for anticoagulation instead of heparin. After one day of treatment, bedside echocardiography showed that the thrombus had not decreased (Figure 1B). We added urokinase 50000 U/h for thrombolysis. Six hours later, there was no obvious bleeding sign, and the dosage of urokinase was increased to 100000 U/h. Twenty-four hours after thrombolysis, the thromboelastogram showed that the patient's R time was 10.3 min, K time was 6.2 min, alpha angle was 50.9°, max amplitude was 35.2 mm, and LY30 was 0.0%. Thirty-four hours after thrombolysis, blood leakage increased at the ECMO catheter in the femoral artery. The dose of argatroban was reduced to 0.6 mg/h, the dose of urokinase was reduced to 50000 U/h, and local compression was added to stop the bleeding. However, the bleeding was not controlled. Therefore, urokinase was stopped 46 h after initiation, and the total dose of urokinase was 4.6 million U (changes in the patient's coagulation function during thrombolysis are shown in Table 1). During thrombolysis, the left ventricular thrombus gradually decreased (Figure 1C) and then disappeared on the second day after urokinase was stopped (Figure 1D and E). No signs of thromboembolism were found on head, chest and abdominal computed tomography (CT). We successfully removed ECMO on the ninth day.

OUTCOME AND FOLLOW-UP

One month later, the left anterior descending branch stent was found to be blocked, the stent was re-inserted, and the patient was successfully discharged from hospital with New York Heart Association class II-III.

DISCUSSION

VA-ECMO provides good hemodynamic support for adults with cardiogenic shock. However, thrombosis is an important complication during VA-ECMO support and can occur in lines, oxygenators, pumps, and ventricles. The reported incidence of these complications is as high as 17%[2]. Among them, left ventricular thrombus is a serious complication. According to the registration report of Extracorporeal Life Support Organization in 2017, left ventricular thrombus accounts for 5%-6% of all complications of VA-ECMO. Left ventricular thrombus leads to increased mortality.

The formation of left ventricular thrombus in ECMO is mainly related to the primary disease (such as myocardial infarction)[3], decreased myocardial contractility[4], critical illness, sedation, frequent blood transfusion[5], ECMO tubing and the membrane oxygenator in contact with blood leading to fibrinogen and thrombin activation[6], *etc*. The patient in this report had the abovementioned high-risk factors for thrombosis. At the same time, the patient's antithrombin-III (AT-III) was only 40%-60%, and the anticoagulant efficiency of heparin decreased[7], which eventually led to the formation of a left ventricular thrombus.

The fundamental way to prevent left ventricular thrombus formation is anticoagulant therapy and the prevention of left ventricular dilatation[8]. However, there are few guidelines for the treatment of left ventricular thrombus. At present, the guidelines of the American Heart Association (AHA)[9], American Stroke Association and American College of Cardiology (ACC)[10] mainly recommend anticoagulation. In this case, heparin was initially administered for anticoagulation. However, the

Table 1 Changes in coagulation function during thrombolysis

Thrombolysis time	-8 h	0 h	8 h	16 h	24 h	32 h	40 h	48 h	56 h	64 h
PT (s)	24	16.5	20.4	19.7	Null	19.9	21	14	18.5	19.5
APTT (s)	64.1	59.9	40.8	50.9	Null	55.3	53.1	44.1	56.1	51.3
FIB (g/L)	3.4	3.55	4.18	4.34	Null	3.3	2.69	1.92	2.37	2.72
AT-III (%)	46.6	48.1	49.9	56	Null	66.9	62.1	59.2	70.7	68.1
FDP (mg/L)	18	8.21	16.1	34.1	Null	129.2	184.4	365.3	141.8	99
D-D (mg/L)	6.27	2.59	7.61	18.55	Null	53.28	75.92	85.36	55.58	36.67

PT: Prothrombin time; APTT: Activated partial thromboplastin time; FIB: Fibrinogen; AT-III: Antithrombin III; FDP: Fibrinogen degradation product; D-D: D dimer.

patient's AT-III was low, and did not increase significantly after plasma transfusion. At the same time, plasma transfusion may bring the risk of coagulation. According to the literature reports, 27% of patients developed intracardiac thrombus after plasma transfusion[11]. Therefore, in this case, argatroban anticoagulation was administered when left ventricular thrombus occurred, but anticoagulation alone failed to decrease the thrombus.

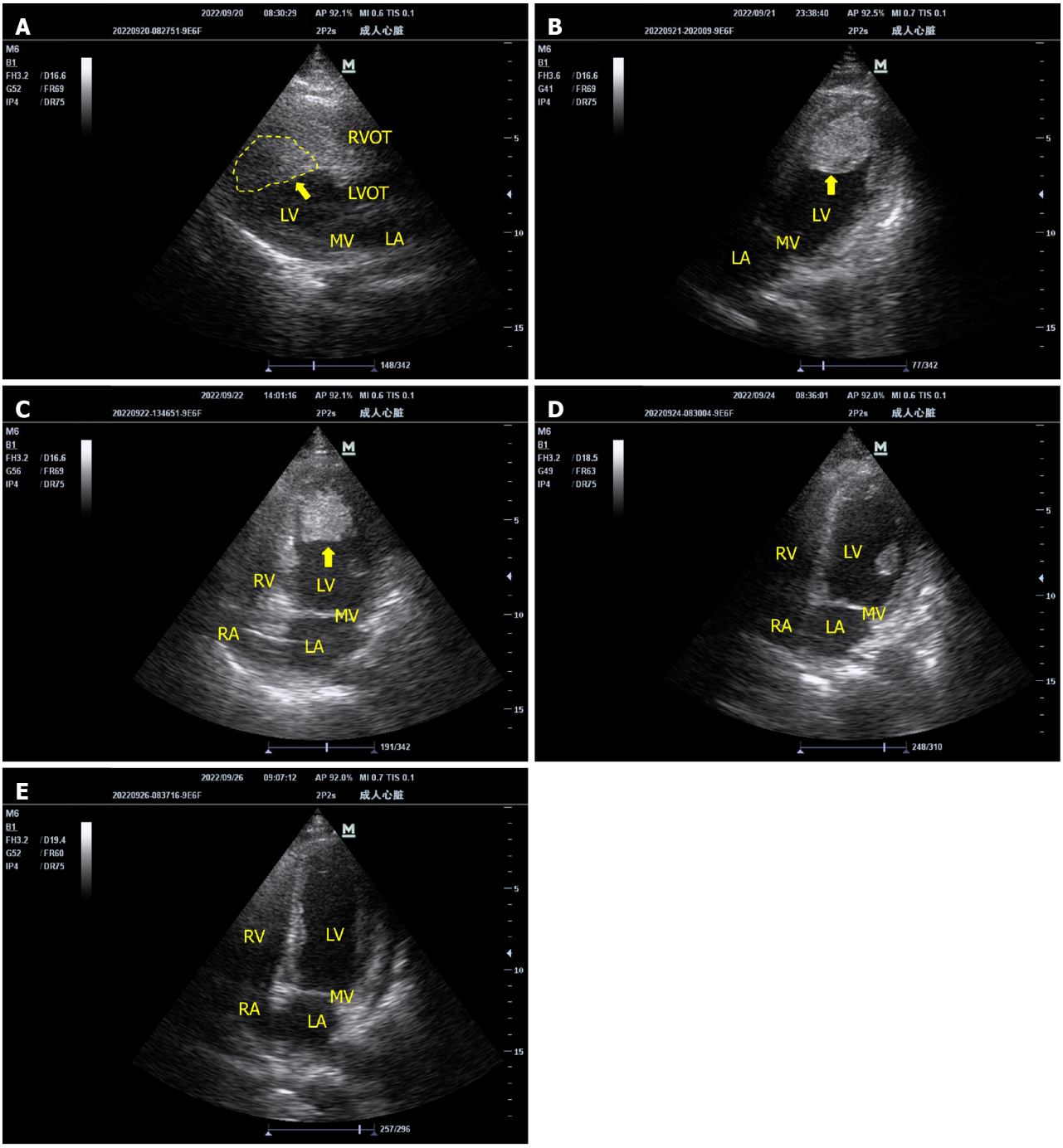
There are also many reports on surgical thrombectomy or thrombus removal[12,13]. However, this approach exposes patients to additional surgical risks and further complications[14]. Ventriculotomy negatively affects the contractility of an already failing heart[15], and anticoagulation after surgery is a huge challenge. Installing a left ventricular decompression device such as the Impella reduces thrombosis by decreasing blood stasis in the left ventricle[16]. Use of the AngioVac system (AngioVac®) to remove ECMO-associated ventricular thrombi has also been reported[17]. Local thrombolysis in the left ventricle has been performed using a left ventricular decompression tube[18], and the thrombus was even removed from the cut aorta through a bronchoscope[15].

At present, there is no convincing evidence in the guidelines that a thrombolytic drug is superior to other drugs[19]. The best thrombolytic agent is still under debate[20]. At present, in most infants and young children, systemic thrombolysis is used to treat ECMO-related left ventricular thrombus[18,21]. The thrombolytic drug used is alteplase. There are few reports on the application of urokinase in left ventricular thrombus. Although the advantages of alteplase have become increasingly prominent in recent years, clinicians have a better understanding of the dose, time, safety and efficacy of urokinase [19]. It has been reported that compared with alteplase, urokinase has a higher thrombus lysis rate[22], lower bleeding risk and better safety[23]. In the meta-analysis conducted by Kharel *et al*[24] it was shown that the efficacy and safety of urokinase in thrombolysis were not inferior to those of alteplase. The 2019 Chinese Stroke Association guidelines indicate that urokinase is still a safe and effective thrombolytic agent[25]. Therefore, in this case, urokinase was used for thrombolysis.

Urokinase is extracted from human urine and is without antigenicity. It acts directly on the endogenous fibrinolytic system to drive the conversion of fibrinogen into fibrinolytic enzyme, thereby rapidly dissolving fresh thrombi. Following 24 h of thrombolytic therapy in our patient, the thromboelastogram showed a hypocoagulable state, and bedside echocardiography showed that the thrombus had decreased. At the same time, fibrinogen degradation product and D dimer initially increased and then decreased, while fibrinogen did not significantly decrease. As there was thrombus dissolution at this time, rather than coagulation activation, thrombolysis was considered effective. However, 34 h after thrombolysis, hemorrhage occurred at the catheter site. Following treatment measures such as local compression which were ineffective, urokinase was stopped, argatroban anticoagulation was continued, and the bleeding was controlled. Seventy-two hours after thrombolytic therapy, the left ventricular thrombus had disappeared. At that time, we were also worried that the thrombus would break off and cause embolism in other areas. However, no clinical manifestations of embolism were observed, and no obvious signs of vascular embolism were seen on head, chest and abdominal CT. The patient recovered and was discharged from hospital.

CONCLUSION

The cornerstone of left ventricular thrombosis prevention in ECMO is systemic anticoagulation and prevention of left ventricular dilation. Systemic thrombolysis with urokinase is a treatment option following the formation of left ventricular thrombus.



DOI: 10.12998/wjcc.v11.i14.3323

Figure 1 The change of left ventricular thrombus after intravenous thrombolysis. A: Bedside echocardiography on September 20 (parasternal long axis view); B: Bedside echocardiography on September 21 (apical four-chamber view); C: Bedside echocardiography on September 22 (apical four-chamber view); D: Bedside echocardiography on September 24 (apical four-chamber view); E: Bedside echocardiography on September 26 (apical four-chamber view).

FOOTNOTES

Author contributions: Wang YD wrote the article, Lin JF reviewed the medical records, Huang XY conducted the literature review and Han XD revised the article; all authors have read and approved the final version to be submitted.

Informed consent statement: Informed written consent was obtained from the patient to publish this case report and accompanying images.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Ya-Dong Wang 0000-0003-2683-2449; Jin-Feng Lin 0000-0001-9146-1299; Xiao-Ying Huang 0009-0000-8279-3857; Xu-Dong Han 0000-0001-9733-678X.

S-Editor: Liu JH
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Makdisi G**, Hashmi ZA, Wozniak TC, Wang IW. Left ventricular thrombus associated with arteriovenous extra corporeal membrane oxygenation. *J Thorac Dis* 2015; **7**: E552-E554 [PMID: 26716054 DOI: 10.3978/j.issn.2072-1439.2015.11.18]
2 **Murphy DA**, Hockings LE, Andrews RK, Aubron C, Gardiner EE, Pellegrino VA, Davis AK. Extracorporeal membrane oxygenation-hemostatic complications. *Transfus Med Rev* 2015; **29**: 90-101 [PMID: 25595476 DOI: 10.1016/j.tmrv.2014.12.001]
3 **Rabbani LE**, Waksmonski C, Iqbal SN, Stant J, Sciacca R, Apfelbaum M, Sayan OR, Giglio J, Homma S. Determinants of left ventricular thrombus formation after primary percutaneous coronary intervention for anterior wall myocardial infarction. *J Thromb Thrombolysis* 2008; **25**: 141-145 [PMID: 17562128 DOI: 10.1007/s11239-007-0064-2]
4 **Lee KS**, Jung Y, Jeong IS, Song SY, Na KJ, Oh SG. Acute biological mitral valve thrombosis after the left atrial venting in a patient with a venoarterial extracorporeal membrane oxygenator. *J Card Surg* 2022; **37**: 437-439 [PMID: 34741553 DOI: 10.1111/jocs.16122]
5 **Doyle AJ**, Hunt BJ. Current Understanding of How Extracorporeal Membrane Oxygenators Activate Haemostasis and Other Blood Components. *Front Med (Lausanne)* 2018; **5**: 352 [PMID: 30619862 DOI: 10.3389/fmed.2018.00352]
6 **Chen T**, Yao L, Fan X, Zhu C. Massive hollow catheter thrombus in venovenous extracorporeal membrane oxygenation assisted lung transplantation: A case report. *Medicine (Baltimore)* 2021; **100**: e24235 [PMID: 33429823 DOI: 10.1097/MD.0000000000024235]
7 **Sievert A**, Uber W, Laws S, Cochran J. Improvement in long-term ECMO by detailed monitoring of anticoagulation: a case report. *Perfusion* 2011; **26**: 59-64 [PMID: 21057061 DOI: 10.1177/0267659110385513]
8 **Takei Y**, Ejima Y, Toyama H, Takei K, Ota T, Yamauchi M. A case of a giant cell myocarditis that developed massive left ventricular thrombus during percutaneous cardiopulmonary support. *JA Clin Rep* 2016; **2**: 41 [PMID: 29492436 DOI: 10.1186/s40981-016-0067-0]
9 **O'Gara PT**, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127**: e362-e425 [PMID: 23247304 DOI: 10.1161/CIR.0b013e3182742cf6]
10 **Kleindorfer DO**, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, Lennon O, Meschia JF, Nguyen TN, Pollak PM, Santangeli P, Sharrief AZ, Smith SC Jr, Turan TN, Williams LS. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021; **52**: e364-e467 [PMID: 34024117 DOI: 10.1161/STR.0000000000000375]
11 **Williams B**, Wehman B, Mazzeffi MA, Odonkor P, Harris RL, Kon Z, Tanaka KA. Acute Intracardiac Thrombosis and Pulmonary Thromboembolism After Cardiopulmonary Bypass: A Systematic Review of Reported Cas. *Anesth Analg* 2018; **126**: 425-434 [PMID: 28682954 DOI: 10.1213/ANE.0000000000002259]
12 **Alhussein M**, Moayedi Y, Posada JD, Ross H, Hickey E, Rao V, Billia F. Ventricular Thrombosis Post-Venoarterial Extracorporeal Membrane Oxygenation. *Circ Heart Fail* 2017; **10** [PMID: 28188269 DOI: 10.1161/circheartfailure.116.003757]
13 **Kim BJ**, Song SH, Shin YR, Park HK, Park YH, Shin HJ. Intracardiac Thrombosis Involving All Four Cardiac Chambers after Extracardiac Membranous Oxygenation Associated with MTHFR Mutations. *Korean J Thorac Cardiovasc Surg* 2016; **49**: 207-209 [PMID: 27298801 DOI: 10.5090/kjtcs.2016.49.3.207]
14 **Ogawa S**, Richardson JE, Sakai T, Ide M, Tanaka KA. High mortality associated with intracardiac and intrapulmonary thromboses after cardiopulmonary bypass. *J Anesth* 2012; **26**: 9-19 [PMID: 22005756 DOI: 10.1007/s00540-011-1253-x]
15 **Perri JL**, Wieselthaler GM. Left ventricular thrombus with extracorporeal membrane oxygenation: Novel technique of bronchoscope-guided thrombus retrieval. *JTCVS Tech* 2022; **15**: 130-132 [PMID: 36276696 DOI: 10.1016/j.xjtc.2022.08.008]
16 **Imada T**, Shibata SC, Okitsu K, Fujino Y. Unexpected bioprosthetic mitral valve thrombus during left ventricular assist

device implantation. *JA Clin Rep* 2017; **3**: 15 [PMID: 29457059 DOI: 10.1186/s40981-017-0086-5]

17 **Griffith KE**, Jenkins E, Copenhaver W, Williams DM. Novel use of the AngioVac® system to remove thrombus during simultaneous extracorporeal membrane oxygenation life support. *Perfusion* 2016; **31**: 164-168 [PMID: 26034197 DOI: 10.1177/0267659115589622]

18 **Sangalli F**, Greco G, Galbiati L, Formica F, Calcinati S, Avalli L. Regional thrombolysis with tenecteplase during extracorporeal membrane oxygenation: a new approach for left ventricular thrombosis. *J Card Surg* 2015; **30**: 541-543 [PMID: 25940057 DOI: 10.1111/jocs.12556]

19 **Gong M**, He X, Song J, Zhao B, Shi W, Chen G, Gu J. Catheter-Directed Thrombolysis With a Continuous Infusion of Low-Dose Alteplase for Subacute Proximal Venous Thrombosis: Efficacy and Safety Compared to Urokinase. *Clin Appl Thromb Hemost* 2018; **24**: 1333-1339 [PMID: 29768935 DOI: 10.1177/1076029618775514]

20 **Righini M**, Le Gal G, Bounameaux H. Venous thromboembolism diagnosis: unresolved issues. *Thromb Haemost* 2015; **113**: 1184-1192 [PMID: 25503584 DOI: 10.1160/TH14-06-0530]

21 **Gunnarsson B**, Heard CM, Martin DJ, Brecher ML, Steinhorn RH. Successful lysis of an obstructive aortic and renal artery thrombus in a neonate on extracorporeal membrane oxygenation. *J Perinatol* 2000; **20**: 555-557 [PMID: 11190598 DOI: 10.1038/sj.jp.7200466]

22 **Keric N**, Döbel M, Krenzlin H, Kurz E, Tanyildizi Y, Heimann A, König J, Kempski O, Ringel F, Masomi-Bornwasser J. Comparative analysis of fibrinolytic properties of Alteplase, Tenecteplase and Urokinase in an *in vitro* clot model of intracerebral haemorrhage. *J Stroke Cerebrovasc Dis* 2020; **29**: 105073 [PMID: 32807475 DOI: 10.1016/j.jstrokecerebrovasdis.2020.105073]

23 **Bao H**, Gao HR, Pan ML, Zhao L, Sun HB. Comparative study on the efficacy and safety of alteplase and urokinase in the treatment of acute cerebral infarction. *Technol Health Care* 2021; **29**: 85-90 [PMID: 32925123 DOI: 10.3233/THC-202382]

24 **Kharel S**, Nepal G, Joshi PR, Yadav JK, Shrestha TM. Safety and efficacy of low-cost alternative urokinase in acute ischemic stroke: A systematic review and meta-analysis. *J Clin Neurosci* 2022; **106**: 103-109 [PMID: 36274296 DOI: 10.1016/j.jocn.2022.09.015]

25 **Liu L**, Chen W, Zhou H, Duan W, Li S, Huo X, Xu W, Huang L, Zheng H, Liu J, Liu H, Wei Y, Xu J, Wang Y; Chinese Stroke Association Stroke Council Guideline Writing Committee. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke Vasc Neurol* 2020; **5**: 159-176 [PMID: 32561535 DOI: 10.1136/svn-2020-000378]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3330-3339

DOI: 10.12998/wjcc.v11.i14.3330

ISSN 2307-8960 (online)

CASE REPORT

Successful remimazolam sedation-epidural block in an older patient with severe chronic obstructive pulmonary disease: A case report

Jia-Jia Yu, Huan-Shuang Pei, Yu Meng

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Amornyotin S, Thailand; Han JH, South Korea

Received: February 15, 2023
Peer-review started: February 15, 2023
First decision: March 14, 2023
Revised: March 18, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 16, 2023

Jia-Jia Yu, Huan-Shuang Pei, Yu Meng, Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei Province, China

Corresponding author: Huan-Shuang Pei, MD, Associate Professor, Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, No. 12 Jian-Kang Road, Chang' an District, Shijiazhuang 050000, Hebei Province, China. wxhmz99999@163.com

Abstract

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is associated with high morbidity and mortality rates worldwide. Older patients have a degenerative cardiopulmonary function, weak compensatory capacity, and poor surgical tolerance. Therefore, the mode of anesthesia must be optimized. Remimazolam is a new ultrashort-acting benzodiazepine with a rapid onset of action, rapid metabolism, and mild effects on pulmonary circulation. Remimazolam sedation combined with an epidural block has not been reported in hypertensive older adults with severe COPD and inguinal mass resection.

CASE SUMMARY

We report the case of a 73-year-old man with hypertension and severe COPD, who underwent resection of an enlarged inguinal mass that he had noticed more than 7 mo before presentation. The patient presented with a "right inguinal mass" and was recommended to undergo an enlarged inguinal mass resection. Surgery was relatively challenging, due to the large mass (13 cm × 8 cm × 7 cm), hard texture, and poor mobility. Considering the advanced age of the patient, grade III hypertension, and severe COPD, we administered remimazolam combined with an epidural block for anesthesia to ensure perioperative safety and careful consideration. The anesthetic effect was precise; the procedure was performed smoothly without any complications, and the patient was successfully anesthetized. However, anesthetic management in such cases has not yet been reported by previous studies.

CONCLUSION

Remimazolam sedation combined with an epidural block is safe and effective in older patients with hypertension and severe COPD.

Key Words: Remimazolam; Older adult; Chronic obstructive pulmonary disease; Epidural block; Case report

Core Tip: Chronic obstructive pulmonary disease (COPD) is associated with high morbidity and mortality rates. Older patients have degenerative systems with weak compensatory capacity. Therefore, their status must be carefully evaluated to optimize the anesthesia plan when choosing an anesthetic agent for surgery. Remimazolam sedation combined with an epidural block in older adults with hypertension and severe COPD has rarely been reported. Our management experience shows that remimazolam sedation combined with an epidural block is safe and effective in older adults with hypertension and severe COPD.

Citation: Yu JJ, Pei HS, Meng Y. Successful remimazolam sedation-epidural block in an older patient with severe chronic obstructive pulmonary disease: A case report. *World J Clin Cases* 2023; 11(14): 3330-3339
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3330.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3330

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has high morbidity and mortality rates worldwide. Older patients have degenerative systems and weak compensatory capacity. Therefore, careful assessment of patient status and optimization of anesthesia is required when selecting an anesthetic agent for surgery. The sedative effect of remimazolam is mild in the pulmonary circulation, and a long-term intravenous infusion is nonaccumulative. Flumazenil can reverse this sedative effect by facilitating the response to intraoperative emergencies. Remimazolam sedation combined with an epidural block in older patients with hypertension and severe COPD has not been reported.

In this case report, we describe the anesthetic management of a 73-year-old man with hypertension and severe COPD, who underwent an enlarged inguinal mass resection with remimazolam sedation combined with an epidural block. Based on our experience with this patient, we conclude that remimazolam sedation combined with an epidural block is safe and effective in older adults with hypertension and severe COPD. This report provides new ideas for the safe administration of anesthesia in older patients with severe COPD.

CASE PRESENTATION

Chief complaints

The patient was a 73-year-old man with a height of 169 cm and weight of 48 kg, who presented to the clinic with a complaint of > 7 mo right inguinal mass.

History of present illness

The patient had undergone radical distal major gastrectomy under general anesthesia 7 years ago and was transferred to the intensive care unit for transitional treatment after the operation. The patient recovered well and was discharged.

History of past illness

The patient had a history of hypertension for > 7 years. He was receiving oral reserpine, and blood pressure (BP) control was stable 2 wk before the operation; when reserpine was discontinued, BP control was fair. The patient had no history of coronary heart disease or diabetes mellitus.

Personal and family history

The patient denied any relevant family history of cancer.

Physical examination

On physical examination, the patient's vital signs were as follows: Body temperature (T), 36.6 °C; BP, 145/86 mmHg; heart rate (HR), 62 beats per min; respiratory rate (RR), 16 breaths per min. The patient was conscious, cooperated with physical examinations, and was admitted to the ward. He presented with a barrel chest, low-breath sounds in both lungs, and no wheezing was heard. There was no precordial bulging, with a regular heart rhythm, and no extra heart or pericardial friction sounds were heard. A 13 cm × 8 cm × 7 cm mass with a hard texture, and poor mobility was observed in the right inguinal region.

Laboratory examinations

The results of routine preoperative blood tests, biochemistry tests, coagulation function tests, and other laboratory tests were normal.

Imaging examinations

Chest computed tomography (CT) revealed subpleural inflammation in the lower lobe of the right lung, emphysema, pulmonary bullae, increased translucency in the lower lung fields of both lungs, non-smooth and depressed diaphragms on both sides, a blunt costophrenic angle, and aortic calcification.

Auxiliary tests

Electrocardiography (ECG) showed sinus rhythm, normal ECG, and a 72 beats/min ventricular rate. Echocardiography revealed degenerative aortic valve changes combined with mild regurgitation, reduced left ventricular diastolic function, and a left ventricular ejection fraction of 65%. Pulmonary function showed a forced expiratory volume in 1 s (FEV1): 1.10 L, with a measured value of 43.5% of the expected value, a FEV1/forced vital capacity (FVC) of 62%, and a lung carbon monoxide diffusion to alveolar ventilation ratio of 0.95 L·min^{-1}·mmHg^{-1}, with a measured value of 77.6% of the expected value. The pulmonary function has been reported to include severe obstructive ventilation dysfunction, mildly reduced total diffusion function, severely increased peripheral airway resistance, abnormal small airway function, and severely increased pulmonary elastic resistance (Figure 1).

Preoperative assessment

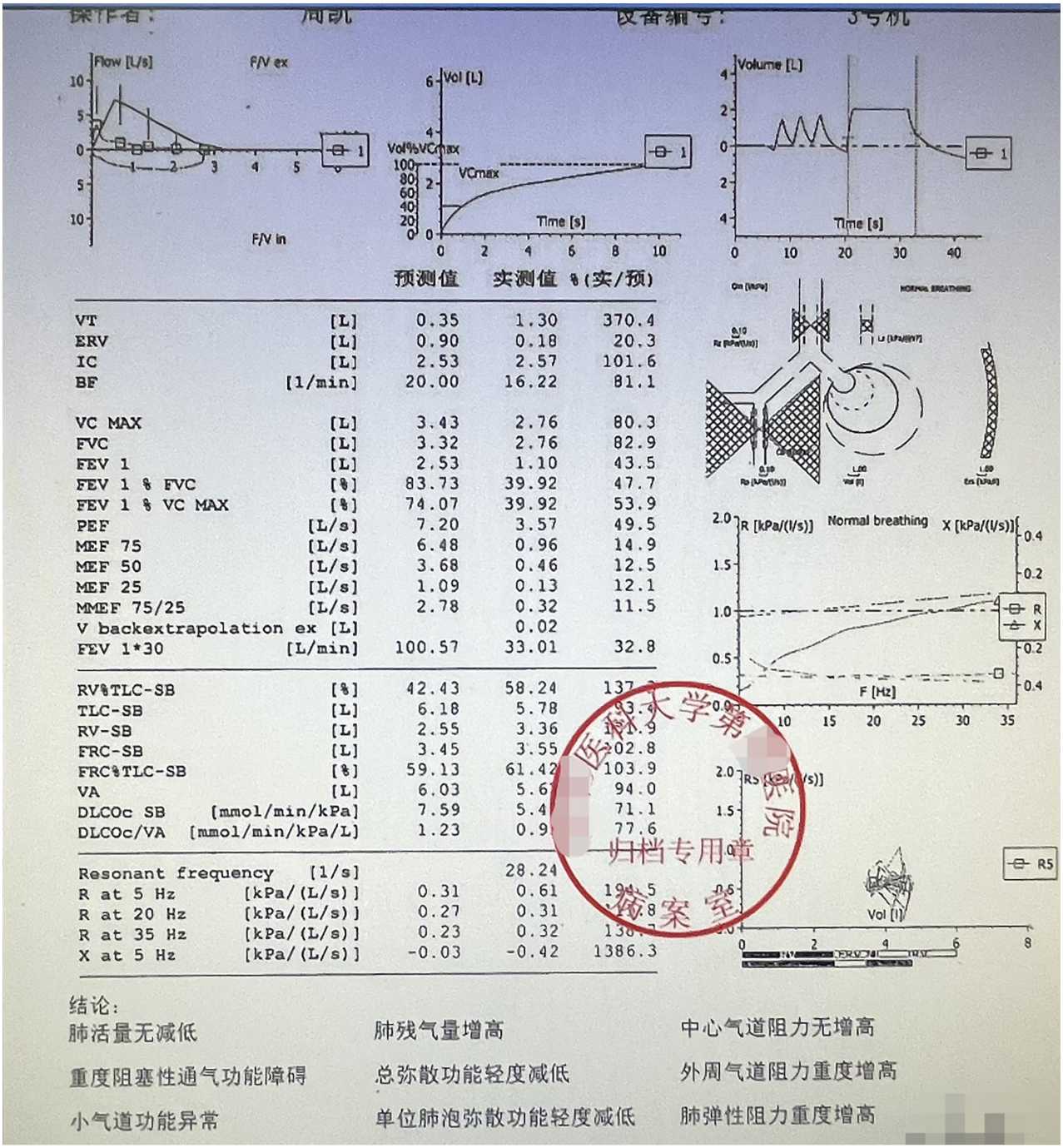
ASA grade III, class II cardiac function, metabolic equivalent of 4 metabolic equivalents, clinical frailty scale grade 4, thyromental distance > 6 cm, mouth opening > 3 fingers, and mallampati grade II.

FINAL DIAGNOSIS

The patient was diagnosed with a right inguinal mass, radical distal gastrectomy, high-risk grade III hypertension, and severe COPD.

TREATMENT

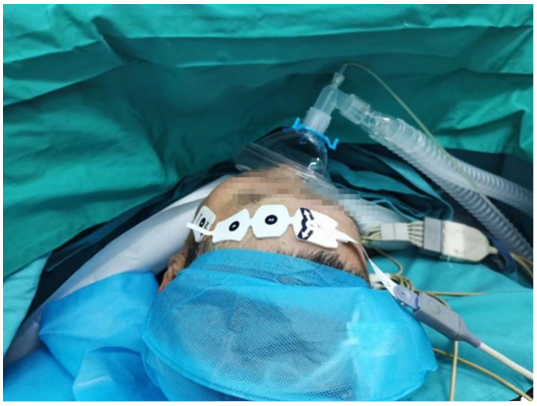
The patient was admitted at 15:40, complaining of extreme nervousness and strongly requesting to be kept asleep during the operation. With the patient's previous history of hypertension and emotional stress following admission, the operator was eager to determine whether the anesthesiologist could provide the patient with moderate sedation to maintain perioperative circulatory stability. Left upper extremity venous access was secured after admission, and cuff BP, ECG, Peripheral capillary oxygen saturation (SpO_2), and bispectral index (BIS) were monitored (BP, 165/85 mmHg; HR, 85 beats/min; RR, 16–18 beats/min; SpO_2, 96%; and BIS, 98). Oxygen was administered at a rate of 6 L/min using a face mask, and sedation was provided with 2 mg remimazolam (ambulatory blood pressure [ABP], 180/90 mmHg; HR, 82 beats/min; RR, 16–18 beats/min; SpO_2, 95%; and BIS, 97). Arterial blood gas metrics on admission were as follows: fraction of inspiration O2 (FiO_2), 0.21; potential of hydrogen, 7.43; pressure of carbon dioxide ($PaCO_2$), 36.3 mmHg; and pressure of oxygen (PaO_2), 69.8 mmHg. At 15:52, BP was 150/84 mmHg, HR was 72 beats/min, SpO_2 was 100%, and BIS was 75–80, with stable spontaneous breathing. During the 8-min observation period, the patient's vital signs remained stable. Induction of anesthesia: epidural puncture and tube placement were performed at 16:00. The patient was placed in the right lateral position, and the median approach was taken. An 18-gauge Tuohy needle was used to puncture the L1-2 intervertebral space, and a negative pressure test was positive. After confirming entry of the puncture needle into the epidural cavity, the epidural catheter was placed headward, the puncture needle was withdrawn, the epidural catheter was fixed at an 8-cm scale, and the patient was placed supine. At 16:10, the epidural catheter was connected to a 5-mL syringe. Blood-free cerebrospinal fluid was withdrawn and injected into the 2% lidocaine test at 16:15. The patients were asked about any complaints of discomfort. His ABP was 140/80 mmHg, 75 beats/min, 16–18 beats/min, SpO_2 was 95%, and BIS was 87. The level of anesthesia block was determined, and an additional 2% lidocaine (6.5 mL was injected *via* the epidural catheter). At 16:25, the level of the anesthesia block was determined again, and 5 mg of remimazolam was injected to sedate the patient. Surgery was initiated at 16:30. To ensure stable intraoperative sedation, remimazolam (40 mg/h) was infused intravenously using a micropump. At 17:05, 5 mL of 2% lidocaine was injected epidurally. At 18:00, the operation was completed, and the intravenous infusion of remimazolam was stopped. Subsequently, 50 mg flurbiprofen was administered. The operation lasted 90 min, with 650 mL crystalloid infusion and blood loss of 50 mL. The operation was performed under rimazolam sedation combined with an epidural block. During the operation, the patient was in a continuous sleep state, during which the BIS was stabilized at shallow sedation, circulation was stable, spontaneous breathing was stable, no hypotension or respiratory



DOI: 10.12998/wjcc.v11.i14.3330

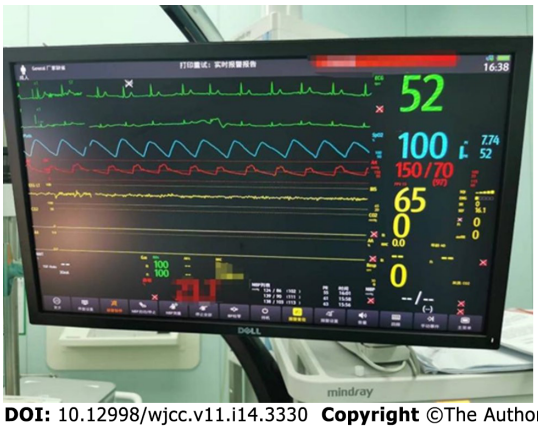
Figure 1 Preoperative pulmonary function.

depression was observed, no vasoactive drugs were applied, no jaw-supporting assisted breathing was performed, the airway tools prepared before the operation were not used, the anesthetic effect was exact, and the operation was completed successfully with complete resection of the right inguinal mass. The intraoperative management metrics were as follows: ABP was maintained at 135–150/80–90 mmHg; HR, 65-75 beats/min; pure oxygen, 5 L/min (administered using a face mask under spontaneous breathing); SpO_2 96–100%; RR, 16–18 beats/min; and BIS fluctuated between 65–80 (Figures 2 and 3). If the systolic BP decreased by > 20% of the basal value or < 100 mmHg, 4 μg of norepinephrine was administered; if the systolic BP increased by > 20% of the basal value or > 180 mmHg, 10–25 mg of uradil was administered; if the HR was < 50 beats/min, 0.3–0.5 mg of atropine was administered, and if the HR was > 100 beats/min, 0.5 mg/kg of esmolol was administered with repeat dosing if necessary. Remimazolam dosage was adjusted according to the BIS, maintaining the BIS fluctuating between 65 and 80 and avoiding too shallow or deep sedation.



DOI: 10.12998/wjcc.v11.i14.3330

Figure 2 Intraoperative status of the patient.



DOI: 10.12998/wjcc.v11.i14.3330

Figure 3 Intraoperative vital signs of the patient.

OUTCOME AND FOLLOW-UP

The patient gained clear consciousness at 18:02; ABP was maintained between 136–148/80–85 mmHg, HR between 70 and 75 beats/min, with stable spontaneous respiration; SpO_2 up to 96% under air inhalation; BIS between 92 and 96; no respiratory distress, nausea, or vomiting; and no complaints of incisional pain, injection pain, dizziness, headache, or other discomforts. The patient's vital signs were stable for 30 min, and he returned to the ward at 18:32. He was discharged 6 d after surgery and followed up for 2 mo after the operation.

DISCUSSION

COPD remains one of the most common and deadly diseases, and is the third leading cause of death globally[1]. COPD is a progressive inflammatory disease characterized by persistent and irreversible airflow limitation (AL), and respiratory symptoms are usually associated with exposure to harmful particles or gases. Patients with COPD are prone to dyspnea due to AL during expiration and inspiration caused by pulmonary lesions or narrowing of the airways in the lungs, generally defined as AL, associated with small airway obstruction and low FEV. COPD is diagnosed in patients with chronic bronchitis and emphysema when AL is present and is not fully reversible[2]. COPD is usually accompanied by an abnormal decline in lung function, and chronic respiratory failure is the leading cause of death. Because patients with COPD have limited lung function, the severity of COPD should be carefully evaluated preoperatively, including comprehensive history, spirometry, and arterial blood gas analysis. Our patient had an FEV1/FVC ratio of 62% and an FEV1 of 1.10 L. As a percentage of the expected value, the measured value was 43.5%, AL was present, chest CT suggested emphysema, and the diagnosis of severe COPD was confirmed.

Surgical operations can cause stress, anxiety, and fear in patients, and hormonal and metabolic changes that affect the autonomic and immune systems of the body, leading to elevated BP, increased HR, elevated blood glucose, and enhanced protein and lipid metabolism and can even lead to

postoperative myocardial injury and cognitive dysfunction, affecting the prognosis of patients[3]. In older patients with hypertension, these stress responses are more likely to lead to dramatic hemodynamic fluctuations, increase the risk of perioperative cardiovascular and cerebrovascular accidents, increase the incidence of postoperative cognitive dysfunction in older patients, and affect patient prognosis. Previous studies have demonstrated a strong link between stress responses and neuronal injury. Excessive inflammatory responses can be generated under intense stress, which in turn, can stimulate neurological injury. This cascade affects homeostasis and aggravates stress responses in patients. Subsequently, an excessive inflammatory response activates the oxidative stress response by expressing various catalytic enzymes[4]. This enhanced inflammatory response induces the acute exacerbation of COPD and aggravates its severity in COPD patients.

This case involved an older adult with hypertension grade III and severe COPD, ASA grade III; a 13 cm × 8 cm × 7 cm mass in the right inguinal region, hard and poorly mobile; and an enlarged right inguinal mass proposed for resection. Patients are at high risk because they are highly stressed after admission. The selection and management of the anesthesia protocol require extra attention to maintain circulatory stability and avoid drastic hemodynamic fluctuations; therefore, it is necessary to provide continuous and precise analgesia and stable sedation to minimize the stress response. As patients also suffer from severe COPD and have a poor pulmonary function, the selection and management of anesthesia should focus on avoiding COPD-triggering factors, reducing the occurrence of perioperative hypoxemia, minimizing the occurrence of perioperative cardiopulmonary disease complications, and improving patient prognosis. Therefore, accurate analgesia and moderate sedation are key to the successful management of this case. For this reason, the design of the anesthesia plan should ensure that the anesthesia method chosen can provide precise and continuous analgesia and can respond to the adjustment of the operation style and operation time; sedation treatment chosen should meet the needs of the patient and the operator while maintaining the stability of the patient's perioperative pulmonary circulation; anesthesia plan chosen should minimize the perioperative COPD triggering factors, avoid the acute exacerbation of COPD and aggravation of COPD, and minimize the perioperative pulmonary complications as the top priority; and strengthen the hemodynamic and depth of sedation monitoring to facilitate individualized and precise anesthesia management.

How do you receive good analgesia? Local, regional blocks, and general and intralesional anesthesia can provide analgesia for inguinal mass resection; however, each has its advantages and disadvantages. For smaller masses, this procedure is routinely performed under local anesthesia. In older patients, local anesthesia can maintain hemodynamic stability and voluntary respiratory function; reduce the risk of tracheal extubation, bronchoconstriction, and respiratory depression after general anesthesia; reduce the need for postoperative mechanical ventilation; reduce postoperative pulmonary complications; and facilitate the reduction of postoperative cognitive dysfunction. However, in this case, the inguinal mass was large, hard, and poorly mobile, and surgery was relatively difficult. Therefore, the analgesic effect of simple local anesthesia is unsatisfactory and significantly reduces patient comfort. Regional nerve block anesthesia slightly affects the body’s pulmonary circulation, but its blocking range is limited; maintaining a long operation time after a single injection is challenging, and it can easily cause tissue damage and complications during the puncture process. General anesthesia has the advantages of rapid onset, high comfort during anesthesia, and no memory of the whole procedure. However, it has a strong inhibitory effect on the patient’s central nervous system, which can easily lead to postoperative cognitive dysfunction and increase the incidence of delirium in older adult patients; general anesthetic drugs have a particular inhibitory effect on cardiovascular vessels. In older adults, owing to degenerative changes in the central nervous and cardiovascular systems, the elasticity of blood vessels becomes poor, which can easily cause hypotension; stimulation, such as tracheal intubation and extubation, can lead to violent circulatory fluctuations, and hemodynamics are very unstable under stress; when endotracheal intubation is performed under general anesthesia, which bypasses the defensive protection of the mouth and nose, the bronchus is directly connected to the outside world. The bacteria and secretions in the oral cavity can easily invade the respiratory tract. The gastrointestinal tract can be easily damaged by muscle relaxation or misuse. When general anesthesia is administered, the respiratory system is affected by using anesthetic drugs that inhibit the efficiency of postoperative sputum excretion and increase the probability of pulmonary infection[5]. Patients with advanced COPD experience adverse consequences following general anesthesia, tracheal intubation, and intermittent positive pressure ventilation. This increases the incidence of postoperative pulmonary complications and the risk of hypoxemia, laryngospasm, pneumatic injuries, bronchospasm, and compromised circulatory stability. In particular, circulatory fluctuations are more likely to occur in older patients with combined underlying diseases, which significantly increase the risk of cardiovascular complications.

Endotracheal anesthesia is advantageous in patients with COPD. However, subarachnoid block anesthesia can cause a series of physiological disturbances, the severity of which is closely related to the block level. A high block level can lead to respiratory and circulatory depression, causing severe hypotension and respiratory muscle paralysis, especially in older patients with hypertension and poor cardiopulmonary function. This makes it challenging to meet the need for prolonged surgery after a single injection. In contrast, epidural block anesthesia provides both definitive analgesia and mild effects on pulmonary circulation, and additional local anesthetics can be added as needed to accommodate prolonged surgery. The patient was diagnosed with an enlarged inguinal mass. Although

the mass was superficial, it was large (13 cm × 8 cm × 7 cm), hard, and poorly mobile. Combined with the fact that this patient was an older adult with grade III hypertension and severe COPD, poor responsiveness to cardiopulmonary function, and weak self-replacement ability, considering the relative difficulty of the operation, the operation time might have been longer, and the operation technique might have to be changed intraoperatively. We concluded that epidural block anesthesia was more advantageous than other anesthetic modalities for resolving analgesia in this patient.

How can good sedation be achieved? Implementation of safe and effective sedation in older patients with hypertension and severe COPD should be considered. Sedation that is too deep increases the risk of respiratory depression, aggravates the degree of COPD, and increases the inhibition of circulation, which is unfavorable for older adult patients with combined hypertension. Sedation that is too shallow results in poor patient cooperation, and the patient is in a state of stress, which is not conducive to circulatory stability and can easily induce an acute COPD attack. Therefore, choosing the appropriate sedative drugs is crucial in maintaining an appropriate sedation depth and ensuring safe and effective sedation. Commonly used sedative drugs, such as propofol and midazolam, and the new drug, dexmedetomidine, have some problems with clinical application. Propofol has a rapid onset of action, short elimination half-life, rapid sleep after intravenous administration, rapid awakening, no post-awakening euphoria, and low incidence of postoperative nausea and vomiting. It can induce amnesia, without any behavioral impairment. However, it causes intravenous pain and can increase stress reactions due to injection pain; it has dose-dependent circulatory and respiratory depressant effects and can cause hypotension, hypoventilation, and even apnea[6]. Because this patient was an older adult with hypertension and severe COPD, propofol could have increased the risk of respiratory and circulatory depression, increased stress response, and precipitated an acute COPD attack. Midazolam is a drug representing the benzodiazepine with sedative, anxiolytic, anticonvulsant, and amnesic effects. However, midazolam may lead to the loss of airway reflexes, increase the risk of respiratory depression or aspiration, and induce delirium to some extent. Prolonged administration can lead to accumulation and delayed sedative effects, which must be antagonized by administering flumazenil, if necessary[7]. Here, we report the case of an older patient with a high risk of delirium who also had severe COPD and poor pulmonary function. The application of midazolam increased the difficulty of respiratory management. Dexmedetomidine is a highly specific alpha-2 agonist with anesthetic, analgesic, and antisympathetic properties. It exerts sedative and weak analgesic effects, without significant respiratory depression. It can produce a unique sedative effect similar to physiological sleep, making it the drug of choice for superficial sedation. However, it is prone to the side-effects of hypotension and bradycardia [8]. Continuous intraoperative intravenous infusions of larger doses of dexmedetomidine can significantly attenuate the body's physiological regulatory response to hypovolemia[9], especially in older patients with hypertension and a vertebral canal. Furthermore, hypotension and sinus bradycardia are more likely to increase in older patients with hypertension and endovascular anesthesia. Additionally, the onset of action of dexmedetomidine is 10–15 min, which is slow and has a long elimination half-life and accumulation effect. Its application in older patients can prolong the action time and increase the safety risks of anesthesia.

Remimazolam is a new ultrashort-acting benzodiazepine, a derivative of midazolam, a drug obtained by introducing a metabolizable methyl propionate side chain to the structure of midazolam, which also acts on γ-aminobutyric acid type A receptors, exerts inhibitory effects on neurons and reduces neuronal excitability[10]. Remimazolam is metabolized by nonspecific plasma esterase hydrolysis and has no cumulative effects. Wiltshire *et al*[11] reported that the average peak blood concentration of 0.01–0.30 mg/kg of remimazolam can be reached in about 1 min with rapid metabolism. Continuous intravenous infusion of remimazolam for 2 h has a maximum half-life of 7–8 min, and flumazenil rapidly reverses its sedative effect. Compared with propofol, remimazolam has a rapid onset of action but does not cause significant respiratory and circulatory depression. Remimazolam has a faster onset of action, stronger sedation, and shorter recovery time. Previous studies have demonstrated that remimazolam is safe for sedation in patients undergoing gastrointestinal endoscopy, with minimal effects on the pulmonary circulation. According to clinical observations, the incidence of hypotension and hypoxemia due to remimazolam administration is extremely low. In addition to its sedative effects, recent animal experiments have suggested that remimazolam also has anti-inflammatory effects. Liu *et al*[12] first found that remimazolam inhibited mitogen-activated protein kinase and phosphoinositide 3-kinase signaling pathway activation and interfered with TLR4 expression associated with Rab5a in the cell surface response to lipopolysaccharides, attenuating the inflammatory response in mouse macrophages. Fang *et al*[13] reported that remimazolam acts dose-dependently by activating peripheral benzodiazepine receptors and inhibiting macrophage p38 phosphorylation, attenuating the inflammatory response in rats with acute liver injury associated with sepsis. These animal studies broadened our understanding of the pharmacological effects of remimazolam, suggesting that it may have anti-inflammatory effects in clinical settings. However, further clinical trials are required to confirm our findings. Future studies on the anti-inflammatory effects of remimazolam in a clinical setting are needed to investigate whether its anti-inflammatory effects can reduce the triggers of acute exacerbations in patients with COPD and produce a more positive effect on perioperative sedation in such patients.

Table 1 Case report timeline

Item		Timeline
Preoperative	1	Discovery of right inguinal mass for > 7 mo
	2	History of hypertension for > 7 years
	3	Pulmonary function was reported to have severe obstructive ventilation dysfunction, mildly reduced total diffusion function, severely increased peripheral airway resistance, abnormal small airway function, and severely increased pulmonary elastic resistance
	4	The operation was performed under remimazolam sedation combined with epidural block anesthesia
Perioperative	5	The patient was admitted to the room at 15:40. The cuff blood pressure, electrocardiograph, saturation of pulse oximetry, and bispectral index was monitored
	6	Invasive blood pressure was monitored and arterial blood gas analysis was conducted. Sedation was provided with 2 mg remimazolam
	7	Induction of anesthesia: epidural puncture and tube placement were performed at 16:00
	8	At 16:25, the level of anesthesia block was determined again, and 5 mg remimazolam was injected to sedate the patient
	9	Surgery was initiated at 16:30
	10	To ensure stable intraoperative sedation, 40 mg/h remimazolam was infused intravenously using a micropump. At 17:05, 5 mL of 2% lidocaine was injected epidurally
	11	At 18:00, the operation was completed
Postoperative	12	The patient gained clear consciousness at 18:02, the patient's vital signs were stable
	13	The patient's vital signs were stable for 30 min, and he was returned to the ward at 18:32
	14	The patient was discharged 6 d after surgery
	15	The patient was followed up 2 mo after the operation

The administration of remimazolam with epidural block anesthesia in older patients with hypertension and severe COPD has not yet been reported. A well-controlled sedative drug is more beneficial for this patient because the intraoperative dosage of sedative drugs can be regulated according to BIS monitoring, especially when intraoperative sedation is too deep and sudden respiratory depression occurs. It is easy to reduce the anesthesia depth immediately and wake up the patient at any time. The administration of effective antagonist drugs can reverse the sedative effect at any time, which was the best choice for this patient. Therefore, the pharmacological effects of remimazolam are theoretically beneficial.

The anesthetic protocol used in the present case involved remimazolam sedation combined with an epidural block. Immediately after entering the room and connecting to the intravenous access, 2 mg remimazolam was injected intravenously to sedate the patient. After testing the level of the anesthetic block, 5 mg remimazolam was added to relieve the patient's nervousness, reduce the stress response, and stabilize pulmonary circulation. Invasive arterial BP and BIS monitoring were performed to facilitate individualized circulation management and regulation of sedation depth. Epidural block anesthesia was selected for the L1-2 interval. A trial dose of 3 mL of 2% lidocaine was injected, and an additional 2% lidocaine (6.5 mL was added after the anesthetic level was determined). Five milliliters of 2% lidocaine were administered epidurally 50 min after epidural block anesthesia, which induced definite analgesia. Continuous intraoperative intravenous infusion of remimazolam (40 mg/h) using a micropump ensured stable intraoperative sedation. Intraoperatively, the patient's vital signs were stable, with BP maintained at 135–150/80–90 mmHg, HR at 65–75 beats/min, SpO_2 between 96% and 100%, and BIS fluctuating between 65 and 80 beats/min. Intraoperative arterial blood gas metrics were as follows: FiO_2, 0.40; pH, 7.40; $PaCO_2$, 41.1 mmHg; and PaO_2, 288.8 mmHg. The operative time was 90 min, and the intravenous infusion of remimazolam was stopped at the end of the operation. The patient gained clear consciousness 2 min after surgery, with a BIS score of 92, stable spontaneous breathing, and stable circulation. Arterial blood gas metrics at the end of the operation were as follows: FiO_2, 0.21; pH, 7.40; $PaCO_2$, 39.2 mmHg; and PaO_2, 139.9 mmHg. After 30 min of observation, the patient's vital signs were stable, and he returned to the ward. His vital signs stabilized after returning to the room. Airway tools and vasoactive drugs prepared before the induction of anesthesia were not used. Upon returning to the ward, the BP was 147/74 mmHg, HR was 70 beats/min, and SpO_2 was 99%. No postoperative anesthesia-related complications were observed. The patient recovered well and was discharged. At the 2-mo postoperative follow-up, the patient did not complain of discomfort. In this case, the successful application of remimazolam sedation and epidural block anesthesia, ensured perioperative safety and provided comfortable anesthesia (Table 1).

CONCLUSION

In conclusion, in the case of an older patient with hypertension and severe COPD who underwent inguinal mass resection, we chose regimazolam sedation combined with an epidural block anesthesia protocol. Under BIS monitoring, a single dose of regimazolam was administered preoperatively, and a continuous intravenous infusion of regimazolam was used intraoperatively, which provided the patient with continuous and stable intraoperative sedation and definitive analgesia, preserving perioperative safety, meeting the patient's comfort needs, and ensuring the successful completion of the surgery. This is a case report, and further clinical trials are required. We expect that the superior pharmacological effects of remimazolam will provide new ideas for developing protocols to induce comfortable anesthesia in such patients.

Remimazolam sedation combined with an epidural block is safe and effective in older adult patients with hypertension and severe COPD.

FOOTNOTES

Author contributions: Yu JJ and Meng Y participated in anesthesia management in the present case, and both were major contributors to this manuscript; Pei HS helped revise the manuscript; and all authors have read and approved the final version of the manuscript.

Informed consent statement: The patient profiled in this case report provided written informed consent for the anonymized publication of his case report findings and all accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Jia-Jia Yu 0000-0002-6865-3580; Huan-Shuang Pei 0000-0002-9064-0233; Yu Meng 0000-0001-5678-237X.

S-Editor: Liu XF
L-Editor: Filipodia
P-Editor: Chen YX

REFERENCES

1 **Sandelowsky H**, Weinreich UM, Aarli BB, Sundh J, Høines K, Stratelis G, Løkke A, Janson C, Jensen C, Larsson K. COPD - do the right thing. *BMC Fam Pract* 2021; **22**: 244 [PMID: 34895164 DOI: 10.1186/s12875-021-01583-w]
2 **Fazleen A**, Wilkinson T. Early COPD: current evidence for diagnosis and management. *Ther Adv Respir Dis* 2020; **14**: 1753466620942128 [PMID: 32664818 DOI: 10.1177/1753466620942128]
3 **Xiong MY**, Fu TT, Liu JD, Wang XH, Tao Z, Chen SB. Effect of serratus anterior plane block on stress response and postoperative analgesia in patients undergoing thoracoscopic cardiac surgery under cardiopulmonary bypass. *J Clin Anesthesiol* 2022; **38**: 1066-1070
4 **Fang Q**, Wang YL, Zhang ZZ, Wang HY, Luo H, Song XM. Correlation between different anesthesia methods and outcomes after hip replacement in elderly patients. *J Clin Anesthesiol* 2020; **36**: 971-974 [DOI: 10.12089/jca.2020.10.008]
5 **Chen W**, Chen JJ, Kong JH. Effects of transversus abdominis plane block combined with intravenous injection of hydromorphone on stress response and postoperative analgesia in patients undergoing laparoscopic colorectal cancer surgery. *J Clin Anesthesiol* 2022; **38**: 1025-1030 [DOI: 10.12089/jca.2022.10.003]
6 **Veselis RA**, Pryor KO, Reinsel RA, Mehta M, Pan H, Johnson R Jr. Low-dose propofol-induced amnesia is not due to a failure of encoding: left inferior prefrontal cortex is still active. *Anesthesiology* 2008; **109**: 213-224 [PMID: 18648230 DOI: 10.1097/ALN.0b013e31817fd8ae]
7 **DAS-Taskforce 2015**, Baron R, Binder A, Biniek R, Braune S, Buerkle H, Dall P, Demirakca S, Eckardt R, Eggers V, Eichler I, Fietze I, Freys S, Fründ A, Garten L, Gohrbandt B, Harth I, Hartl W, Heppner HJ, Horter J, Huth R, Janssens U, Jungk C, Kaeuper KM, Kessler P, Kleinschmidt S, Kochanek M, Kumpf M, Meiser A, Mueller A, Orth M, Putensen C, Roth B, Schaefer M, Schaefers R, Schellongowski P, Schindler M, Schmitt R, Scholz J, Schroeder S, Schwarzmann G, Spies C, Stingele R, Tonner P, Trieschmann U, Tryba M, Wappler F, Waydhas C, Weiss B, Weisshaar G. Evidence and

consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) - short version. *Ger Med Sci* 2015; **13**: Doc19 [PMID: 26609286 DOI: 10.3205/000223]

8 **Bailard NS**, Ortiz J, Flores RA. Additives to local anesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations. *Am J Health Syst Pharm* 2014; **71**: 373-385 [PMID: 24534592 DOI: 10.2146/ajhp130336]

9 **Wu XM**, Xue ZG, Ma H, Wang G, Shi XY, Huang SQ, Li WZ, Wang TL, Li LH, Zhang MZ, Yu WF, Li J, Huang WQ. Expert consensus on the clinical application of dexmedetomidine (2018). *J Clin Anesthesiol* 2018; **34**: 820-823 [DOI: 10.12089/jca.2018.08.024]

10 **Sneyd JR**, Rigby-Jones AE. Remimazolam for anaesthesia or sedation. *Curr Opin Anaesthesiol* 2020; **33**: 506-511 [PMID: 32530890 DOI: 10.1097/ACO.0000000000000877]

11 **Wiltshire HR**, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg* 2012; **115**: 284-296 [PMID: 22253270 DOI: 10.1213/ANE.0b013e318241f68a]

12 **Liu X**, Lin S, Zhong Y, Shen J, Zhang X, Luo S, Huang L, Zhang L, Zhou S, Tang J. Remimazolam Protects Against LPS-Induced Endotoxicity Improving Survival of Endotoxemia Mice. *Front Pharmacol* 2021; **12**: 739603 [PMID: 34867346 DOI: 10.3389/fphar.2021.739603]

13 **Fang H**, Zhang Y, Wang J, Li L, An S, Huang Q, Chen Z, Yang H, Wu J, Zeng Z. Remimazolam reduces sepsis-associated acute liver injury by activation of peripheral benzodiazepine receptors and p38 inhibition of macrophages. *Int Immunopharmacol* 2021; **101**: 108331 [PMID: 34810122 DOI: 10.1016/j.intimp.2021.108331]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3340-3350

DOI: 10.12998/wjcc.v11.i14.3340

ISSN 2307-8960 (online)

CASE REPORT

De novo mutation of *NAXE* (*APOAIBP*)-related early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy-1: A case report

Le Ding, Ting-Ting Huang, Guo-Huan Ying, Shang-Yu Wang, Hai-Feng Xu, Hao Qian, Faiza Rahman, Xiao-Peng Lu, Hu Guo, Guo Zheng, Gang Zhang

Specialty type: Clinical neurology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lucke-Wold B, United States; Reis F, Brazil

Received: February 16, 2023
Peer-review started: February 16, 2023
First decision: March 14, 2023
Revised: March 26, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Le Ding, Ting-Ting Huang, Guo-Huan Ying, Shang-Yu Wang, Hai-Feng Xu, Hao Qian, Xiao-Peng Lu, Hu Guo, Guo Zheng, Gang Zhang, Department of Neurology, Children's Hospital of Nanjing Medical University, Nanjing 210008, Jiangsu Province, China

Faiza Rahman, Rehman Medical Institute Peshawar, Peshawar 39250, Pakistan

Corresponding author: Gang Zhang, MD, PhD, Doctor, Department of Neurology, Children's Hospital of Nanjing Medical University, No. 72 Guangzhou Road, Nanjing 210008, Jiangsu Province, China. zhanggangnjmu@126.com

Abstract

BACKGROUND

Early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy-1 (PEBEL1) is a rare autosomal recessive severe neurometabolic disease. The aim of this study was to investigate the clinical characteristics and genetic pathogenicity of PEBEL1 caused by rare *NAXE* (or *APOA1BP*)-related defects.

CASE SUMMARY

The patient was a girl aged 2 years and 10 mo. She was hospitalized due to walking disorder for > 40 d. The clinical manifestations were ataxia, motor function regression, hypotonia, and eyelid ptosis. Within 1 mo of hospitalization, she developed sigh breathing, respiratory failure, cerebellar edema and brain hernia, and finally she died. Changes were found in cranial imaging, including cerebellar edema accompanied by symmetrical myelopathy. Through whole exome sequencing, we detected *NAXE* compound heterozygous variation (NM 144772.3) c.733A>C (p. Lys245Gln, dbSNP: rs770023429) and novel variation c.370G>T (p.Gly124Cys) in the germline gene. The clinical features and core phenotypes of this case were consistent with 18 previously reported cases of PEBEL1.

CONCLUSION

This is the first case of NAXE-related PEBEL1 with severe clinical phenotype in Mainland China. The p.Gly124Cys mutation discovered in this case has enriched the pathogenic variation spectrum of *NAXE*.

Key Words: Encephalopathy; Respiratory insufficiency; Cerebral edema; *NAXE* gene; *APOAIBP* gene; Novel variation; Case report

Core Tip: We report a girl with early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy-1 (PEBEL1), and review the reported cases in the literature. The disease has rapid progression with an unfavorable prognosis. Gene detection is the only diagnostic method. We report the first case of PEBEL1 with severe clinical phenotype in Mainland China.

Citation: Ding L, Huang TT, Ying GH, Wang SY, Xu HF, Qian H, Rahman F, Lu XP, Guo H, Zheng G, Zhang G. *De novo* mutation of *NAXE* (*APOAIBP*)-related early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy-1: A case report. *World J Clin Cases* 2023; 11(14): 3340-3350
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3340.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3340

INTRODUCTION

Early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy 1 (PEBEL1, OMIM: #617186) is a rare autosomal recessive severe neurometabolic disease[1]. At present, more than 10 cases have been reported worldwide since 2016[1-3], but only one case has been reported in China. In this study, the clinical data of a child with PEBEL1 treated in the Department of Neurology, Children's Hospital Affiliated to Nanjing Medical University in July 2021 were retrospectively analyzed, and the related literature was reviewed to improve the understanding, diagnosis, and treatment of the disease.

CASE PRESENTATION

Chief complaints

The patient was a girl aged 2 years and 10 mo. She was hospitalized because of walking disorder for > 40 d.

History of present illness

Forty days ago, she presented with unstable walking and was suspected of having synovitis and stayed in bed at home. She had an episode of fever 30 d prior to that, and the fever spike was 38°C. Blood examination in the outpatient clinic showed leukocytosis, and the fever subsided after oral administration of cephalosporin for 1 wk. During this period, the patient did not leave bed or walk again. Two weeks ago, she developed binocular movement disorder, slow eyeball pursuit, and slight drooping eyelids. Gradually, the patient had wobbling in sitting, and resisted sitting, and cried when urinating, so she was admitted to hospital.

History of past illness

There was a sudden suspicious episode of choking during a meal 3 mo ago, with gaze, unconsciousness, and clenched teeth for 6-7 min, which was relieved after patting on the back and vomiting. There was no abnormality in computed tomography (CT) examination of the head and chest in the local hospital. She was scratched by a cat 2 mo ago and was injected with rabies vaccine three times in 2 wk. Fifty days ago, she suddenly developed generalized weakness and bowed her head during playing, and then her limbs became stiffer, which lasted for about 1 min, followed by vomiting and incontinence. The follow-up was as usual, and the parents made an appointment for a video electroencephalogram examination, which was not done because the patient was immobilized at home.

Personal and family history

There was no special personal history, and the milestone of intellectual and motor development was normal since childhood. Her parents were in good health and denied any consanguinity. The 11-year-old brother also was in good health.

Physical examination

There was no special personal history, and the milestone of intellectual and motor development was

normal since childhood. Her parents were in good health and denied any consanguinity. The 11-year-old brother also was in good health.

Laboratory examinations

After admission, blood routine tests were done. Biochemical studies, blood ammonia, blood lactic acid, erythrocyte sedimentation rate, procalcitonin, six items of coagulation, complete set of autoantibodies, cellular immunity, humoral immunity, four items of infectious diseases, and seven items of thyroid function tests were normal. Screening of hereditary metabolic diseases in hematuria was not abnormal. Four items of tumor: nonspecific enolase was 40.33 ng/mL (0–16.3 ng/mL), a-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9 were normal. Cerebrospinal fluid biochemistry showed: protein 0.27 g/L and glucose 4.82 mmol/L. Routine cerebrospinal fluid analysis showed: nucleated cell count 3×10^6/L; cerebrospinal fluid-MP, epidermolysis bullosa, cytomegalovirus and herpes simplex virus deoxyribonucleic acid was negative; cerebrospinal fluid and blood autoimmune encephalitis antibody, central demyelination antibody, and peripheral nerve disease spectrum antibody were negative; and cerebrospinal fluid pathogen macro gene was negative.

Imaging examinations

Plain CT of the chest and abdomen showed no abnormalities, with normal abdominal contents and obvious bladder filling. No abnormality was found in skull magnetic resonance imaging (MRI), magnetic resonance (MR) angiography and MR venography on day 2 after admission, and spinal MRI showed T2 high signal in the spinal cord at the T7–10 level (poor coordination, heavy artifact) (Figure 1). Electroencephalography showed background moderation, poor rhythmicity and responsiveness, with spike waves and spike slow waves in bilateral anterior and middle temporal regions during sleep, which were not synchronized between left and right.

Further diagnostic work-up

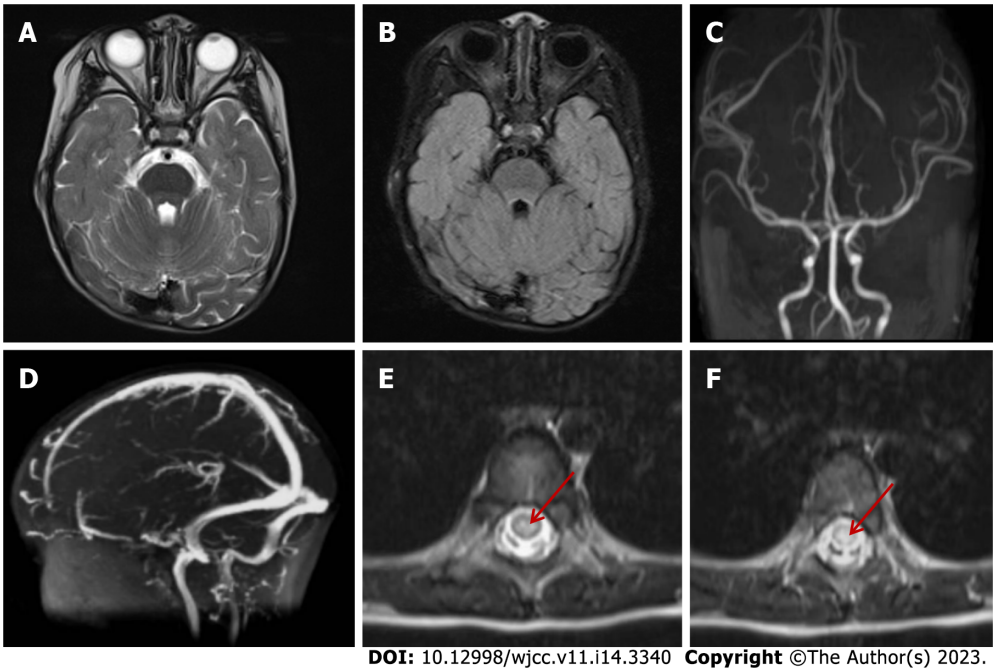
With the approval of the Medical Ethics Committee of the hospital (approval number: 202111116-1) and the informed consent of the guardians of the child, 2 mL peripheral blood from the patient and her parents were taken for whole exome sequencing (Beijing Zhiyin Dongfang). The whole-exome library was constructed using xGen ®Exome Research Panel v1.0 (IDT, United States) capture probe, and the NovaSeq 6000 (Illumina, United States) series sequencer was used for high-throughput sequencing. The compound heterozygous mutations c.733A>C (p.Lys245Gln, dbSNP: rs770023429) and c.370G>T (p.Gly124Cys) in *NAXE* (*APOA1BP*) inherited from her parents were identified and verified by Sanger sequencing (Figure 2). According to the American Society of Medical Genetics 2015[3], Lys245Gln (reported in the PS1+PM1, gnomAD East Asia MAF: 0.0019, PEBEL1 case[4]) was likely pathogenic and Gly124Cys (PM1+PM2+PP3, no MAF record) was annotated as unknown pathogenicity variation. The variant amino acid residues were analyzed using VarSite (https://www.ebi.ac.uk/thornton-srv/databases/VarSite); a variant analysis tool provided by European Institute of Bioinformatics, and the two variants were both highly evolutionarily conservative (Figure 3). The conservatism of Lys245Gln in 174 homologous sequences was 0.5, which was lower than that of Gly124Cys in 190 homologous sequences (0.1). Using SWISS-MODEL and Swiss-pdb Viewer software to predict the pathogenicity of the mutation sites, the protein structure, the residues of the mutation site, and the functional sites nearby, it is suggested that the possible pathogenicity, c.733A>C site is shown in Figure 4, c.370G>T mutation site is shown in Figure 5.

FINAL DIAGNOSIS

The patient was diagnosed with PEBEL1.

TREATMENT

After admission, a detailed examination was done and the patient was treated with acyclovir, dexamethasone (0.5 mg/kg), gammaglobulin (2 g/kg), and other anti-inflammatory drugs. Urinary retention occurred on the day 3 and indwelling catheterization was performed. On day 5, the patient developed confusion, irregular respiratory rhythm, and poor response, and was transferred to the pediatric intensive care unit. This was followed by a decrease in heart rate and blood oxygen saturation, and she received cardiopulmonary resuscitation and mechanical ventilation. Nutritional support with levocarnitine and coenzyme Q10 was given, and simultaneous high-dose methylprednisolone (20 mg/kg) was given for 3 d, and plasma exchange was performed for 2.5 h on day 10. Bilateral pupil dilation, the disappearance of light reflex and deep coma appeared on day 12. Cranial CT suggested diffuse cerebellar swelling with hydrocephalus and ventricular dilatation, and further improvement of cranial CT angiography enhancement suggested an unclear display of straight sinus and no significant



DOI: 10.12998/wjcc.v11.i14.3340

Figure 1 The imaging findings of brain and spinal cord magnetic resonance on day 2 after admission. A and B: T2-weighted magnetic resonance imaging and fluid-attenuated inversion-recovery imaging of the head, respectively, showed no abnormal signals in the brainstem, cerebellum, and cerebral cortex; C: Magnetic resonance arterial angiography of the head was normal; D: Brain magnetic resonance venography was normal; E and F: T2 hyperintensity in T7-10 horizontal transverse section of thoracic spinal cord (indicated by red arrow).

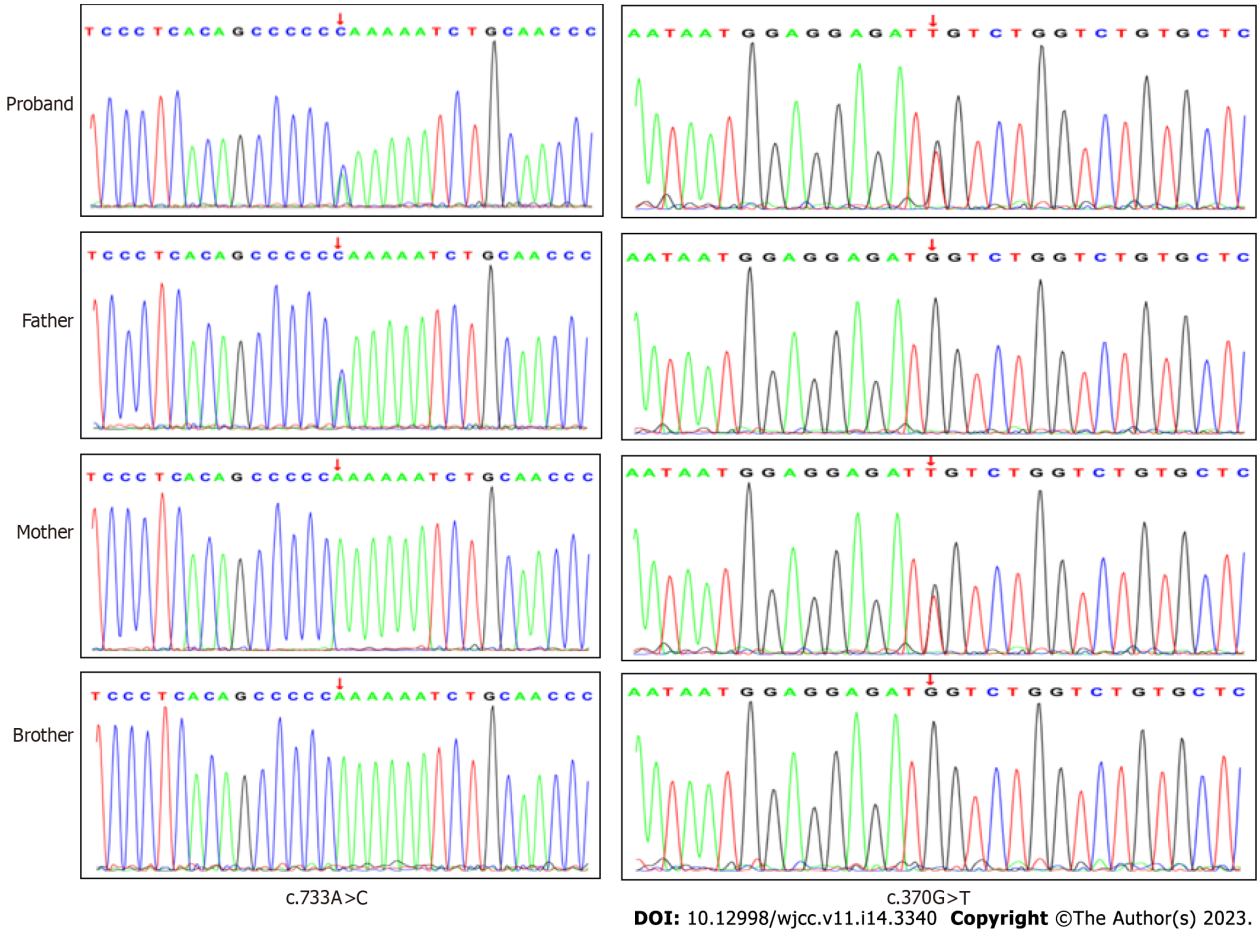
parenchymal enhancing mass shadow was seen (Figure 6). On day 14, after multidisciplinary team discussion, intraventricular drilling and drainage, and intracranial pressure probe implantation were performed. About 100 mL cerebrospinal fluid was drained after surgery, and the intracranial pressure was maintained at 20–74 mmHg. On day 17, whole exosome sequencing detected *NAXE* compound heterozygous mutation, and we added 100 mg nicotinamide intravenous drip. The patient gradually deteriorated and developed a slow heart rate, hypotension, central diabetes insipidus and electrolyte disturbance, and was treated with symptomatic support such as volume expansion, plasma, albumin, electrolyte supplement, blood transfusion, and maintenance of blood pressure using dopamine, norepinephrine, epinephrine, and posterior pituitary hormone. On day 26, cerebral MRI showed cerebellar swelling, possible herniation of the cerebellar curtain notch, and multiple abnormal signals in the brain parenchyma and cervical spinal cord (Figure 7).

OUTCOME AND FOLLOW-UP

After 30 d, the child became brain dead and her parents abandoned treatment.

DISCUSSION

PEBEL1 is a rare fatal encephalopathy caused by a double allele mutation of *NAXE* (*APOA1BP*) on chromosome 1q22. In 2016, Spiegel[2] reported for the first time that five children from Israel, who were near relatives were affected. The age at onset was 6-12 mo, with loss of motor function after infection, bedridden at the age of 2 years, mechanically ventilated, and finally in a vegetative state. Four patients died between 1 and 3 years of age, and one child was supported by a ventilator until 5.5 years of age, and MRI revealed deep white matter lesions. Kremer *et al*[1] summarized the clinical features of five patients who presented with infantile/early childhood onset, usually caused by fever with rapidly progressive deterioration of neurological function. The patients showed muscular hypotonia, motor development regression, cognitive loss, ataxia, nystagmus, seizures, quadriplegia, and respiratory failure, which eventually led to a vegetative state and brain death. Brain and spinal cord imaging may show white matter abnormalities, cerebral atrophy, cerebellar edema, and myelopathy. It has also been reported[1] that a large area of subacute bullous dermatosis occurred within a few weeks after the onset of neurological symptoms.



DOI: 10.12998/wjcc.v11.i14.3340

Figure 2 Verification of *NAXE* (NM_144772.3) complex heterozygous variation in the patient by Sanger sequencing.

The keywords NAXE, APOAIBP, NAD(P)HX epimerase and AIBP were searched in PubMed, ClinVar, Wanfang, and CNKI, and papers with clear clinical data were selected. As of October 2021, 17 reported pathogenic *NAXE* variants in 12 cases had been collected (Table 1). These included 11 missense mutations (Glu85Asp, Ala94Asp, Gly121Arg, Arg129Pro, Gly189Ser, Ile214Val, Ile214Ser, Asp218Asn, Asp218Val, Lys245Gln and Gly253Ser, 64.7%, 11/17), two splice site mutations (c. 516+1G>A and c. 665-1G>A, 11.8%, 2/17), two nonsense mutations (Tyr59Ter and Gln66Ter,11.8%,2/17), one frameshift mutation (Ala248fs, 5.9%, 1/17), and one deletion/insertion mutation (c.804_807delinsA/Lys270del, 5.9%, 1/17)[1,2,4-7]. The Lys245Gln detected in the present case was the reported homozygous pathogenic variant[4]. The clinical characteristics of the present case and 18 previous cases from 12 families are summarized as follows[1-8]. The age of onset of PEBEL1, except for a German family with two girls who developed the disease at the age of 20 and 22 years, respectively[4], was < 3 years in 89% of the patients (17/19). Most cases were induced by febrile infection (58%, 11/19). The main manifestations were rapidly progressive or recurrent respiratory insufficiency (79%, 15/19), motor cognitive regression (79%, 15/19), decreased muscle strength and muscle tone (79%, 15/19), ataxia (42%, 8/19), nystagmus (32%, 6/19), strabismus (21%, 4/19), seizures (21%,4/19), bilateral blepharoptosis (11%, 2/19), dysarthria and dysphagia (21%, 4/19), and skin erythema rash (11%, 2/19). Eleven of the 19 patients had brain MRI changes, including brain edema (55%, 6/11), brain white matter abnormalities (27%, 3/11), brain atrophy (27%, 3/11), myelopathy (27%, 3/11), cortical and basal ganglia lesions (10%, 1/11), and brain stem and intracranial hemorrhage (10%, 1/11). The cerebrospinal fluid lactic acid test was elevated in seven of the 19 cases, (71%, 5/7), and 12 of 19 cases died of end-stage coma within 3 years of age (63%, 12/19).

In the present case, the patient had normal development since childhood and had a history of rabies vaccination in the early stage of onset, and the nervous system symptoms were gradually aggravated after fever. It was possible to be misdiagnosed as an immune inflammatory disease; however, the condition still deteriorated rapidly after active immunotherapy, with respiratory failure, cerebellar edema, and cerebral herniation, which posed major challenges to clinicians. Carefully combing the medical history, we found that the patient had two paroxysmal events within 3 mo of PREBLE1 onset, which were suspected to be epileptic seizures. Physical examination on admission showed that the patient had droopy eyelids, eye movement disorder, and hypotonia of the extremities, and the pathological reflex was positive and the spinal cord lesions were symmetrical. Due to the rapid change

Table 1 General situation and clinical features of our case and 12 previously reported cases

	Ref.	Gender	Nationality	*NAXE* variation	Age at onset	Age at death	Inducement	Clinical characteristics	MRI features
1	This study	F	China	p.Lys245Gln; p.Gly124Cys	2 yr 10 mo	3 yr	Fever	Respiratory insufficiency, motor regression, poor eye contact, hypotonia, dysphagia, nystagmus, drowsiness, bilateral ptosis	Cerebellar edema, myelopathy
2	[1]	M	China	p.Glu85Asp; p.Gly121Arg	2 yr	Unknown	Fever/infection	Decreased muscle tone of the extremities, weakening abdominal wall reflex and cremaster reflex, unsteady walking, finger-nose test and Romberg sign positive	Brain atrophy
3	[6]	M	Iran	p.Gly189Ser	2 yr	3 yr	Unknown	Neuromotor development and cognitive regression, unclear speech, uncoordinated hand movement, nystagmus, poor coordination, impaired finger–nose test, increased lactic acid in cerebrospinal fluid	Bilateral temporal cortex, basal ganglia lesions
4	[2]	M	Turkey	p.Arg129Pro; p.Ile214Ser	1.5 yr	3 yr	Unknown	Cognitive impairment, axial dystonia, quadriplegia, strabismus, increased deep tendon reflex of lower extremities, ankle clonus, bilateral Babinski sign positive	Not significant
5-1	[5]	F	Germany	c.665-1G>A; p.Gly253Ser	22 yr	> 29 yr	Unknown	Recurrent illness, initial headache, respiratory insufficiency, developmental disabilities, seizures, myoclonus, comatose state, cerebellar ataxia, spastic quadriplegia, dysarthria, dysphagia, cervical dystonia, non-infectious fever, psychiatric symptoms	Not significant
5-2	[5]	F	Germany	c.665-1 G>A; p.Gly254Ser	20 yr	22 yr	Alcohol, cannabis	Recurrent illness, initial headache, respiratory insufficiency, comatose state, cerebellar ataxia, cognitive impairment, myoclonus, nystagmus, diplopia, neuropsychiatric symptoms, hypokinesia	Not significant
6	[5]	M	Saudi Arabia	p.Lys245Gln	Unknown	Unknown	Unknown	Respiratory insufficiency, progressive motor development delay, dystonia, septicemia	Unknown
7	[5]	M	Jordan	p.Asp218Asn	1 d	Unknown	Unknown	Respiratory insufficiency, coma, developmental disabilities, hypodystonia, strabismus, bradycardia, decreased serum creatinine, hypoventilation, thrombocytosis, mitral regurgitation	White matter abnormalities, brainstem MRI signal intensity abnormalities, intracranial hemorrhage, brain atrophy
8	[5]	M	India	p.Ile214Val	Unknown	Unknown	Unknown	Developmental disabilities, elevated lactic acid in cerebrospinal fluid, pigmented retinopathy, elevated serum creatine phosphokinase	
9	[3]	M	Gambia	p.Tyr59Ter	20 mo	21 mo	Fever/infection	Recurrent illness, respiratory insufficiency, coma, ataxia, seizures, bullous dermatosis, elevated lactic acid in cerebrospinal fluid and blood, quadriplegia, nystagmus, torticollis	Cerebral edema, myelopathy
10	[3]	F	Croatia	p.Gln66*, c.516+1G>A	15 mo	2 yr	Fever/infection	Recurrent illness, respiratory insufficiency, coma, delayed psychomotor development, tremor, ataxia, dystonia, edema	Cerebral edema, brain atrophy, myelopathy

								and erythema rash, elevated lactic acid in cerebrospinal fluid	
11	[3]	M	Germany	p.Lys270del	16 mo	18 mo	Fever/infection	Rapid progression, respiratory insufficiency, progressive ataxia, developmental disabilities, coma, elevated cerebrospinal fluid lactic acid, nystagmus, bilateral ptosis	Cerebral edema
12-1	[3]	M	Poland	p.Asp218Val; p.Ala248fs	16 mo	29 mo	Unknown	Recurrent illness, respiratory insufficiency, coma, ataxia, dystonia, focal redness, skin changes in psoriasis of the neck, increased lactic acid in cerebrospinal fluid, dysarthria, nystagmus	Cerebral edema
12-2	[3]	M	Poland	p.Asp218Val; p.Ala248fs	8 mo	2 yr	Unknown	Recurrent illness, respiratory insufficiency, coma, seizures, dystonia, elevated lactic acid in cerebrospinal fluid	Brain dysplasia, acute hydrocephalus

F: Female; M: Male; MRI: Magnetic resonance imaging.

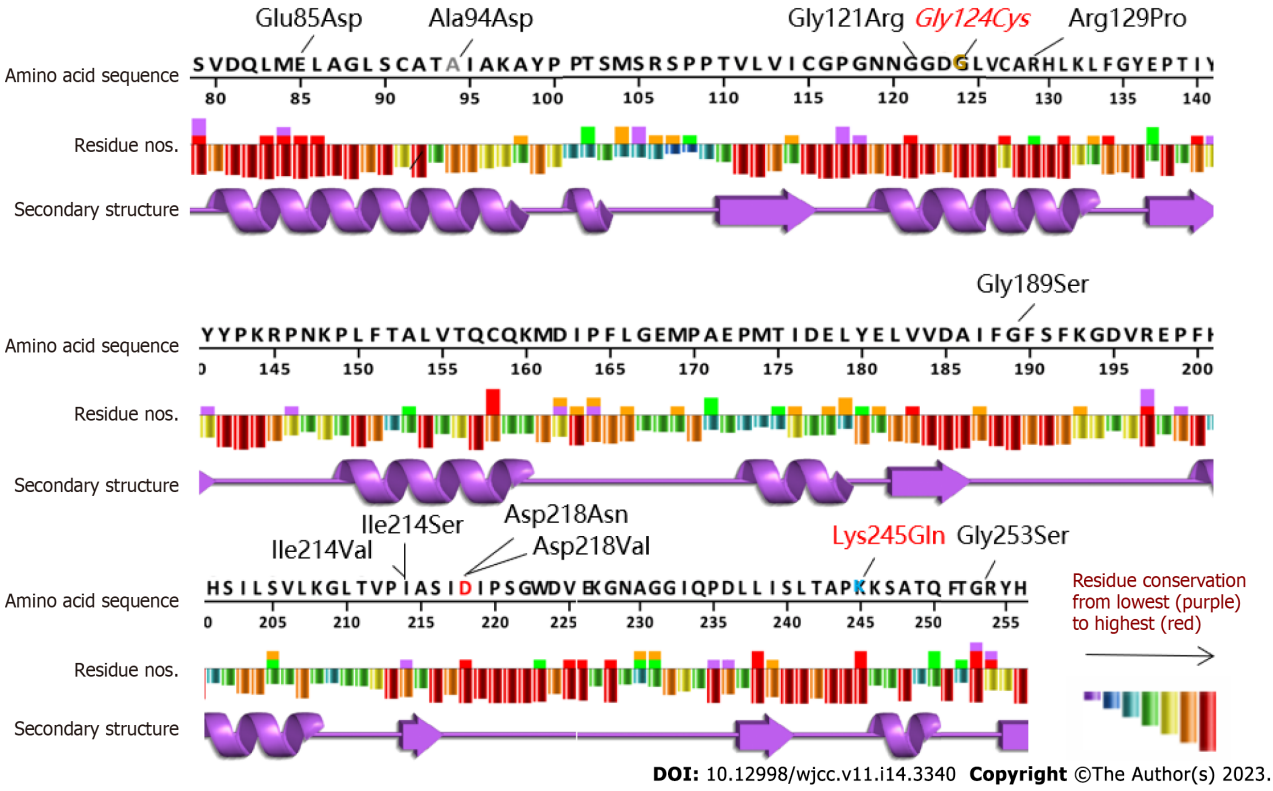
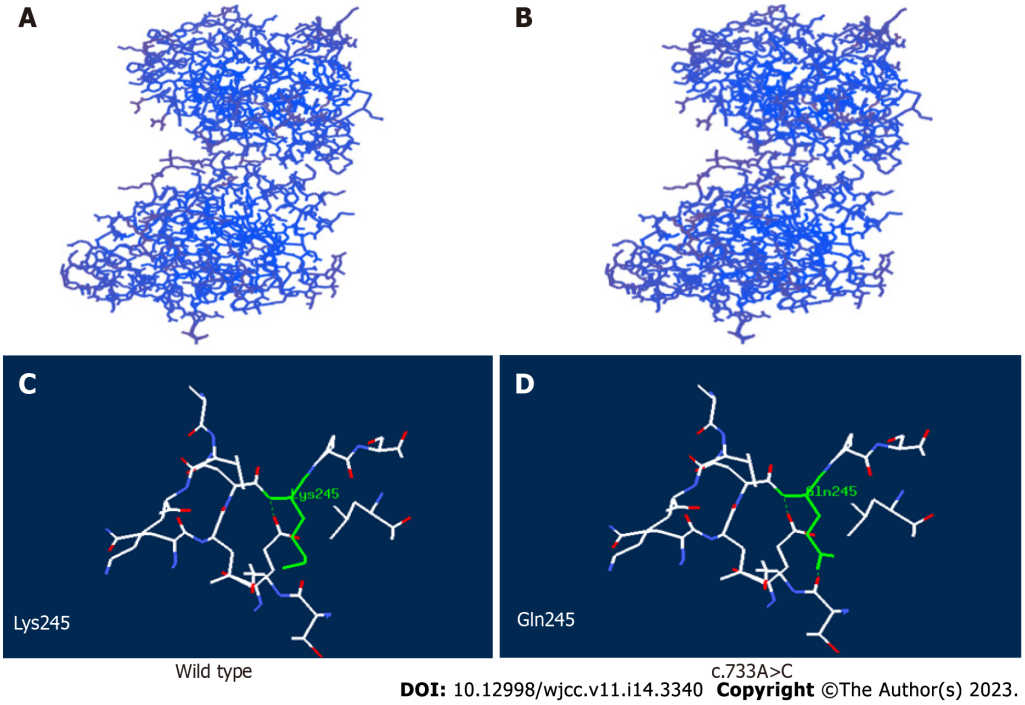


Figure 3 Conservative analysis of *NAXE* variation sites. The variants are indicated in red, and the new variants are expressed in italics. The analysis tool used EMBL-EBI VarSite (https://www.ebi.ac.uk/thornton-srv/databases/VarSite) and compared > 100 homologous sequences in different species.

of the disease, electromyographic examination was not conducted, and it was necessary to be alert to the possibility of hereditary metabolic diseases (mitochondria), so gene detection was performed as soon as possible. The clinical features, imaging findings, and disease progression of the child were consistent with the characteristics of PEBEL1.

The human nicotinamide nucleotide repair system consists of two chaperone enzymes: NAD(P)HX differential isomerase (NAXE, formerly known as APOA1BP, OMIM:608862), which converts R-NAD(P)HX to S-NAD(P)HX, and the NAD(P)HX dehydratase (NAXD, formerly CARKD, OMIM:615910), which converts SNAD(P)HX back to NAD(P)H[9] in an ATP-dependent manner. The presence of NAD(P)HX repair enzymes in all tissues and species, coupled with the core metabolism of their cofactors which play a protective role, suggests that the repair system is essential for life maintenance[10].



DOI: 10.12998/wjcc.v11.i14.3340

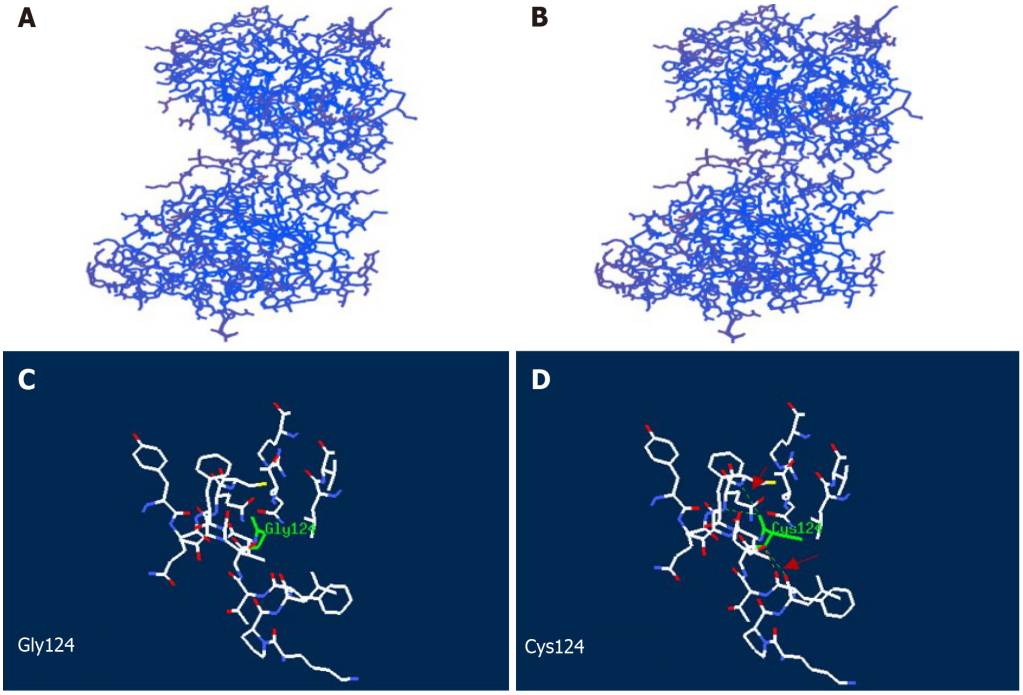
Figure 4 Structural analysis of wild-type and the variant *APOA1BP* with c.733A>C mutation. A: The three-dimensional structure of wild-type (WT); B: The three-dimensional structure of the mutant; C: The residue of missense mutant site together with the nearby functional site of WT; D: The residue of missense mutant site together with the nearby functional site of the mutant. Residues of the mutant sites are highlighted in green.

The *NAXE* (*APOAIBP*) gene encodes NAD(P)HX differential isomerase or apolipoprotein AI binding protein (AIBP), located on the 1q22 chromosome. There are five transcripts, including six exons (https://www.uniprot.org/uniprot/Q8NCW5), spanning 2.5 kb and composed of 288 amino acids. It contains mitochondrial transport peptide (residues 1–47), NAD(P)H hydrate isomerase (residues 48–288), yjefn terminal domain (residues 65–275), two NAD(P)HX region (residues 119–223, residues 189–195). NAXE protein exists in cerebrospinal fluid and urine, and is widely expressed in the kidneys, heart and liver [11]. In *in vitro* experiments in fibroblasts from PEBEL1 patients, NAXE deficiency caused a significant increase in circulating NADHX and two NADHX isoforms (S and R isoforms) under normal body temperature (37°C). The elevated levels of circulating NADHX were greater in NAXE-deficient cells after treatment with heat stress (40°C), and the elevation of S- and R-type NADHX isoforms was attenuated. In addition, the activity of intact mitochondria in the muscle tissue of two patients also decreased significantly[1]. These prove that NAXE deficiency leads to the accumulation of the toxic metabolites of the biochemical reaction cofactors NADH and NADPH, circulating NADHX, then affects the oxidative phosphorylation of mitochondria and leads to the deficiency/disorder of mitochondrial energy metabolism. Therefore, it can be predicted that the brain with high demand for energy supply produced by mitochondria is particularly vulnerable to the damage of NAD(P)HX repair, which can also explain the deterioration of neurological symptoms clinically in children after fever. Although *NAXE* is highly expressed in the human brain (https://gtexportal.org/home/gene/NAXE), the mechanism of its defect in the central nervous system is still unclear.

Vitamin B3 and coenzyme Q are specific treatments for elevated NAD^+ levels, so they are also expected to benefit PEBEL1 patients. A 22-year-old female patient reported by TRINH[4] in Germany, in addition to receiving vitaminB3 treatment (niacin 40 mg bid to 2 × 40 mg bid), received anticonvulsant therapy (topiramate 50 mg bid, clomazone 20 mg/d, lamotrigine 300 mg/d, levetiracetam 1000 mg/d, piracetam 2400 mg/d, vitamin D3, esomeprazole, and laxative). The patient survived up to 29 years of age and had significant improvement in spasticity with some recovery in motor abilities. In our case, the patient had acute onset and progressed rapidly. Although nicotinamide (vitamin B3) and coenzyme Q were used on day 17 of onset, they still could not reverse/delay brain edema, and the fatal pathological changes need to be proved by practice.

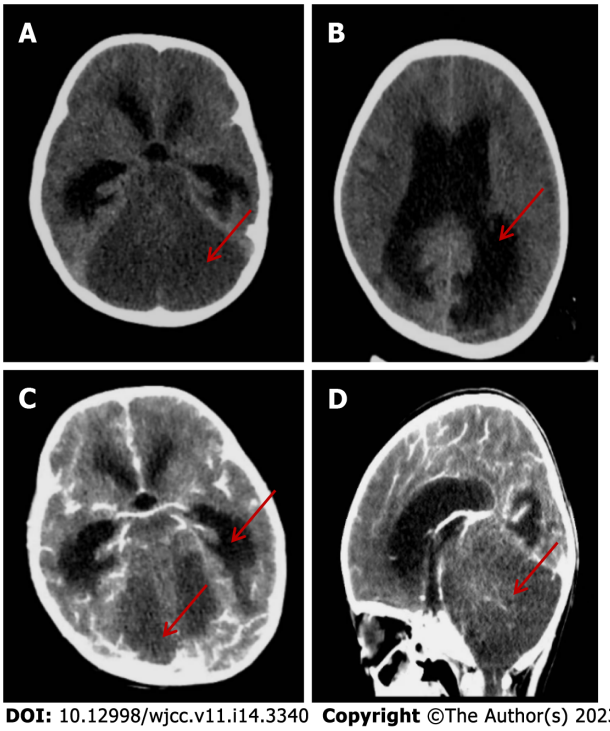
CONCLUSION

This is the first case of severe clinical phenotypic PEBEL1 reported in Mainland China, and a compound heterozygous variation of the *NAXE* gene was detected and a new variant Gly124Cys was identified, which expanded the pathogenicity variation spectrum of PEBEL1. Due to the rapid progress of PEBEL1



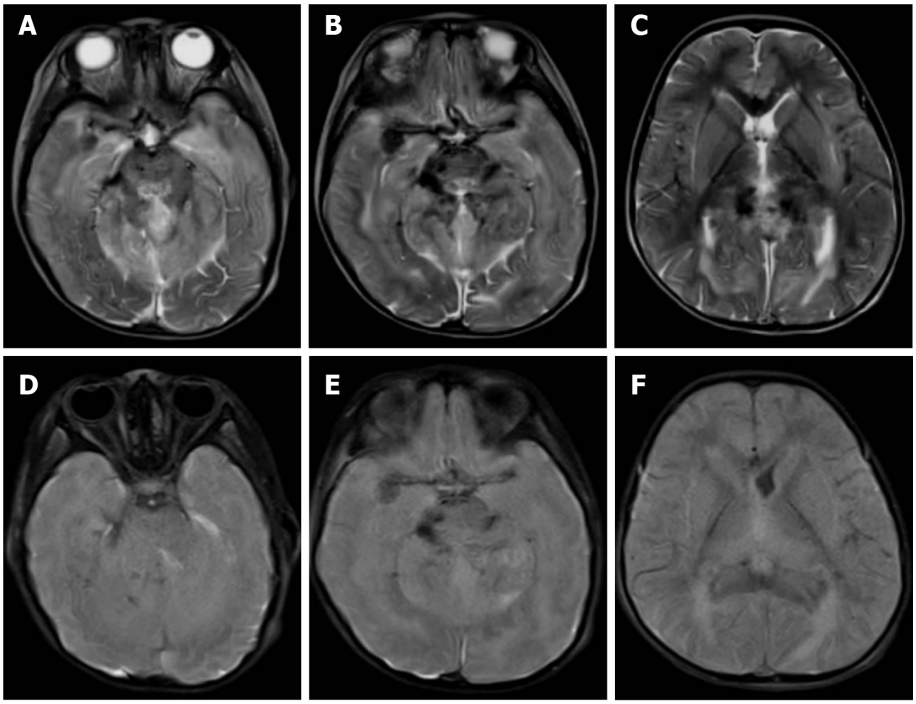
DOI: 10.12998/wjcc.v11.i14.3340

Figure 5 Structural analysis of wild-type and variant *APOA1BP* with c.370G>T mutation. A: The three-dimensional structure of wild-type (WT); B: The three-dimensional structure of the mutant; C: The residue of missense mutant site together with the nearby functional site of WT; D: The residue of missense mutant site together with the nearby functional site of the mutant. Residues of the mutant sites are highlighted in green solid line. The computed hydrogen bonds are shown as green dashed lines and red arrow.



DOI: 10.12998/wjcc.v11.i14.3340

Figure 6 The imaging findings of head computed tomography on day 12 after admission. A: There was a large area of diffuse hypointense signal in the posterior fossa, and the cerebellar parenchymal structure was unclear; B: There was marked dilatation of the supratentorial ventricles and obstructive hydrocephalus with paraventricular edema; C: No parenchymal enhancement mass was found on contrast-enhanced scan; D: The sagittal view showed supratentorial elevation with diffuse brain swelling on contrast-enhanced scan.



DOI: 10.12998/wjcc.v11.i14.3340

Figure 7 The imaging findings of head magnetic resonance on day 26 after admission. A-C: T2-weighted imaging showed blurred boundary between gray matter and white matter, structural disorder of brain stem and cerebellar hemisphere, and multiple long T2 signal shadows; D-F: Fluid-attenuated inversion-recovery (FLAIR) images showed blurred gray and white matter, disordered structure, high FLAIR signal around the cerebellum and lateral ventricle, and significant narrowing of the lateral ventricle.

and mostly sporadic cases, its early presentation, often characterized by acute onset of fever-induced deterioration of central nervous function or even cerebral edema, is not easy to indicate hereditary diseases, which may be an important reason for the lack of awareness of the disease among clinicians. For patients suspected of PEBEL1, vitamin B3 and coenzyme Q therapy should be tried first, and gene detection should be carried out as soon as possible to make a definite diagnosis. For the family of this case, we suggest that the *NAXE* mutation test should be used as a necessary part of prenatal genetic screening.

FOOTNOTES

Author contributions: Zheng G and Ding L designed and performed the study; Huang TT, Ying GH, and Wang SY wrote the draft manuscript and were equal contributors to the study; Xu HF and Qian H collected the data; Rahman F, Lu XP, Guo H, and Zheng G carried out data analysis and language revising; All authors approved the final manuscript for submission.

Supported by the Epilepsy Research Fund of Chinese Anti-Epilepsy Association, No. CU-A-2021-17; Nanjing Municipal Health Bureau key project, No. ZKX21047; and the Postdoctoral Research Foundation of China, No. 2020M671550.

Informed consent statement: Written informed consent for publication was obtained from the parents.

Conflict-of-interest statement: All the authors have no financial relationship with any commercial entity with a potential interest in the subject of this manuscript.

CARE Checklist (2016) statement: All the authors have no financial relationship with any commercial entity with a potential interest in the subject of this manuscript.

Country/Territory of origin: China

ORCID number: Le Ding 0000-0002-8710-1685; Ting-Ting Huang 0000-0001-5177-416X; Guo Zheng 0000-0001-7525-9680; Gang Zhang 0000-0001-5729-7667.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Kremer LS**, Danhauser K, Herebian D, Petkovic Ramadža D, Piekutowska-Abramczuk D, Seibt A, Müller-Felber W, Haack TB, Płoski R, Lohmeier K, Schneider D, Klee D, Rokicki D, Mayatepek E, Strom TM, Meitinger T, Klopstock T, Pronicka E, Mayr JA, Baric I, Distelmaier F, Prokisch H. NAXE Mutations Disrupt the Cellular NAD(P)HX Repair System and Cause a Lethal Neurometabolic Disorder of Early Childhood. *Am J Hum Genet* 2016; **99**: 894-902 [PMID: 27616477 DOI: 10.1016/j.ajhg.2016.07.018]

2 **Spiegel R**, Shaag A, Shalev S, Elpeleg O. Homozygous mutation in the APOA1BP is associated with a lethal infantile leukoencephalopathy. *Neurogenetics* 2016; **17**: 187-190 [PMID: 27122014 DOI: 10.1007/s10048-016-0483-3]

3 **Richards S**, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17**: 405-424 [PMID: 25741868 DOI: 10.1038/gim.2015.30]

4 **Trinh J**, Imhoff S, Dulovic-Mahlow M, Kandaswamy KK, Tadic V, Schäfer J, Dobricic V, Nolte A, Werber M, Rolfs A, Münchau A, Klein C, Lohmann K, Brüggemann N. Novel NAXE variants as a cause for neurometabolic disorder: implications for treatment. *J Neurol* 2020; **267**: 770-782 [PMID: 31745726 DOI: 10.1007/s00415-019-09640-2]

5 **Yu D**, Zhao FM, Cai XT, Zhou H, Cheng Y. [Clinical and genetic features of early-onset progressive encephalopathy associated with NAXE gene mutations]. *Zhongguo Dang Dai Er Ke Za Zhi* 2018; **20**: 524-258 [PMID: 30022751 DOI: 10.7499/j.issn.1008-8830.2018.07.002]

6 **Incecık F**, Ceylaner S. Early-onset progressive encephalopathy associated with NAXE gene variants: a case report of a Turkish child. *Acta Neurol Belg* 2020; **120**: 733-735 [PMID: 31758406 DOI: 10.1007/s13760-019-01242-z]

7 **Mohammadi P**, Heidari M, Ashrafi MR, Mahdieh N, Garshasbi M. A novel homozygous missense variant in the NAXE gene in an Iranian family with progressive encephalopathy with brain edema and leukoencephalopathy. *Acta Neurol Belg* 2022; **122**: 1201-1210 [PMID: 34120322 DOI: 10.1007/s13760-021-01717-y]

8 **Choi SH**, Agatisa-Boyle C, Gonen A, Kim A, Kim J, Alekseeva E, Tsimikas S, Miller YI. Intracellular AIBP (Apolipoprotein A-I Binding Protein) Regulates Oxidized LDL (Low-Density Lipoprotein)-Induced Mitophagy in Macrophages. *Arterioscler Thromb Vasc Biol* 2021; **41**: e82-e96 [PMID: 33356389 DOI: 10.1161/ATVBAHA.120.315485]

9 **Marbaix AY**, Noël G, Detroux AM, Vertommen D, Van Schaftingen E, Linster CL. Extremely conserved ATP- or ADP-dependent enzymatic system for nicotinamide nucleotide repair. *J Biol Chem* 2011; **286**: 41246-41252 [PMID: 21994945 DOI: 10.1074/jbc.C111.310847]

10 **Marbaix AY**, Tyteca D, Niehaus TD, Hanson AD, Linster CL, Van Schaftingen E. Occurrence and subcellular distribution of the NADPHX repair system in mammals. *Biochem J* 2014; **460**: 49-58 [PMID: 24611804 DOI: 10.1042/BJ20131482]

11 **Ritter M**, Buechler C, Boettcher A, Barlage S, Schmitz-Madry A, Orsó E, Bared SM, Schmiedeknecht G, Baehr CH, Fricker G, Schmitz G. Cloning and characterization of a novel apolipoprotein A-I binding protein, AI-BP, secreted by cells of the kidney proximal tubules in response to HDL or ApoA-I. *Genomics* 2002; **79**: 693-702 [PMID: 11991719 DOI: 10.1006/geno.2002.6761]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3351-3355

DOI: 10.12998/wjcc.v11.i14.3351

ISSN 2307-8960 (online)

CASE REPORT

Iatrogenic atlantoaxial rotatory subluxation after thyroidectomy in a pediatric patient: A case report

Woo-Joon Hong, Jung-Kil Lee, Jong-Hwan Hong, Moon-Soo Han, Shin-Seok Lee

Specialty type: Surgery

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mei XF, China; Nambi G, Saudi Arabia

Received: February 23, 2023
Peer-review started: February 23, 2023
First decision: March 28, 2023
Revised: April 2, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: May 16, 2023

Woo-Joon Hong, Jung-Kil Lee, Jong-Hwan Hong, Moon-Soo Han, Department of Neurosurgery, Chonnam National University Hospital & Medical School, Gwangju 61469, South Korea

Shin-Seok Lee, Department of Rheumatology, Department of Internal Medicine, Chonnam National University Medical School & Hospital, Gwangju 61469, South Korea

Corresponding author: Jung-Kil Lee, MD, PhD, Professor, Department of Neurosurgery, Chonnam National University Hospital & Medical School, 42, Jebong-ro, Dong-gu, Gwangju 61469, South Korea. jkl@chonnam.ac.kr

Abstract

BACKGROUND

Atlantoaxial rotatory subluxation (AARS) is an uncommon disease with a greater prevalence among children than adults, and it is mostly associated with trauma. Iatrogenic spinal injury accounts for a low percentage of injuries. However, in AARS, 20%-40% of cases are associated with surgery, and 48% are caused by infection. Here, we describe our experience with a case of iatrogenic AARS after general anesthesia.

CASE SUMMARY

A 12-year-old girl presented with right-sided torticollis and cervical motion limit. The patient had undergone thyroidectomy 2 mo ago. Computed tomography revealed AARS with bilateral locked facets. Following the failure of repeated external reduction under general anesthesia, the patient underwent an open surgical reduction. The patient gained atlantoaxial alignment without any complications. Follow-up radiographs showed a normal appearance without instability. The cervical spine of children is more predisposed to injury due to anatomical and biomechanical differences. AARS secondary to infection and surgery is known as Grisel's syndrome, which involves non-traumatic AARS. Several cases of AARS after surgery and other procedures with no evidence of inflammation have been reported. Our experience shows that surgery requiring hyperextension of the neck after general anesthesia should also be included as a risk factor.

CONCLUSION

Surgeons and anesthesiologists should be careful not to excessively extend the neck during pediatric surgery. Moreover, clinicians caring for pediatric patients with recent head and neck procedures must be aware of common AARS presentations.

Key Words: Atlantoaxial joint; Joint subluxation; Adolescent; Grisel's syndrome; Case report

Core Tip: Atlantoaxial rotatory subluxation (AARS) is a rare condition with a higher prevalence in children, often associated with trauma or infection, and occasionally surgery. This case highlights iatrogenic AARS after general anesthesia and the importance of caution during surgery for AARS in pediatric patients.

Citation: Hong WJ, Lee JK, Hong JH, Han MS, Lee SS. Iatrogenic atlantoaxial rotatory subluxation after thyroidectomy in a pediatric patient: A case report. *World J Clin Cases* 2023; 11(14): 3351-3355
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3351.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3351

INTRODUCTION

Atlantoaxial rotatory subluxation (AARS) is an uncommon disease with a greater prevalence among children than adults, and it is mostly associated with trauma. Traumatic spinal injuries in children have been reported to be relatively rare, accounting for 1%-10% of all spinal injuries. The incidence of traumatic spinal injuries increases with age, with most injuries being associated with car accidents, followed by falls and sports. Other causes comprise only 3% of spinal injuries, including iatrogenic causes[1,2]. Therefore, iatrogenic spinal injury accounts for only a low percentage of injuries. However, in AARS, 20%-40% of cases are associated with surgery, and 48% are caused by infection (Grisel's syndrome)[3,4]. As mentioned above, AARS has a high prevalence in the pediatric population. The cervical spine is the most vulnerable and commonly injured part of the pediatric spine. Moreover, pediatric spine kinematics is significantly different from that of adults. The facet joints are more horizontally oriented and provide less resistance to rocking and translation between the vertebrae, and the uncinate processes are not developed. Therefore, cervical dislocation after a surgical procedure in pediatric patients is a complication that may occur more often than expected. Nevertheless, only few cases of cervical dislocation due to the surgical position of the patient have been reported. Here, we describe our experience with a case of AARS after thyroid surgery.

CASE PRESENTATION

Chief complaints

The patient complained of right-sided torticollis and cervical motion limit.

History of present illness

A 12-year-old female patient visited our department with right torticollis and cervical motion limit 2 mo ago.

History of past illness

The patient underwent thyroidectomy 2 mo ago. The symptoms appeared after thyroidectomy.

Personal and family history

There was no significant past or family history.

Physical examination

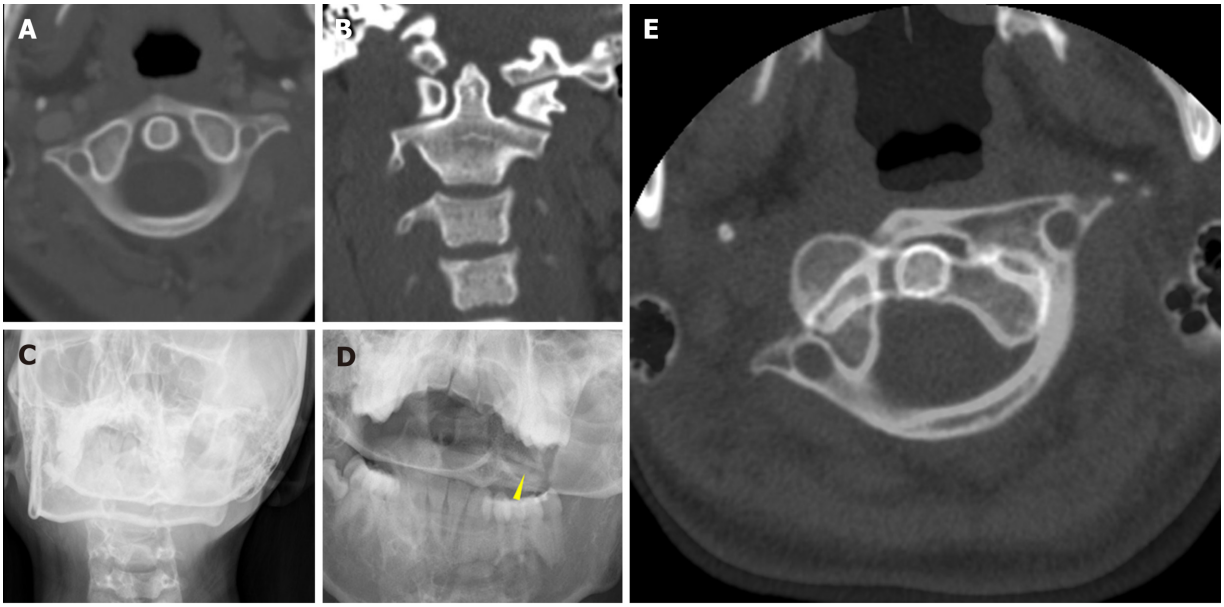
There was no motor weakness or sensory change.

Laboratory examinations

There were no significant laboratory findings.

Imaging examinations

Plain radiographs demonstrated torticollis and the "cock robin" position of the head (Figure 1A and B). Cervical computed tomography (CT) revealed AARS with bilateral locked facets (Figure 1C and D). Neck CT before thyroidectomy showed the normal alignment of the atlantoaxial joint.



DOI: 10.12998/wjcc.v11.i14.3351

Figure 1 Preoperative imaging. A: Computed tomography of the neck before thyroidectomy showing no subluxation of C1–2; B: Computed tomography coronal view after thyroidectomy showing the asymmetry of the lateral atlantodental interval; C: Plain radiograph showing the "cock robin" position of the head; D: Open mouth view showing the asymmetrical atlantodental interval and narrowing atlantoaxial joints (yellow arrow); E: Computed tomography showing the anterior subluxation of C1 on C2 at the left facet joint and the posterior subluxation of C1 on C2 at the right facet joint.

FINAL DIAGNOSIS

The patient was diagnosed with iatrogenic AARS with bilateral locked facets based on imaging and clinical findings.

TREATMENT

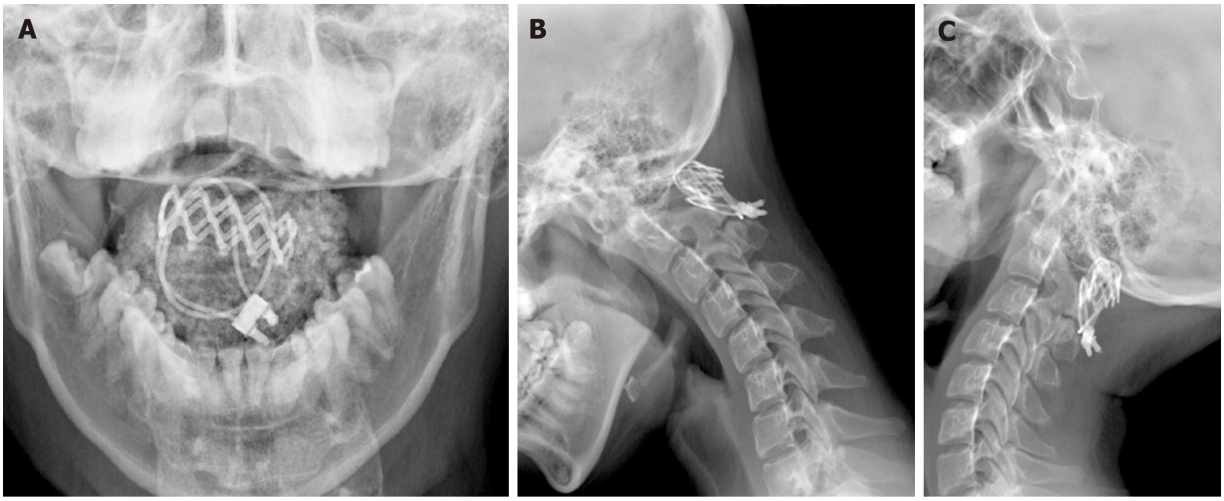
Halter neck traction with 5 pound weight was applied with sedatives and analgesia. Follow-up CT was performed after a week of continuous halter traction; however, AARS remained. Following the failure of repeated external reduction under general anesthesia, we decided on an open surgical reduction. First, through a posterior cervical midline approach, we exposed the C1 and C2 Lamina. Manual reduction was performed by wiring C1, which failed. As there was no other alternative, we sacrificed the C2 root, and the facet subluxation was reduced by manual traction. After confirming the reduction, iliac bone graft and interspinous wiring were performed. The patient gained atlantoaxial alignment without any complications.

OUTCOME AND FOLLOW-UP

After surgery, the patient's torticollis was corrected, and she was discharged without any complications. One-year follow-up dynamic radiographs showed a normal appearance without instability (Figure 2). The patient remained asymptomatic without recurrence until 8 years after surgery.

DISCUSSION

Pediatric AARS can be divided into three main categories depending on their cause: Traumatic, congenital, and inflammatory. Traumatic and congenital causes are related to instability. The cervical spine of children is more predisposed to injury than that of adults due to anatomical and biomechanical differences. In children, the head mass is relatively high, and neck muscles are underdeveloped. The vertebral bodies are anterior wedge-shaped, the facets are angled horizontally, the uncinate process is absent, and the ligaments and joint capsules are highly elastic. Various congenital abnormalities contribute to vertebral dysplasia, leading to instability of the cervical spine (*e.g.*, Klippel-Feil syndrome, Chiari malformation, and Down syndrome). Due to this instability, the pediatric spine is relatively



DOI: 10.12998/wjcc.v11.i14.3351

Figure 2 Postoperative cervical dynamic radiographs of a stable atlantoaxial joint. A: Open mouth radiograph showing the reduction of the "cock robin" position of the head; B and C: Lateral flexion dynamic radiograph showing C1–2 fusion and no instability.

vulnerable to external forces and is easily damaged by minor trauma.

AARS secondary to infection is known as Grisel's syndrome. It can be caused by infections, such as in otitis media, viral syndromes, or pharyngitis. Additionally, AARS after head and neck surgery has been occasionally reported in the literature. Symptoms associated with inflammatory reactions after surgery have been observed[3]. The specific mechanism of Grisel's syndrome is unknown; however, the hematogenous spread of infection from the pharynx to the cervical spine with hyperemia and abnormal relaxation of the atlantoaxial ligaments is accepted as a reasonable explanation[5]. Therefore, AARS rarely appears immediately and is usually detected during postoperative recovery, and laboratory tests show increased inflammatory markers. The most common inflammatory markers measured in clinical practice are C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In our case, both CRP and ESR were in a normal range 2 wk after thyroidectomy. In addition, the patient had no specific neurological symptoms other than mild neck discomfort, which could be considered a postoperative change.

Several cases of AARS after surgery and other procedures, such as ventricular abdominal shunt surgery, otitis media surgery, and central venous catheter insertion, have been reported with no evidence of inflammation in pediatric patients[6-8]. The common features of these cases include a pediatric population and a head rotation procedure under general anesthesia. The use of muscle relaxants and general anesthesia loosens the neck muscles, which increases instability in the cervical joint. In addition, pediatric spine kinematics may contribute to the development of AARS. According to Kim *et al*[9], the risk factors for iatrogenic AARS could include pediatric surgery, oropharyngeal inflammation, general anesthesia, and extreme rotation of the head. Nevertheless, we believe that surgery requiring hyperextension of the neck after general anesthesia should also be included as a risk factor.

Early diagnosis is crucial for patients with cervical dislocation, including AARS. Late diagnosis may lead to late management, thereby resulting in invasive treatment. This case required surgical treatment with posterior C1–C2 fusion, resulting in extended hospital stay, additional expenses, and complications. We hope that our experience may help other clinicians prevent such rare and unfortunate incidents from occurring among pediatric patients.

CONCLUSION

Surgeons and anesthesiologists should be careful not to excessively extend the neck during surgery for pediatric patients and ensure that it is in the normal axis even after the operation is complete. Moreover, clinicians caring for pediatric patients with recent head and neck procedures must be aware of the common presentations of AARS.

FOOTNOTES

Author contributions: Author contributions: Lee JK performed the operation and evaluated the patient; Hong WJ wrote the manuscript; Lee SS and Lee JK provided writing assistance; Hong JH and Han MS evaluated and reviewed the chart.

Supported by The Chonnam National University Hospital Biomedical Research Institute, No. BCRI22023.

Informed consent statement: Informed written consent was obtained from the patient's legal guardian for the publication of this case report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no potential or actual conflicts of interest with regard to this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

ORCID number: Woo-Joon Hong 0000-0001-8533-3979; Jung-Kil Lee 0000-0002-9143-4917; Jong-Hwan Hong 0000-0002-7864-1145; Moon-Soo Han 0000-0001-9594-1193; Shin-Seok Lee 0000-0001-6810-7355.

S-Editor: Ma YJ
L-Editor: Wang TQ
P-Editor: Zhang YL

REFERENCES

1 **Bilston LE**, Brown J. Pediatric spinal injury type and severity are age and mechanism dependent. *Spine (Phila Pa 1976)* 2007; **32**: 2339-2347 [PMID: 17906576 DOI: 10.1097/BRS.0b013e3181558886]
2 **Carreon LY**, Glassman SD, Campbell MJ. Pediatric spine fractures: a review of 137 hospital admissions. *J Spinal Disord Tech* 2004; **17**: 477-482 [PMID: 15570118 DOI: 10.1097/01.bsd.0000132290.50455.99]
3 **Karkos PD**, Benton J, Leong SC, Mushi E, Sivaji N, Assimakopoulos DA. Grisel's syndrome in otolaryngology: a systematic review. *Int J Pediatr Otorhinolaryngol* 2007; **71**: 1823-1827 [PMID: 17706297 DOI: 10.1016/j.ijporl.2007.07.002]
4 **Pang D**, Li V. Atlantoaxial rotatory fixation: part 3-a prospective study of the clinical manifestation, diagnosis, management, and outcome of children with alantoaxial rotatory fixation. *Neurosurgery* 2005; **57**: 954-72; discussion 954 [PMID: 16284565 DOI: 10.1227/01.neu.0000180052.81699.81]
5 **Richter GT**, Bower CM. Cervical complications following routine tonsillectomy and adenoidectomy. *Curr Opin Otolaryngol Head Neck Surg* 2006; **14**: 375-380 [PMID: 17099343 DOI: 10.1097/01.moo.0000247525.56076.54]
6 **Brisson P**, Patel H, Scorpio R, Feins N. Rotary atlanto-axial subluxation with torticollis following central-venous catheter insertion. *Pediatr Surg Int* 2000; **16**: 421-423 [PMID: 10955579 DOI: 10.1007/s003839900318]
7 **Hashide S**, Aihara Y, Nagahara A, Mitsuyama T, Okada Y. Atlantoaxial Rotatory Subluxation after Removal of a Ventriculoperitoneal Shunt in the Supine-Lateral Position. *Pediatr Neurosurg* 2015; **50**: 229-232 [PMID: 26202450 DOI: 10.1159/000433601]
8 **Sakaida H**, Akeda K, Sudo A, Takeuchi K. Atlantoaxial rotatory fixation as a rare complication from head positioning in otologic surgery: Report of two cases in young children. *Patient Saf Surg* 2017; **11**: 5 [PMID: 28184249 DOI: 10.1186/s13037-016-0116-7]
9 **Kim B**, Iwata K, Sugimoto K, Suzuki S, Ema Y, Tsunobuchi H, Nishiwaki K. Significance of prevention and early treatment of a postoperative twisted neck: atlantoaxial rotatory subluxation after head and neck surgery. *J Anesth* 2010; **24**: 598-602 [PMID: 20339878 DOI: 10.1007/s00540-010-0932-3]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3356-3361

DOI: 10.12998/wjcc.v11.i14.3356

ISSN 2307-8960 (online)

CASE REPORT

Bladder metastasis from epidermal growth factor receptor mutant lung cancer: A case report

Cai-Bao Jin, Ling Yang

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Konala VM, United States; Sehrawat A, India

Received: March 2, 2023
Peer-review started: March 2, 2023
First decision: March 24, 2023
Revised: April 2, 2023
Accepted: April 7, 2023
Article in press: April 7, 2023
Published online: May 16, 2023

Cai-Bao Jin, Ling Yang, Department of Thoracic Oncology, Hubei Cancer Hospital, Wuhan 430000, Hubei Province, China

Corresponding author: Ling Yang, MD, Chief Doctor, Department of Thoracic Oncology, Hubei Cancer Hospital, No. 116 Zhuodaoquan South Road, Wuhan 430000, Hubei province, China. 348711624@qq.com

Abstract

BACKGROUND

Bladder metastasis from lung cancer with epidermal growth factor receptor (EGFR) mutation is extremely rare. Here, we report a case of bladder metastasis from lung adenocarcinoma with EGFR mutation.

CASE SUMMARY

A 53-year-old female patient was diagnosed with advanced lung adenocarcinoma with EGFR exon 19 deletion. Multiple nodules on the bladder wall were found by regular examination of the pelvic cavity through computed tomography during targeted therapy. Further cystoscopy and histological examination of bladder biopsy tissues confirmed the bladder metastasis from lung adenocarcinoma. In addition, genetic analysis of the bladder metastasis revealed EGFR T790M mutation. The patient achieved a good response to a third-generation EGFR tyrosine kinase inhibitor.

CONCLUSION

During routine follow-up of lung cancer patients, imaging examination of the pelvic cavity should be performed to avoid missing bladder metastasis. The ultimate diagnosis of bladder metastasis sill depends on the pathological result of biopsy tissues.

Key Words: Bladder metastasis; Lung cancer; EGFR mutation; Tyrosine kinase inhibitor; Histological examination; Case report

Core Tip: Bladder metastasis from lung cancer with epidermal growth factor receptor (EGFR) mutation is extremely rare. We reported a case of bladder metastasis from lung adenocarcinoma with EGFR mutation. During routine follow-up of lung cancer patients, imaging examination of the pelvic cavity should be performed to avoid missing bladder metastasis. The ultimate diagnosis of bladder metastasis sill depends on the pathological result of biopsy tissues as determined by cystoscopy. Bladder metastasis with EGFR mutation seems to respond well to the treatment of EGFR tyrosine kinase inhibitors.

Citation: Jin CB, Yang L. Bladder metastasis from epidermal growth factor receptor mutant lung cancer: A case report. *World J Clin Cases* 2023; 11(14): 3356-3361
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3356.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3356

INTRODUCTION

Bladder cancer is one of the most common urinary carcinomas, only a small percentage of which are metastases from a distant primary cancer. Previous studies have shown that the primary tumors with bladder metastases could originate from stomach, melanoma, breast and lung[1]. In addition, lung cancer with bladder metastasis is especially rare. Here, we described a case of bladder metastasis from lung adenocarcinoma that was found during targeted therapy by accident. In particular, genetic analysis of the bladder metastasis tissue showed epidermal growth factor receptor (EGFR) exon 19 deletion and exon 20 T790M mutation.

CASE PRESENTATION

Chief complaints

A lung cancer patient returned to the hospital for re-examination with a complaint of significant loss of appetite during targeted therapy.

History of present illness

Significant loss of appetite started one month before the patient's return to the hospital.

History of past illness

In April 2019, a 53-year-old woman went to the hospital with pain in the left leg and was found to have a pulmonary nodule. Positron Emission Tomography-Computed Tomography showed a solid mass in the upper lobe of the left lung, multiple small nodules in the bilateral lungs and bone destruction in the left ischium and femur. Brain magnetic resonance imaging revealed multiple nodules in the left temporal lobe and cerebellum. The pathological diagnosis based on the left lung mass biopsy sample was adenocarcinoma. Genetic analysis of the biopsy tissue revealed EGFR exon 19 deletion. The first-generation EGFR tyrosine kinase inhibitor icotinib was administered. The patient achieved stable disease, but clinical symptoms did not improve significantly. A chemotherapy regimen (pemetrexed) was administered for two cycles simultaneously during targeted therapy in July 2019. Until January 2022, the patient continued to show significant loss of appetite.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

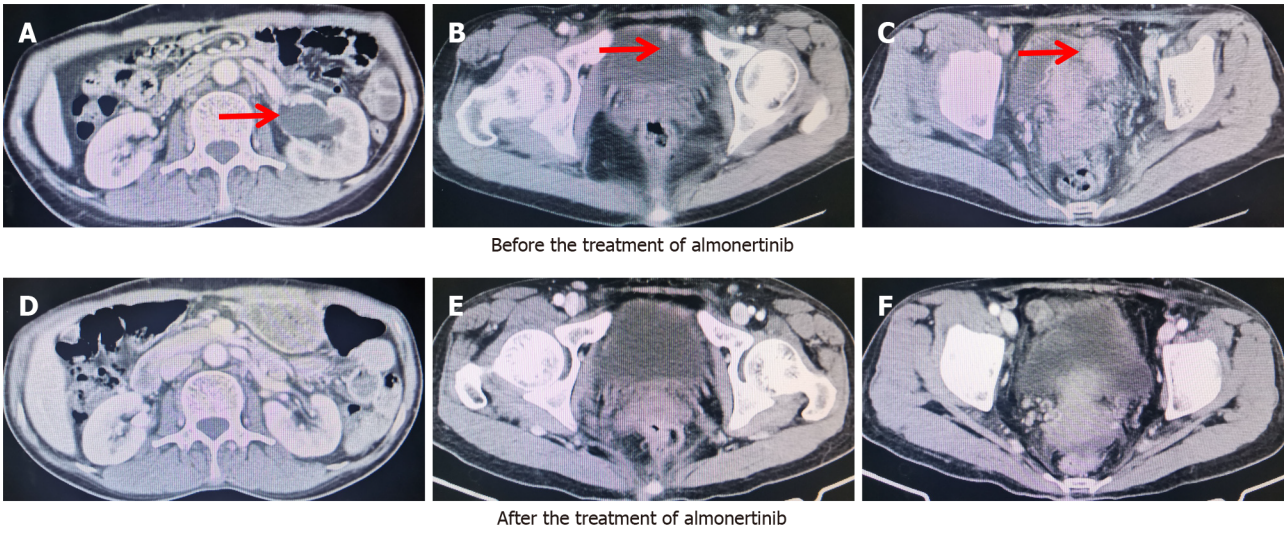
Her vital signs were as follows: Body temperature, 36.6°C; blood pressure, 120/80 mmHg; heart rate, 85 beats per min; respiratory rate, 20 breaths per min. Furthermore, there was no positive signs related to the disease.

Laboratory examinations

Levels of serum tumor markers were as follows: Carcinoembryonic antigen, 263 ng/mL; carbohydrate antigen 125, 64.5 U/mL; squamous cell carcinoma antigen, 0.99 ng/mL. No abnormality was found in routine blood and urine analyses.

Imaging examinations

Examination of the chest, abdomen and pelvic cavity through computed tomography revealed multiple



DOI: 10.12998/wjcc.v11.i14.3356

Figure 1 Computed tomography images recorded tumor regression of bladder metastasis after almonertinib therapy. A-C: Before treatment; D-F: After treatment.

nodules on the bladder wall (Figure 1). The lesions of the lung and brain were stable.

FINAL DIAGNOSIS

To determine the origin of the nodules on the bladder wall, cystoscopic examination was subsequently performed. The cystoscopy analysis revealed multiple solid lesions on the anterior and bottom walls of the bladder (Figure 2). Bladder lesion biopsy was performed, and histological examination showed that the sample was a bladder metastasis derived from lung adenocarcinoma. Immunohistochemistry analysis showed positive staining for TTF-1 and CK7 and negative staining for P40 and GATA3 (Figure 3). Furthermore, genetic analysis of the mass biopsy showed EGFR exon 19 deletion and exon 20 T790M mutation.

Given the above findings combined with the patient's medical history, the final diagnosis was bladder metastasis derived from lung adenocarcinoma with EGFR exon 19 deletion and exon 20 T790M mutation.

TREATMENT

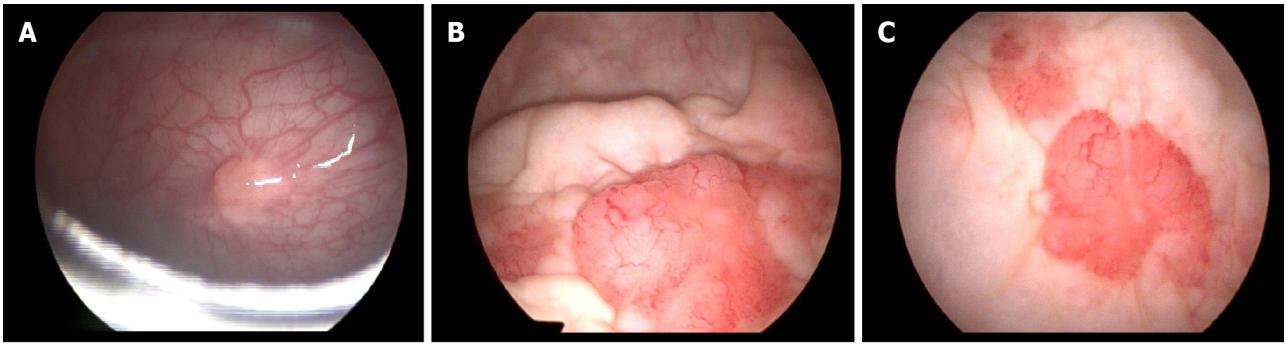
In February 2022, the patient began to receive targeted therapy with the third-generation EGFR tyrosine kinase inhibitor almonertinib and achieved a partial response.

OUTCOME AND FOLLOW-UP

One year after the treatment with almonertinib, the patient had sustained partial remission. There were no obvious adverse events.

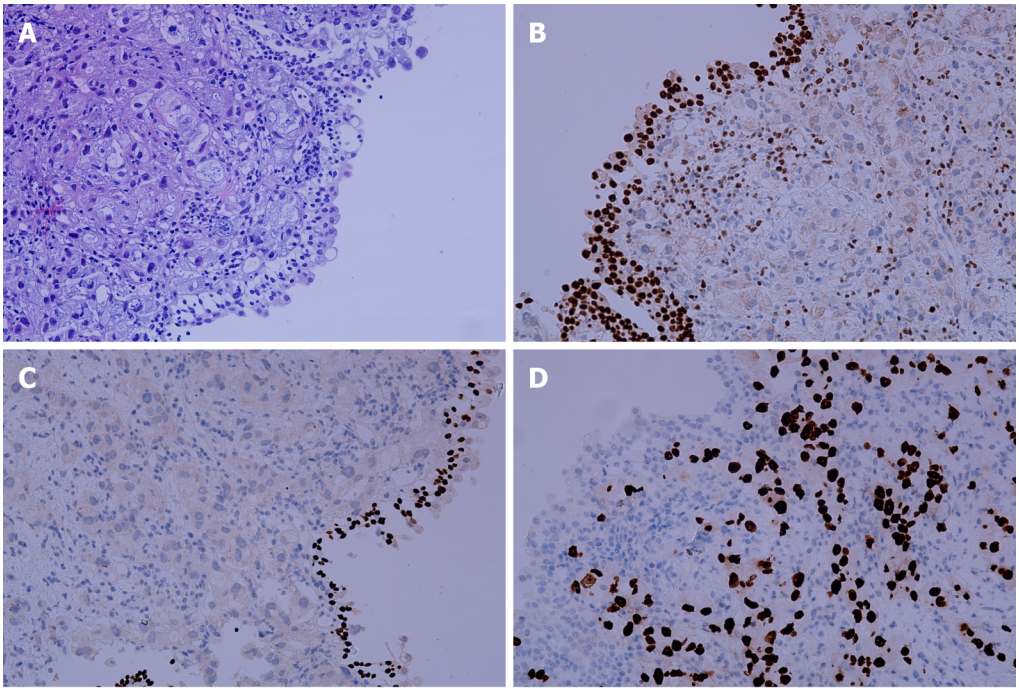
DISCUSSION

Lung cancer is the most common cancer in males worldwide and the most frequent cause of cancer-related death. The main hematogenous metastatic sites for lung cancer are the bone, brain, liver, and adrenal glands. Metastasis in the bladder, which is an uncommon distant metastatic site, has been reported in only a few cases thus far. According to the timing of occurrence, bladder metastasis can be divided into two types: synchronous and metachronous metastasis. Synchronous bladder metastasis is mostly found during examinations of the primary site. For the metachronous type, the mean time from the diagnosis of lung cancer to the occurrence of bladder metastasis is one year[2]. In our case, bladder metastasis occurred thirty-three months after the initial diagnosis of lung cancer.



DOI: 10.12998/wjcc.v11.i14.3356

Figure 2 Cystoscopy analysis revealed multiple solid lesions on the anterior and bottom walls of the bladder. A: Solid lesion on the anterior wall; B and C: Solid lesion on the bottom wall.



DOI: 10.12998/wjcc.v11.i14.3356

Figure 3 Histopathological findings in metastatic bladder sample. A: Hematoxylin and eosin stained sections; B Negative staining for GATA3; C: Negative staining for P40; D: Positive staining for thyroid transcription factor 1.

For primary bladder cancer, a common clinical manifestation is macroscopic hematuria at diagnosis. Macroscopic hematuria is also a late-stage manifestation of bladder metastasis, as malignant cells must infiltrate the bladder lining. In addition to hematuria, hydronephrosis is another common symptom that can present in combination with hematuria. In addition, other symptoms, such as pelvic pain and dysuria, can also suggest the possibility of bladder metastasis of lung cancers. In our case, the patient had no typical symptoms related to bladder metastasis. However, left hydronephrosis was seen on imaging examination, which disappeared after effective targeted therapy.

During routine follow up of lung cancer patients, the examination of the pelvic cavity through computed tomography or magnetic resonance imaging should be performed to avoid overlooking bladder metastasis. The definite diagnosis is based on pathological examination of the bladder biopsy tissues.

Cystoscopy plays an important role in the diagnosis of bladder tumors. Some studies have indicated that bladder metastasis is likely to be isolated, while primary bladder tumors are frequently found in multiples. In our case, multiple lesions were found on cystoscopy. According to the previous cases, a common location of bladder metastasis is the lateral walls of the bladder[2]. Because of the route of blood circulation, bladder metastases are usually located in the lamina propria or muscularis propria of the bladder wall, while primary bladder tumors often originate from the mucosa. In our case, multiple bladder metastases were found on the anterior and bottom walls of the bladder.

Primary bladder cancer cases mostly include urothelial carcinoma. According to previously reported cases, the most common pathological type of bladder metastasis from lung cancer is adenocarcinoma [2]. Confirmed diagnosis of bladder tumors depends on immunohistochemistry analysis of biopsy tissues. In our case, the immunohistochemistry analysis showed positive staining for TTF-1 and CK7 and negative staining for P40 and GATA3. The marker CK-7 represents epithelial origin and thus cannot distinguish between lung and bladder cells. The marker GATA3 suggests urothelial differentiation and thus helped eliminate the possibility of urothelial origin. The positive TTF-1 staining suggested that the primary lung adenocarcinoma was the origin with high sensitivity and specificity. Therefore, we confirmed the diagnosis of bladder metastasis from lung cancer by combined analysis of these markers.

In previously published case reports, there were only two cases mentioning the gene mutation status of the lung cancer[3,4]. Both lung cancer patients with bladder metastasis had sensitive EGFR mutations and lacked the T790M mutation before and after the treatment with targeted therapy or chemotherapy. However, in our case, the T790M mutation was detected using bladder biopsy tissue after the progression on first-line targeted therapy. Moreover, the bladder metastasis responded well to targeted therapy with third-generation EGFR tyrosine kinase inhibitors. Due to the limited reported cases and available information, no correlation between the clinical characteristics of lung cancer patients and the occurrence of bladder metastasis has been found until now.

CONCLUSION

Bladder metastasis from lung cancer with EGFR mutation is extremely rare. During routine follow-up of lung cancer patients, imaging examination of the pelvic cavity should be performed to avoid missing bladder metastasis. The ultimate diagnosis of bladder metastasis sill depends on the pathological result of biopsy tissues as determined by cystoscopy. Bladder metastasis with EGFR mutation seems to respond well to the treatment of EGFR tyrosine kinase inhibitors.

FOOTNOTES

Author contributions: Jin CB performed the research and wrote the paper; Yang L supervised the report.

Informed consent statement: Patient was not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Cai-Bao Jin 0000-0003-3544-5774; Ling Yang 0000-0002-5914-9614.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Zaghbib S**, Chakroun M, Saadi A, Boussaffa H, Znaidi N, Rammeh S, Ayed H, Chebil M. Isolated bladder metastasis from lung adenocarcinoma: a case report. *J Surg Case Rep* 2021; rjab195 [PMID: 34055288 DOI: 10.1093/jscr/rjab195]

2 **Sanguedolce F**, Loizzi D, Sollitto F, Di Bisceglie M, Lucarelli G, Carrieri G, Bufo P, Cormio L. Bladder Metastases from Lung Cancer: Clinical and Pathological Implications: A Systematic Review. *Oncology* 2017; **92**: 125-134 [PMID: 28056456 DOI: 10.1159/000454731]

3 **Li X**, Zhang L, Zeng L, Wang X, Song W, Zhong D. Difficult differential diagnosis of bladder pedicled masses about metastasis from non-small cell lung cancer: A case report. *Cancer Biol Ther* 2021; **22**: 106-111 [PMID: 33612067 DOI: 10.1080/15384047.2020.1840885]

4 **Kuga T**, Machida K, Ito H, Matsuo M. Bilateral Hydronephrotic Bladder Metastasis from Lung Cancer. *Intern Med* 2018; **57**: 1801 [PMID: 29434150 DOI: 10.2169/internalmedicine.9535-17]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 16; 11(14): 3362-3368

DOI: 10.12998/wjcc.v11.i14.3362

ISSN 2307-8960 (online)

CASE REPORT

Primary rectal mucosa-associated lymphoid tissue lymphoma treated with only endoscopic submucosal dissection: A case report

Wan-Sik Lee, Myung-Giun Noh, Young-Eun Joo

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Li XB, China; Osawa S, Japan; Sugimoto M, Japan

Received: March 6, 2023
Peer-review started: March 6, 2023
First decision: March 24, 2023
Revised: April 3, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 16, 2023

Wan-Sik Lee, Young-Eun Joo, Department of Internal Medicine, Chonnam National University Medical School, Hwasun-eup 58128, South Korea

Myung-Giun Noh, Department of Pathology, Chonnam National University Medical School, Hwasun-eup 58128, South Korea

Corresponding author: Young-Eun Joo, MD, PhD, Professor, Department of Internal Medicine, Chonnam National University Medical School, 264 Seoyang-ro, Hwasun-eup, Hwasun-gun, Hwasun-eup 58128, South Korea. yejoo@chonnam.ac.kr

Abstract

BACKGROUND

Mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct subtype of non-Hodgkin B cell lymphoma that mostly involves the gastrointestinal tract. The stomach is the most commonly affected site whereas colorectal involvement occurs very rarely. Given its rarity, the management and clinical outcome of colorectal MALT lymphoma are not well established yet.

CASE SUMMARY

From the superficial capillary bed in the lower rectum. Endoscopic ultrasonography showed homogenous hypoechoic lesions in the deep mucosal layer. Endoscopic submucosal dissection (ESD) was done for accurate histologic diagnosis and treatment and both the rectal lesions were completely removed *en bloc* and subsequently diagnosed as primary rectal MALT lymphoma. Herein, we report a case of primary rectal MALT lymphoma in a 68-year-old woman that was treated by only ESD, and the 12-month follow-up revealed no tumour recurrence.

CONCLUSION

These results of our case and previous reports suggest that endoscopic resection alone may be a feasible and safe treatment for primary colorectal MALT lymphoma and allows organ preservation.

Key Words: Rectum; Mucosa-associated lymphoid tissue lymphoma; Endoscopic submucosal dissection

Core Tip: Colorectal involvement of Mucosa-associated lymphoid tissue (MALT) lymphoma occurs rarely and the management of colorectal MALT lymphoma are not well established yet. We report a rare case of colorectal MALT lymphoma treated with endoscopic resection alone. To date, only six cases of primary colorectal MALT lymphomas treated with endoscopic resection alone, including our patient, have been documented in the medical literature. Among the reported cases, there was no recurrence during follow-up. These results of our case and previous reports suggest that endoscopic resection alone may be a feasible and safe treatment for primary colorectal MALT lymphoma and allows organ preservation.

Citation: Lee WS, Noh MG, Joo YE. Primary rectal mucosa-associated lymphoid tissue lymphoma treated with only endoscopic submucosal dissection: A case report. *World J Clin Cases* 2023; 11(14): 3362-3368
URL: https://www.wjgnet.com/2307-8960/full/v11/i14/3362.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i14.3362

INTRODUCTION

Gastrointestinal lymphoma is an uncommon disease that constitutes a small proportion of gastrointestinal neoplasms. Primary gastrointestinal mucosa-associated lymphoid tissue (MALT) lymphoma is a rare type of non-Hodgkin lymphoma that comprises 1%-4% of gastrointestinal non-Hodgkin lymphomas[1-3]. Most primary gastrointestinal MALT lymphomas occur in the stomach, and colorectal involvement occurs very rarely. Thus, the management and clinical outcome of colorectal MALT lymphoma are highly variable and not well established[4-7].

Here, we report a case of a 68-year-old woman with primary rectal MALT lymphoma that was treated with endoscopic submucosal dissection (ESD) alone and present a literature review pertaining to this condition.

CASE PRESENTATION

Chief complaints

A 68-year-old woman visited our clinic for a routine health screening examination.

History of present illness

She had no systemic B symptoms, including abdominal pain, fever, night sweats, and weight loss.

History of past illness

Ten years earlier, she underwent surgery for thyroid cancer. She had been on medication for hypertension and diabetes mellitus for 15 years.

Personal and family history

The patient denied any family history of malignant tumours.

Physical examination

On physical examination, she was afebrile, her blood pressure and pulse were normal, and her abdomen was soft, nondistended, and nontender without hepatosplenomegaly or palpable lymphadenopathy.

Laboratory examinations

Laboratory examinations, including complete blood cell count, liver function test, renal function study, and tumour markers, were within normal limits.

Imaging examinations

Computed tomography scan of the neck, chest, abdomen, and pelvis as well as bone marrow aspiration revealed no significant abnormalities.

FURTHER DIAGNOSTIC WORK-UP

Esophagogastroduodenoscopy showed atrophic gastritis with intestinal metaplasia, and the *Campylobacter*-like organism test was negative for *Helicobacter pylori* (*H. pylori*) infection and the patient

didn't have history of previous *H. pylori* eradication therapy. Colonoscopy showed two subepithelial tumours, measuring 4 and 5 mm and arising from the superficial capillary bed into the lower rectum (Figure 1), that seemed to be neuroendocrine tumours. Endoscopic ultrasonography revealed two homogenous hypoechoic lesions in the deep mucosal layer (Figure 2). As rectal neuroendocrine tumor was suspected according to the endoscopic ultrasonography, the two rectal lesions were removed *en bloc via* ESD for accurate histological diagnosis and treatment (Figure 3).

FINAL DIAGNOSIS

On routine histology, haematoxylin–eosin staining showed a dense aggregate of lymphoid cell in the lamina propria layer forming polypoid-lesion (Figure 4A). These lymphoid cells that had small-to-intermediate nuclei and focally clear cytoplasm, infiltrated into muscularis mucosae but did not infiltrate into submucosa (Figure 4B). Immunohistochemistry to ascertain the nature of tumour cells showed positive staining for CD20 (Figure 4C), but negative results for CD3 and Bcl-6. The Ki-67 Labelling index was 5%. Characteristic lymphocyte-epithelial infiltration of CD20-positive tumor cells was also observed (Figure 4D). The biopsy specimens indicated a diagnosis of MALT lymphoma. In accordance with the Ann Arbor staging system, the tumour was diagnosed as a stage IE primary rectal MALT lymphoma.

TREATMENT

The two rectal lesions were removed *en bloc via* ESD.

OUTCOME AND FOLLOW-UP

The patient has been followed-up regularly at the outpatient clinic. Although follow-up period of the patient has been only 12 mo, there was no evidence of recurrence at 12 mo after the ESD.

DISCUSSION

MALT lymphoma is classified as an extranodal marginal zone B-cell lymphoma of the MALT type[1-3] that frequently involves the gastrointestinal tract, including stomach and small bowel, and very rarely involves the colorectal structures[4-7]. Therefore, the clinical characteristics, treatment, and outcome of primary colorectal MALT lymphoma have not been clearly established yet.

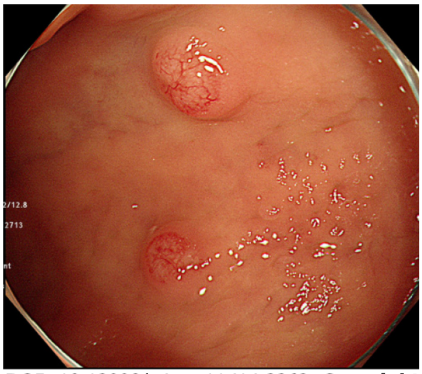
The median age at diagnosis of colorectal MALT lymphoma is approximately 60 years, with a slight female predisposition, and the clinical presentation is most often asymptomatic, followed by abdominal discomfort/pain, positive result on a stool occult blood test, constipation, diarrhoea, tenesmus, and obstruction. The most common lesion site is the rectum, followed by the terminal ileum, cecum, and sigmoid colon. The main endoscopic appearance is of a subepithelial tumour, followed by polyposis, ileitis, and epithelial mass type[7]. Our patient is a 68-year-old woman with an asymptomatic rectal MALT lymphoma that comprised two subepithelial tumours that were found incidentally on screening colonoscopy.

Gastric MALT lymphoma is strongly associated with *H. pylori* infection, and *H. pylori* eradication is the main therapeutic strategy in primary gastric MALT lymphoma[1-3]. However, the association between colorectal MALT lymphoma and *H. pylori* infection is unclear. In our patient, the rectal MALT lymphoma was not associated with an *H. pylori* infection.

Colorectal MALT lymphomas were treated by various modalities, including single or a combination of endoscopic resection, surgery, *H. pylori* eradication with antibiotics, radiation therapy, or chemotherapy. The overall prognosis of colonic MALT lymphoma showed an indolent nature and favourable clinical behaviour[4-7]. However, because of its rarity and indolent nature, the treatment and outcome of colorectal MALT lymphoma is not well established.

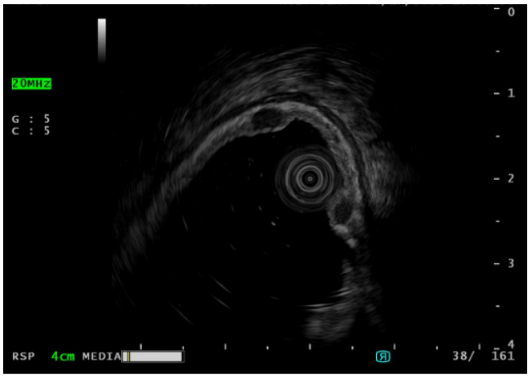
In our case, ESD was undertaken for accurate histological diagnosis and treatment. Rectal lesions were completely resected *en bloc* by ESD and were pathologically confirmed as a rectal MALT lymphoma. Given the stage IE status of lesions limited to only the rectum, based on a discussion with our multidisciplinary medical team, observation without additional treatment was planned. Twelve months after the ESD, the patient had no tumour recurrence.

The first case of endoscopic resection with a hot-snare guillotine technique was reported in primary rectal MALT lymphoma in 2009, wherein empirical *H. pylori* eradication therapy was added despite a negative result on the *H. pylori* test[8]. Another case of stage IE primary rectal MALT lymphoma was



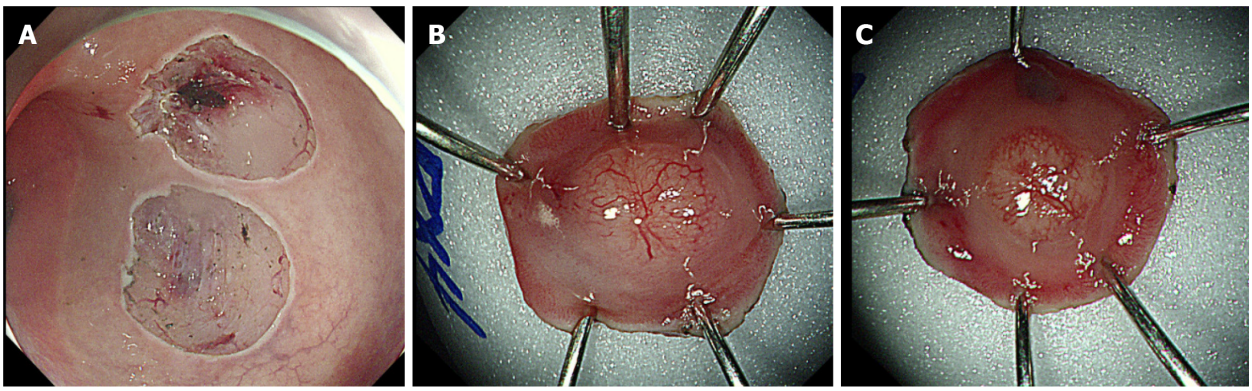
DOI: 10.12998/wjcc.v11.i14.3362

Figure 1 Colonoscopy shows two subepithelial tumors, measuring 4 and 5 mm, within the superficial capillary bed and rising into the rectum.



DOI: 10.12998/wjcc.v11.i14.3362

Figure 2 Endoscopic ultrasonogram shows two homogenous hypoechoic lesions in the deep mucosal layer.



DOI: 10.12998/wjcc.v11.i14.3362

Figure 3 Two rectal lesions have been removed *en bloc* by endoscopic submucosal dissection. A: Two ESD induced ulcers; B: Tumor size was measured 5 mm × 4 mm and specimen size was measured 12 mm × 12 mm; C: Tumor size was measured 4 mm × 4 mm and specimen size was measured 12 mm × 10 mm.

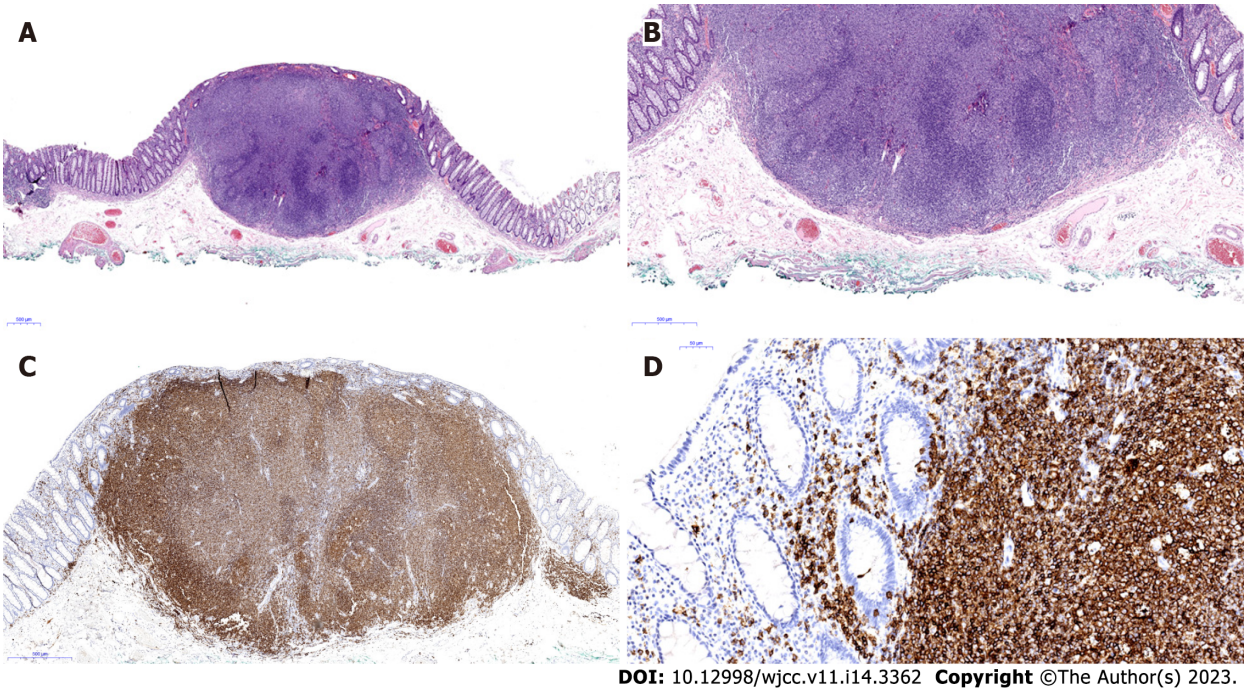
diagnosed by endoscopic mucosal resection (EMR) and treated with radiation therapy[9].

To date, only six cases of primary colorectal MALT lymphomas treated with endoscopic resection alone, including our patient, have been documented in the medical literature (Table 1)[10-14]. The patients were aged 46 to 72 years (mean age, 64.2 years) and included three men and three women. On clinical presentation, three cases were asymptomatic, two had bleeding, and one had weight loss. Two cases are treated with EMR, two with ESD, one with EMR with ligation, and one with endoscopic full-thickness resection. The mean follow-up period was 30.2 mo (range, 12–60 mo). Among the reported cases, there was no recurrence during follow-up.

Table 1 Summary of reported cases of primary colorectal mucosa-associated lymphoid tissue lymphomas treated with endoscopic resection alone

Patient No.	Ref.	Age (yr)/Sex	Symptoms (duration)	Location	Size (cm)	Endoscopic findings	Treatment	Follow up period (mo)	Outcome
1	Lin *et al* [10], 2016	59/M	Positive fecal occult blood test	Colon (25 cm from anal verge)	2.0	Polypoid lesion with wide base, slightly irregular border, and an irregular vascular pattern with mild inflammatory changes	EMR	36	No recurrence
2	Shah *et al* [11], 2021	72/M	Asymptomatic	Mid rectum	2.0	Raised erythematous lesion	EMR	60	No recurrence
3	Yoon *et al*[12], 2021	69/F	Weight loss (3 mo)	Lower rectum	1.0	Subepithelial tumor	EMR with ligation	37	No recurrence
4	Tao *et al* [13],2022	46/M	Asymptomatic	Rectum (10 cm from anal verge)	3.5	Laterally spreading tumor-like lesion	ESD	24	No recurrence
5	Li *et al* [14], 2022	71/F	Hematochezia (1 mo)	Lower rectum	6.0	Hemispheric mass with rough and hyperemic mucosa	Endoscopic full-thickness resection	12	No recurrence
6	Present case	68/F	Asymptomatic	Lower rectum	0.5, 0.3	Two subepithelial tumors with superficial capillary bed	ESD	12	No recurrence

MALT: Mucosa-associated lymphoid tissue; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.



DOI: 10.12998/wjcc.v11.i14.3362

Figure 4 Microscopic findings. A: Endoscopic biopsy specimens show a dense aggregate of lymphoma cells in the lamina propria (hematoxylin and eosin staining, ×20); B: Lymphoma cells infiltrate the mucosal layer above the subepithelial layer (hematoxylin and eosin staining, ×40); C: Immunohistochemical staining shows aggregate of lymphoma cells that stained positive for the B-cell marker CD20 (×400); D: Characteristic lymphocyte-epithelial lesion of CD20-positive lymphoma cells was also observed (x400).

CONCLUSION

These results of our case and previous reports suggest that endoscopic resection alone may be a feasible and safe treatment for primary colorectal MALT lymphoma and allows organ preservation. However, long-term follow-up data are needed to determine the efficacy of this treatment approach in a larger

number of cases that have been treated with endoscopic resection alone.

FOOTNOTES

Author contributions: Lee WS, Noh MG, Joo YE contributed to manuscript writing and editing and data collection; Joo YE contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

ORCID number: Young-Eun Joo 0000-0003-0422-2439.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Violeta Filip P**, Cuciureanu D, Sorina Diaconu L, Maria Vladareanu A, Silvia Pop C. MALT lymphoma: epidemiology, clinical diagnosis and treatment. *J Med Life* 2018; **11**: 187-193 [PMID: 30364585 DOI: 10.25122/jml-2018-0035]
2 **Thieblemont C**, Zucca E. Clinical aspects and therapy of gastrointestinal MALT lymphoma. *Best Pract Res Clin Haematol* 2017; **30**: 109-117 [PMID: 28288705 DOI: 10.1016/j.beha.2017.01.002]
3 **Ishikawa E**, Nakamura M, Satou A, Shimada K, Nakamura S. Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma in the Gastrointestinal Tract in the Modern Era. *Cancers (Basel)* 2022; **14** [PMID: 35053607 DOI: 10.3390/cancers14020446]
4 **Hollie N**, Asakrah S. MALT lymphoma of the colon: a clinicopathological review. *J Clin Pathol* 2020; **73**: 378-383 [PMID: 32034054 DOI: 10.1136/jclinpath-2019-206377]
5 **Won JH**, Kim SM, Kim JW, Park JH, Kim JY. Clinical features, treatment and outcomes of colorectal mucosa-associated lymphoid tissue (MALT) lymphoma: literature reviews published in English between 1993 and 2017. *Cancer Manag Res* 2019; **11**: 8577-8587 [PMID: 31572011 DOI: 10.2147/CMAR.S214197]
6 **Tannoury J**, Amiot A, Lemonnier F, Dupuis J, Gagnière C, Belhadj K, Bras FL, Sobhani I, Haioun C, Copie-Bergman C, Lévy M. Colonic mucosa-associated lymphoid tissue lymphoma: a case series. *Leuk Lymphoma* 2020; **61**: 582-587 [PMID: 31694428 DOI: 10.1080/10428194.2019.1686501]
7 **Jeon MK**, So H, Huh J, Hwang HS, Hwang SW, Park SH, Yang DH, Choi KD, Ye BD, Myung SJ, Yang SK, Byeon JS. Endoscopic features and clinical outcomes of colorectal mucosa-associated lymphoid tissue lymphoma. *Gastrointest Endosc* 2018; **87**: 529-539 [PMID: 28882576 DOI: 10.1016/j.gie.2017.08.027]
8 **Mathew A**, Humburg BC, Bayer MG. A case of rectal MALT lymphoma treated by endoscopic resection. *Am J Gastroenterol* 2009; **104**: 255-256 [PMID: 19098890 DOI: 10.1038/ajg.2008.47]
9 **Hayakawa T**, Nonaka T, Mizoguchi N, Hagiwara Y, Shibata S, Sakai R, Nakayama N, Yokose T, Nakayama Y. Radiotherapy for mucosa-associated lymphoid tissue (MALT) lymphoma of the rectum: a case report. *Clin J Gastroenterol* 2017; **10**: 431-436 [PMID: 28815477 DOI: 10.1007/s12328-017-0769-5]
10 **Lin PC**, Chen JS, Deng P, Wang CW, Huang CH, Tang R, Chiang JM, Yeh CY, Hsieh PS, Tsai WS, Chiang SF. Concurrent colonic mucosa-associated lymphoid tissue lymphoma and adenoma diagnosed after a positive fecal occult blood test: a case report. *J Med Case Rep* 2016; **10**: 24 [PMID: 26818035 DOI: 10.1186/s13256-016-0810-1]
11 **Shah RM**, Kuo V, Schwartz A. Endoscopic mucosal resection and cure for rectal mucosa-associated lymphoid tissue lymphoma. *Proc (Bayl Univ Med Cent)* 2020; **34**: 305-306 [PMID: 33678972 DOI: 10.1080/08998280.2020.1836939]
12 **Yoon BH**, Huh CW. [Rectal Mucosa-associated Lymphoid Tissue Lymphoma Treated with Endoscopic Resection]. *Korean J Gastroenterol* 2021; **78**: 344-348 [PMID: 34955511 DOI: 10.4166/kjg.2021.124]
13 **Tao Y**, Nan Q, Lei Z, Miao YL, Niu JK. Rare primary rectal mucosa-associated lymphoid tissue lymphoma with curative resection by endoscopic submucosal dissection: A case report and review of literature. *World J Clin Cases* 2022; **10**: 7599-7608 [PMID: 36158004 DOI: 10.12998/wjcc.v10.i21.7599]

14 **Li FY**, Zhang XL, Zhang QD, Wang YH. Successful treatment of an enormous rectal mucosa-associated lymphoid tissue lymphoma by endoscopic full-thickness resection: A case report. *World J Gastroenterol* 2022; **28**: 1078-1084 [PMID: 35431493 DOI: 10.3748/wjg.v28.i10.1078]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com