ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 March 9; 12(2): 25-56

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

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NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Bimonthly

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PUBLICATION DATE

March 9, 2023

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World J Clin Pediatr 2023 March 9; 12(2): 25-37

DOI: 10.5409/wjcp.v12.i2.25

ISSN 2219-2808 (online)

OPINION REVIEW

Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance?

Renee J Dufault, Raquel A Crider, Richard C Deth, Roseanne Schnoll, Steven G Gilbert, Walter J Lukiw, Amanda L Hitt

Specialty type: Pediatrics

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): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liao JX, China; Nasrallah O, Syria

Received: November 27, 2022
Peer-review started: November 27, 2022
First decision: December 13, 2022
Revised: December 25, 2022
Accepted: January 9, 2023
Article in press: January 9, 2023
Published online: March 9, 2023

Renee J Dufault, Raquel A Crider, Roseanne Schnoll, Steven G Gilbert, Department of Research, Food Ingredient and Health Research Institute, Naalehu, HI 96772, United States

Renee J Dufault, College of Graduate Health Studies, A.T. Still University, Kirksville, MO 63501, United States

Richard C Deth, Department of Pharmaceutical Sciences, Nova Southeastern University, Fort Lauderdale, FL 33314, United States

Roseanne Schnoll, Department of Health and Nutrition Sciences, Brooklyn College of CUNY, Brooklyn, NY 11210, United States

Steven G Gilbert, Department of Research, Institute of Neurotoxicology and Neurological Disorders, Seattle, WA 98105, United States

Walter J Lukiw, LSU Neuroscience Center, Louisiana State University Health Sciences Center, New Orleans, LA 70112, United States

Amanda L Hitt, Food Integrity Campaign, Government Accountability Project, Columbia, WA 20006, United States

Amanda L Hitt, Department of Legal, Food Ingredient and Health Research Institute, Naalehu, HI 96772, United States

Corresponding author: Renee J Dufault, PhD, Doctor, Department of Research, Food Ingredient and Health Research Institute, PO Box 1055, Naalehu, HI 96772, United States.
rdufault@foodingredient.info

Abstract

In the United States, schools offer special education services to children who are diagnosed with a learning or neurodevelopmental disorder and have difficulty meeting their learning goals. Pediatricians may play a key role in helping children access special education services. The number of children ages 6-21 in the United States receiving special education services increased 10.4% from 2006 to 2021. Children receiving special education services under the autism category increased 242% during the same period. The demand for special education services for

children under the developmental delay and other health impaired categories increased by 184% and 83% respectively. Although student enrollment in American schools has remained stable since 2006, the percentage distribution of children receiving special education services nearly tripled for the autism category and quadrupled for the developmental delay category by 2021. Allowable heavy metal residues remain persistent in the American food supply due to food ingredient manufacturing processes. Numerous clinical trial data indicate heavy metal exposures and poor diet are the primary epigenetic factors responsible for the autism and attention deficit hyperactivity disorder epidemics. Dietary heavy metal exposures, especially inorganic mercury and lead may impact gene behavior across generations. In 2021, the United States Congress found heavy metal residues problematic in the American food supply but took no legislative action. Mandatory health warning labels on select foods may be the only way to reduce dietary heavy metal exposures and improve child learning across generations.

Key Words: Lead exposure; Mercury; Oxidative stress; Methylation patterns; Epigenetic inheritance; Autism

Core Tip: Heavy metal residues are pervasive in the food supply and allowed by the Code of Federal Regulations because of food ingredient manufacturing processes. Children fed food with heavy metal residues may bioaccumulate inorganic mercury and lead in their blood and exhibit symptoms of autism or attention deficit/hyperactivity-disorder. Prenatal dietary exposures to heavy metals may impact gene activity in children and create learning difficulties requiring special education services. Educators see an increase in the prevalence of autism and developmental delay with cases doubling or tripling since 2006. Food quality issues may be impacting epigenetic inheritance of autism and related disorders.

Citation: Dufault RJ, Crider RA, Deth RC, Schnoll R, Gilbert SG, Lukiw WJ, Hitt AL. Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance? *World J Clin Pediatr* 2023; 12(2): 25-37
URL: https://www.wjgnet.com/2219-2808/full/v12/i2/25.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i2.25

INTRODUCTION

The special education system in the United States began developing in the 1970s and is mandated by Congress through the Individuals with Disabilities Education Act (IDEA). This act is codified in title 34 of the Code of Federal Regulations and governs how states must meet the educational needs of students between the ages of 3 and 21 who are developmentally impaired, either cognitively or intellectually, and have difficulty learning in the general education classroom. IDEA requires states to provide a free and appropriate public education to each disabled student at no cost to the parents. Through IDEA, the United States Department of Education is authorized to provide federal funding to states in the form of grants which are distributed each year and based on the child count or number of children in each state in need of special education services[1]. The funding is used by states to pay for special education teachers who provide academic services, school psychologists, occupational therapists, transportation, classroom aides, instructional materials, and parent education[2].

Under IDEA, there are 13 disability categories states must use to determine student eligibility for special education and related services[3]. Young children with autism are found eligible for services under different disability categories depending on their age and dominant behaviors[4]. Typical disability categories used to determine eligibility for children exhibiting symptoms of autism include Autism, Developmental Delay, Speech/Language Impairment, or other health impaired (OHI) if attention deficit hyperactivity disorder (ADHD) is a co-morbid condition[5]. In a 2009 review of the literature, Yerys *et al*[6] estimated 30% of children with autism also meet diagnostic criteria for ADHD and another 20% of children with autism exhibit subthreshold clinical symptoms for ADHD. This review provides up-to-date analyses of the prevalence data for disability categories made available to the public by the United States government. Etiology of autism and ADHD and future trends will be discussed from an epigenetic perspective.

CURRENT AUTISM AND ADHD PREVALENCE IN THE UNITED STATES

Medical researchers at the United States Center for Disease Control (CDC) and Prevention have been monitoring the prevalence of autism and developmental disabilities in eight-year-old children living in select communities in up to eleven states since 2000. Between 2000 and 2002, the estimated autism prevalence among eight-year-old children living in these communities was 1/150 or 6.7/1000[7]. By 2018, the autism prevalence in eight-year-old children living in these communities had increased to 1/44 or 23/1000[7]. Autism was 4.2 times more prevalent in boys than girls[7]. CDC researchers collect their autism prevalence data through federal contracts with community medical and educational service providers in CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.

Our review of the data collected by CDC's ADDM network revealed the prevalence of autism among children aged 8 years has increased 70% from 2000 to 2018[8]. Although the increase over the entire period is substantial, more noteworthy is the fact that the rate of change is increasing. From 2000 to 2010, the rate of change was 1.6/1000 per 2-year measurement period. From 2012 to 2018, the rate of change nearly doubled as it increased to 2.7/1000 per 2-year measurement period. Table 1 clearly shows these changes.

The CDC has not set up a network to track ADHD prevalence in any age group or community, however, periodically, the agency studies the prevalence of ADHD using data gathered from the National Health Interview Survey (NHIS)[9]. The most recent analysis of the NHIS data (n = 146457) was conducted by Xu *et al*[10] who found a significant increase in the prevalence of ADHD in a representative sample of United States children aged 4-17 with 14% of boys and 6.3% of girls given the diagnosis in 2015-2016.

Public policy and medical researchers can better understand the magnitude of the problem of autism and ADHD across the United States by studying the special education data collected by the United States Department of Education each year. Newschaffer *et al*[11] first used this data set to determine increasing autism and ADHD prevalence over time in United States children between the ages of 6 and 17 from 1992 to 2001. ADHD prevalence trends can be determined by tracking the children receiving special education services under the OHI category[11,12]. Dufault *et al*[12] reviewed the special education data set available for the years 2005-2010 and found the number of children in the United States between the ages 6-21 receiving services under the IDEA categories of autism and OHI increased 91% and 26% respectively. We conducted an assessment and analysis of the special education data currently available at the United States Department of Education for the years 2006[13], 2011[13], and 2021[14] in preparation for this review and present our results in Table 2.

The overall number of children ages 6-21 in the United States receiving special education services increased 10.4% from 2006 to 2021. The number of children receiving special education services under the autism category increased 242% during the same period. The demand for special education services for children with developmental delay and OHI increased by 184% and 83% respectively. These increases should be alarming to policymakers, teachers, parents, and others who are responsible for educating these learning-disabled children in classrooms across the country given the stable student enrollment in public schools during the last fifteen years. The National Center for Education Statistics (NCES) reported a total enrollment of 49.5 million children in public elementary and secondary schools in grades pre-k to 12 during the fall of 2021[15]. Prior to the COVID pandemic, public school enrollment in grades pre-k to 12 ranged from 49.5 million students in the fall of 2010 to 50.8 million students in the fall of 2019[15]. The NCES created Figure 1 to provide a visual representation of the student enrollment trends in the United States since 2003[16].

While student enrollment in United States schools has remained stable since the early 2000s, our data shows the percentage distribution of children receiving special education services in the autism disability category has nearly tripled between 2006 and 2021. The percentage distribution of children receiving special education services in the developmental delay category has quadrupled over the same period. Figure 2, created using the data in Table 2, shows the burden of care required for children in special education disability categories associated with ADHD and autism compared to all other disability categories in 2006 and 2021. The burden of care for American children with autism or ADHD related special education services has increased dramatically between 2006-2021 even as student enrollment remains stable.

Data collected through the ADDM network and analyzed by CDC medical researchers reveal autism prevalence rates in the United States vary by geographic location[7]. Dufault *et al*[12] analyzed autism prevalence data from the United States and Italy and proposed a macroepigenetic model to explain why autism prevalence may vary across geographic regions depending on nutrition deficits in the population under study, exposure to organophosphate (OP) pesticides, and the influence of various dietary factors known to impact gene expression. Such dietary factors may include high intake of high fructose corn syrup (HFCS) and exposures to heavy metal residues from the consumption of processed foods[12]. Dietary epigenetic factors vary between countries due to policies and regulations that determine allowable exposures to heavy metal and pesticide residues in food and food ingredients[17].

A recent review of the literature indicates the primary factors involved in the development of autism, ADHD, and disruptive child behaviors are exposures to heavy metals[18-21]. Recent clinical trial data collected from cohort studies around the world show mercury is the most common heavy metal

Table 1 Rate of change in Center for Disease Control prevalence estimates among 8-year-old children between 2000-2018

Year	Autism prevalence estimate among 8-year-old children (CDC)	Rate of change
2000	6.7/1000	
2002	6.6/1000	
2004	8/1000	
2006	9/1000	
2008	11.3/1000	
2010	14.7/1000	1.6/1000 (from 2000-2010)
2012	14.5/1000	
2014	16.8/1000	
2016	18.5/1000	
2018	23/1000	2.7/1000 (from 2012-2018)

CDC: Center for Disease Control.

Table 2 Number of United States students ages 6-21 served under Individuals with Disabilities Education Act by disability category & year

Year	Autism	OHI (including ADHD)	Speech/language	Developmental delay (3-9 yr only)	All disabilities
2006	224594	599494	1160904	89931	6081890
2011	407214	734348	1071555	115642	5789884
2021	768179	1097251	1183310	255787	6712010
% Change (2006-2021)	+242.0%	+83.0%	+1.9%	+184.4%	+10.4%

OHI: Other health impaired; ADHD: Attention deficit hyperactivity disorder.

exposure of concern in the development of autism[22,23] and lead is the most common heavy metal exposure of concern in children with ADHD[24-27].

SOURCES OF HEAVY METAL EXPOSURES IN THE UNITED STATES FOOD SUPPLY

Ingredients in the American food supply with allowable lead, arsenic, and mercury residues are abundant[28]. The allowed heavy metal residues are based on the individual food ingredient manufacturing processes. For example, food colors made from petroleum[29] are expected to contain trace amounts of heavy metals because petroleum is extracted from beneath the earth's crust where heavy metals are found[28]. The United States Food and Drug Administration (FDA) therefore has a process in place to ensure the petroleum-based food colors do not contain more than the "allowable" levels of inorganic mercury (≤ 1 ppm Hg), lead (≤ 10 ppm Pb), and arsenic (≤ 3 ppm As)[30]. FDA regulations require manufacturers to test and certify each batch of food coloring to ensure the allowable levels of heavy metals are not exceeded[30]. All food colors requiring FDA certification are referred to as "certified food colors".

In addition to certified food colors, other food ingredients may contain various levels of heavy metal residues. Some preservatives and a few food colors exempt from the FDA certification requirements have legally allowable levels of arsenic, lead, cadmium, or inorganic mercury[28]. Corn sweetener products such as HFCS may also be at risk of mercury contamination due to their manufacturing process which may involve the use of mercury cell chlor-alkali products[31-33] or the direct application of mercuric chloride onto the corn starch at the front end of the refining process[34]. Vegetable oils risk heavy metal contamination from a variety of sources including the use of fertilizers and pesticides during farming and the use of process aids (*e.g.*, phosphoric acid, citric acid) during refining[35]. The use of phosphoric acid may introduce up to 10 ppm Pb and 1 ppm As while the use of citric acid may introduce up to 1 ppm Pb during the vegetable oil refining process[35].

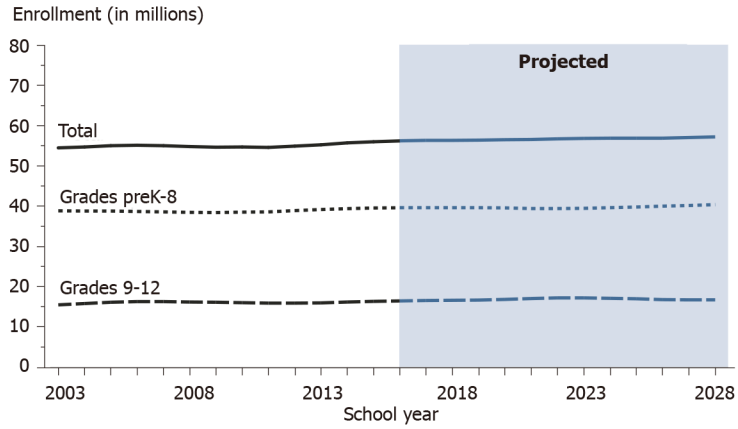

Figure 1 Actual and projected numbers for enrollment in elementary and secondary schools, by grade level: Fall 2003 through fall 2028. Pre-K: Pre-kindergarten. Citation: Hussar WJ, Bailey TM. Projections of education statistics to 2028. Washington: National Center for Education Statistics. Copyright © U.S. Department of Education 2020. Published by National Center for Education Statistics. The authors have obtained the permission for figure using from the National Center for Education Statistics (Supplementary material).

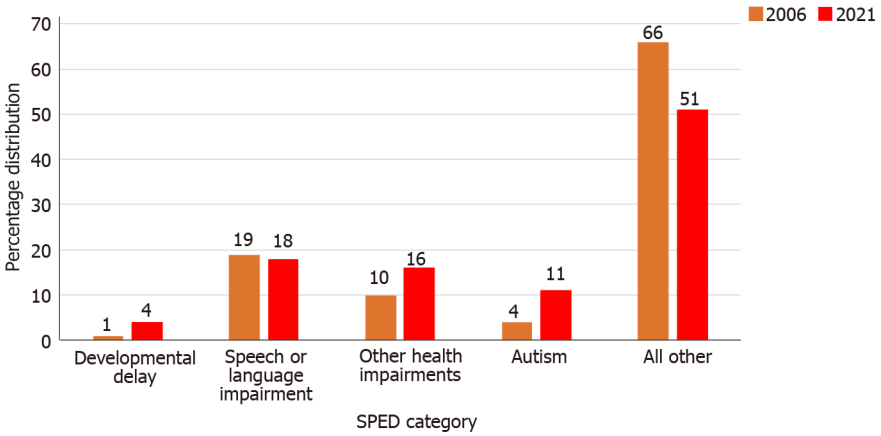

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Figure 2 Percentage distribution of American children receiving special education services, 2006 and 2021. SPED: Special education.

The risk of heavy metal exposure in humans from eating foods containing heavy metal residues was first demonstrated by Khan *et al*[36] who found heavy metal concentrations in foodstuffs significantly correlated with the same heavy metals detected in human blood. Wells *et al*[37] analyzed data (n = 1770 for non-fish eaters, n = 5427 for fish/seafood eaters) from the CDC's National Health and Nutrition Examination Survey (NHANES) and verified mercury exposure from non-fish food occurs in the American population through the consumption of vegetable oil, an ingredient found in many processed foods. In another study using NHANES data (n = 11354), Raehsler *et al*[38] determined a diet high in ultra-processed foods[39], such as a gluten-free diet, may lead to significantly higher levels of mercury, cadmium, and lead in blood.

Vegetable oils, HFCS, and corn syrup solids are common ingredients used in the ultra-processed food supply[40]. The United States Department of Agriculture (USDA) provides estimates of the annual per capita dietary intake of corn sweeteners ("sugar") and vegetable oils ("fat") *via* the Food Availability (Per Capita) Data System[41]. We were able to extract the most current data available from the system to determine the average American consumed 21.6 pounds per year of HFCS in 2019 and 36 pounds per year vegetable oil ("salad and cooking oils") in 2010[41]. Unfortunately, the USDA does not analyze corn sweeteners or vegetable oil products to determine heavy metal residue levels. The USDA also does not track "corn syrup solid" consumption trends. Corn syrup solids and vegetable oils are the primary ingredients in many baby formula food products[42,43].

In 2019, the United States Congress investigated consumer reports alleging elevated levels of toxic heavy metals in the American baby food supply[44]. In response, seven of the largest baby food manufacturers provided internal documents and baby food test results to Congress[44]. After reviewing the manufacturers' information, the United States Congress issued a report in February 2021 that included the following findings: Arsenic, lead, and cadmium residues were present in baby foods made by all the responding companies and mercury residues were detected by the one company that tested

for it[44]. The mercury levels were reported at higher concentrations many times higher than allowed under existing regulations[44]. The United States Congress issued a second report in September 2021 with the recommendation that baby food manufacturers should "voluntarily find substitutes for ingredients that are high in toxic heavy metals"[45].

In addition to the United States Congressional reports, we identified a few other studies conducted to determine heavy metal exposures in baby formula or baby foods. Dabeka and McKenzie[46] measured total mercury levels in 150 infant formula products sold in Canada in 2003. Using the measurement method available at the time, mercury concentrations in 76% of the samples fell below the limit of detection[46]. There were, however, clear cases of low-level mercury contamination (up to 1.5 ng/g) in individual lots of powdered formula[46]. In a sample size of 87, Martins *et al*[47] identified median total mercury concentrations of 0.50 ug/kg in baby formula analyzed in Portugal. In a more recent study, Gardener *et al*[48] analyzed 564 baby food (including infant formula, cereals, meals, juices, snacks) products for cadmium and lead. While lead was only detected in 37% of the samples, cadmium was detected in 57% of the samples collected from the United States food supply[48].

The multiple findings of heavy metal residues in the food supply are important because children diagnosed with symptoms of autism have difficulty metabolizing and excreting heavy metals from their bloodstream due to their biologically embedded epigenome[17]. In the most recent study, Hassan *et al*[49] found higher aluminum, mercury, and lead levels in the blood of children with autism (n = 73) compared to children serving in a healthy age- and sex- matched control group (n = 73). The finding of higher aluminum in this case-control study is alarming because a novel laboratory experiment recently showed significant synergism in the toxicity of aluminum and mercury when added together in a culture of human brain cells[50]. Alabdali *et al*[51] demonstrated the levels of mercury and lead in the blood of children with autism correlate with the severity of their symptoms to include social and cognitive impairment. The synergistic neurotoxic damage caused by dietary inorganic mercury, lead, and cadmium exposures was recently demonstrated in a study conducted on rats[52]. Co-exposures to specific heavy metals cause more extensive damage to brain cells. When studied alone, however, mercury exposure is a significant factor in the development of autism. In agreement with Alabdali *et al*[51], Mostafa *et al*[53] also found mercury levels were significantly higher (P < 0.001) in the blood of children with autism (n = 84) compared to the healthy matched controls (n = 84). There was also a significant (P < 0.0001) and positive linear relationship between mercury in the blood of children with autism and symptom severity[53].

Children diagnosed with ADHD bioaccumulate lead in their blood because of dietary calcium and zinc deficits or losses, in conjunction with lead exposures[17]. In an analysis of NHANES data gathered between 1976-1980 (n = 2926), Mahaffey *et al*[54] found an inverse relationship exists between lead in blood and dietary calcium intake. More recently, Gulson *et al*[55] found a positive association between lead content in the diets of 108 children over a 5-year period and the lead concentration in their blood. There was also a statistically significant inverse relationships between dietary zinc and calcium and lead levels in the children's blood[55]. As dietary zinc and calcium levels increased, the blood lead levels decreased[55]. Lead exposure has historically been recognized by governments and public health agencies to adversely impact child neurodevelopment. According to the CDC, no safe level of lead in blood has been identified and even low levels of lead in blood can negatively impact child intelligence and ability to learn[56].

ETIOLOGY OF AUTISM AND ADHD: AN EPIGENETIC PERSPECTIVE ON HEAVY METAL EXPOSURES AND POOR DIET

Food ingredients with allowable lead, arsenic, cadmium, and mercury residues may impact gene behavior by synergistically interfering with heavy metal excretion[57]. For example, in addition to being a source of lead, arsenic, and mercury exposure, the food color tartrazine (yellow 5) has been shown to negatively impact zinc status of children with ADHD[58,59]. Lower levels of zinc may downregulate metallothionein (MT) gene expression, thereby further reducing heavy metal detoxification and elimination[57,60], especially in children with autism[60,61]. The MT gene promotes the synthesis of the MT protein which is zinc dependent because it requires up to seven zinc atoms per molecule[62]. Hundreds of molecules bind together to make a MT protein strand. With adequate zinc reserves, the MT transporter protein prevents heavy metal accumulation as it continuously swaps zinc for lead, mercury, arsenic, or cadmium as part of the body's metal detoxification and elimination process[63]. Dietary zinc is therefore crucial for supporting the body's effort to rid itself of harmful metals that create conditions for oxidative stress and the development of various disease conditions[64]. The more zinc deficient a child is, or becomes because of his/her diet, the more likely he/she will accumulate heavy metals in his bloodstream due to the disruption in MT gene activity[57]. Zinc is an important macromineral; it is a dietary element needed by the body in copious amounts. Food ingredients, such as yellow 5, that are a source of heavy metal exposure and lead to zinc loss may be eliminated from the food supply to improve child health and learning outcomes.

Another example of a food ingredient that can disrupt macromineral homeostasis in humans is HFCS [57,65]. In a study conducted by the USDA, Milne and Nielsen[65] fed eleven men a mixed Western diet for four 42-d dietary periods. When fed a high fructose diet, the men showed significant calcium ($P < 0.007$) and phosphorus ($P < 0.005$) losses, especially when dietary magnesium intake was low[65]. In their conclusion, Milne and Nielsen[65] suggested further studies are needed to see if a high fructose diet with the accompanied calcium loss and low dietary magnesium lead to the development of osteoporosis. With respect to child health, there is a need to conduct other studies. Because HFCS consumption may lead to calcium losses, its overconsumption by children may result in the bioaccumulation of lead stores in the body[54,55]. More research needs to be done to determine if HFCS consumption adversely impacts children with ADHD or autism by contributing to calcium losses and the bioaccumulation of lead.

The calcium losses that resulted from the consumption of HFCS is a finding of concern especially when the average American consumed 21.6 pounds of HFCS in 2019. Calcium is required by the body in copious amounts to conduct important processes. For example, the paraoxonase (PON1) gene relies on calcium to synthesize the PON1 enzymes that break down and detoxify the metabolites of OP pesticides [66]. PON1 gene expression varies in children with autism and ADHD[67] and can be inhibited by dietary factors such as fructose and heavy metal (*e.g.*, lead, inorganic mercury, or cadmium) intake[66,68,69]. Children with autism and ADHD have nutrient poor diets and are thus thought to be more susceptible to the neurotoxic effects of OP pesticide exposure especially when concurrently exposed to heavy metals[17,67]. A search of the literature did not yield even one study on humans to determine the effect of concurrent or co-exposures to multiple xenobiotic agents found in the food supply.

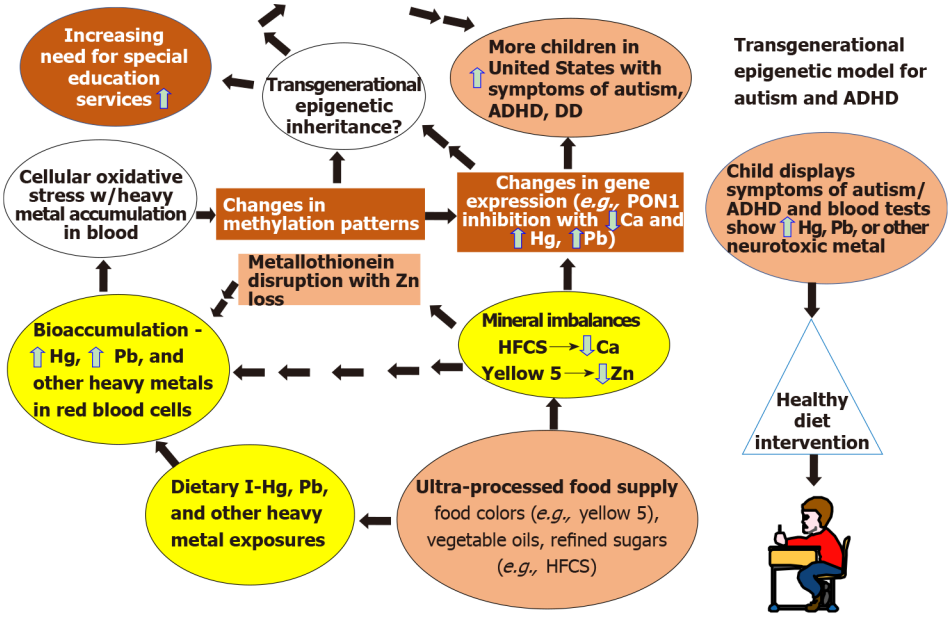
However, Zhou *et al*[70] conducted a recent case-control study on pregnant rats to determine if low concurrent exposures to lead, cadmium, and inorganic mercury *via* diet resulted in adverse outcomes among the pups. The low dose exposures to the heavy metals induced damage to several organs including brain tissue in both the dosed rats and their pups[70]. The heavy metal concentration in blood and brain tissue significantly increased in a dose dependent manner[70]. Zhou *et al*[70] also observed significant increases in oxidative stress, intracellular free calcium, and cell apoptosis in the brain tissue of the cases compared to the controls. Learning and memory deficits and sensory perception issues were also observed in the behavior of the prenatally dosed pups along with the histopathological changes in hippocampus morphology[70]. This is the first study showing dietary low-level lead, cadmium, and inorganic mercury co-exposures in rats are a relevant model for evaluating human dietary heavy metal exposure levels that adversely impact child neurobehavior and development[70]. Zhou *et al*[70] also identified changes in the behavior of select genes in select organs in response to the concurrent heavy metal exposures. Figure 3 shows the updated epigenetic model for how autism and ADHD may develop in children because of concurrent exposures to heavy metals in the food supply.

Dietary nutritional deficits, exposures to food ingredients that induce macromineral imbalances, and heavy metal exposures may impact gene behavior through a variety of mechanisms such as histone or DNA methylation[71,72]. Methylation patterns in the cellular environment may change under conditions of oxidative stress which simply means the cell contains too many molecules made up of reactive oxygen species (ROS). The primary ROS (molecular species) are hydrogen peroxide, superoxide anion, hydroxyl radical. When the cell does not contain enough of the molecules (antioxidants) it needs to neutralize the ROS, it is under oxidative stress and the DNA or RNA methylation pattern can change along with gene behavior. The formation of ROS and the development of oxidative stress can be induced by the presence of heavy metals (*e.g.*, inorganic mercury, lead) in the cellular environment.

As heavy metals accumulate in red blood cells, oxidative stress occurs, and methylation patterns may change. Oxidative stress caused by heavy metal exposure may be alleviated with the introduction of nutrients that serve as antioxidants. Examples of such nutrients include zinc[73] and selenium[74]. It is important to reduce dietary heavy metal intake and improve diet to prevent the bioaccumulation of heavy metals in the blood cells of children who exhibit symptoms associated with autism and/or ADHD[17]. In addition to creating conditions for symptomatic autism and ADHD in childhood[17], heavy metal exposures can create changes in DNA methylation patterns that impact child neurodevelopment in the womb[75-78] and contribute to adverse health outcomes in adulthood[78]. DNA methylation is an important regulator of gene expression; a methyl group which is a molecule made up of one carbon and three hydrogen atoms (CH_3) attaches to DNA and serves as a switch to turn a gene on or off from one generation to the next for better or worse.

EMERGING TRANSGENERATIONAL EPIGENETIC INHERITANCE PATTERNS MAY EXPLAIN INCREASING AUTISM AND ADHD

Changes in methylation patterns and gene behavior that occur in response to heavy metal exposures and nutritional factors are common in the development of disease conditions across generations[79]. The term used to describe these cross generational changes in methylation patterns is "transgenerational epigenetic inheritance[79]". Methylation patterns on genes vary among humans and can be modified by useful or harmful dietary factors[79]. For example, folate and vitamins B6 and B12 are useful dietary



DOI: 10.5409/wjcp.v12.i2.25

Figure 3 Transgenerational epigenetic model for autism and attention deficit/hyperactivity disorder. ADHD: Attention deficit/hyperactivity disorder; HFCS: High fructose corn syrup; I-Hg: Inorganic mercury; Pb: Lead; Ca: Calcium; Zn: Zinc; PON1: Paraoxonase; DD: Developmental delay.

factors that induce the formation of the methyl donor (CH_3) in DNA methylation[79]. Conversely, prenatal inorganic mercury exposure may be a harmful dietary factor because it has been shown to induce changes in methylation levels of the PON1 gene that persist into early childhood[77]. Cardenas *et al*[77] showed changes in methylation levels of PON1 in cord blood from mercury exposures could be used to predict lower cognitive scores in childhood. These findings are not surprising in the child neurodevelopment field of study because we know suppression of the PON1 gene and/or the bioaccumulation of heavy metals create conditions for oxidative stress which is a hallmark feature of autism[80, 81] along with impaired or decreased DNA methylation capacity[12]. The emerging evidence strongly suggests DNA methylation patterns altered by dietary stimuli may be stable or passed on to the next generation and this is of great concern[82].

Changes in DNA methylation patterns during pregnancy, infancy, and adult life can lead to the inheritance of disease conditions such as obesity and diabetes[82]. Ando *et al*[83] recently conducted a rat study and found changes in DNA methylation patterns on a specific gene led to the development of insulin resistance and hyperlipidemia in offspring when pregnant rats were fed a diet consisting of 20% HFCS[83]. This transgenerational epigenetic inheritance of metabolic abnormalities observed in rats has not yet been studied in humans to determine which gene(s) may be impacted by the consumption of HFCS[83]. In the case of autism and ADHD, however, the literature strongly supports the idea that changes in DNA methylation patterns from prenatal exposures to lead and mercury may lead to the inheritance of the same methylation patterns in human offspring[75].

Bozack *et al*[75] investigated the epigenome-wide associations of maternal heavy metal measurements in blood (n = 361) with cord blood DNA methylation (n = 361) and persistent DNA methylation changes in mid-childhood (n = 333, 6-10 years). Of the twelve metals studied, Bozack *et al*[75] found evidence that prenatal exposures to lead and manganese are associated with changes in cord blood DNA methylation patterns which may persist in children when measured at mid-childhood[75]. In a separate meta-analysis of epigenome-wide association studies involving the cord blood of 2477 children, Neumann *et al*[76] found evidence that DNA methylation at birth is strongly associated with the development of ADHD ($P = 1 \times 10^{-7}$).

Persistent DNA methylation changes resulting from prenatal mercury exposures (n = 321) were observed in a study of epigenome-wide methylation patterns conducted by Cardenas *et al*[77]. Among male children, prenatal mercury exposures were associated with cord blood methylation at the PON1 gene locus and lower cognitive test scores measured in early childhood[77]. Cord blood DNA methylation levels at the PON1 gene locus is widely known to be associated with lower PON1 gene activity[77]. In a commentary citing elements of the macroepigenetic model, Dufault and Gilbert[84] explain that because male children have lower PON1 gene activity, prenatal mercury exposure associated with cord blood methylation at the PON1 gene may explain why autism impacts males more often than females. This observation is relevant; CDC reported the finding that autism was 4.2 times more prevalent in boys than girls in 2018[7].

PERSPECTIVES ON FUTURE RESEARCH AND ACTIONS

Research evidence presented in a recent review suggests heavy metal exposures are among the most significant environmental agents impacting human health[85]. Prenatal exposures to lead, inorganic mercury and other heavy metals can induce developmental epigenetic programming in the human population[85]. Research evidence provided in this review supports the idea that food quality issues are impacting epigenetic inheritance. Fortunately, developmental epigenetic modifications, including methylation patterns, may be reversible. More research is needed to identify what intervention measures can be taken to lower dietary heavy metal exposures in children and whether such measures may reverse methylation patterns and gene behaviors.

Switching to a healthy diet and eliminating the intake of ultra-processed foods is currently one intervention used to reduce heavy metals in blood and improve behaviors and learning among children with autism or ADHD[17]. In the current political environment, interventions for mitigating climate change are on the rise along with the trend towards adopting a plant-based animal product alternative (PB-APA) diet[86]. Unfortunately, PB-APA foods tend to be ultra-processed so this trend to increase ultra-processed food intake may have detrimental effects on children. It is important to ensure these "ultra-processed" PB-APA foods do not contribute to child heavy metal exposures. Studies need to be conducted to determine whether the ultra-processed PB-APA food products and the ingredients they are made of are at risk of heavy metal contamination.

The impact of specific food ingredients on macro and micro mineral balance in the human body needs further study. To date only two food ingredients are known to create mineral imbalances: Yellow 5 (tartrazine) and HFCS. There are many more ingredients commonly found in the ultra-processed food supply that could impact mineral balance. Yellow 6 is similar to yellow 5 with the same allowable lead, inorganic mercury, and arsenic residue levels in each manufactured batch; its overconsumption may also lead to zinc loss. A case-control study could be designed to determine the impact of yellow 5 and/or yellow 6 intake on zinc balance, methylation patterns, and MT gene activity levels. Determining how mineral imbalances and dietary exposures to heavy metals impact DNA methylation and gene expression in children with autism or ADHD would be useful.

The mechanisms by which heavy metals bioaccumulate in children with autism and/or ADHD are poorly understood. Dietary factors such as zinc, calcium, and HFCS intake could be key to understanding how dietary heavy metals bioaccumulate in a child's blood. Intervention studies could be designed to consider pre-post intervention dietary intake (survey intake of whole foods and dairy *vs* ultra-processed foods including those with HFCS, vegetable oils, food colors, preservatives), pre-post intervention heavy metal exposures (heavy metal measurements in blood), pre-post intervention DNA methylation patterns, pre-post intervention gene activity levels (*e.g.*, PON1, MT). Instructions for creating a healthy diet intervention that reduces dietary heavy metal exposures are available[17].

With autism and ADHD prevalence climbing at alarming rates with each successive generation it is clear more must be done to reduce dietary heavy metal exposures and improve child nutrition. Unfortunately, until advancements are made on the epigenomic front, we can only moderate the increasing autism and ADHD prevalence through the introduction of policies and laws that eliminate exposures to certain harmful food ingredients and reduce dietary exposures to heavy metal residues.

The United States Congress has taken an excellent first step in collecting heavy metal residue data from food manufacturers[44,45]. Decisive action is needed now to address the autism and ADHD epidemic in the United States. Ethical considerations need to guide the decision making among Congressional members. We must acknowledge what we know and what we don't know about the contaminants in the food supply. In the case of lead and inorganic mercury, we known there is no safe level of exposure, and any exposure is harmful to the developing fetus[87]. With the knowledge that widespread heavy metal contamination exists in the United States food supply, Congress could now choose to ban food ingredients with allowable heavy metals. Alternatively, Congress could mandate warning labels on foods that contain ingredients with allowable heavy metal residues. At least warning labels would serve to inform consumers and expectant parents of the health risks associated with eating food ingredients with allowable lead and inorganic mercury residues.

There is compelling evidence to suggest that mandatory health warning labels do encourage consumers to adopt more healthful purchasing behaviors[88]. Song *et al*[88] conducted a meta-analysis of the impact of color-coded and warning nutrition labelling schemes on consumer behavior. Of the 134 studies analyzed, the traffic light labelling system, nutrient warning, and health warning labels were the most effective front-of-package labeling methods for influencing consumers' purchasing choices[88]. Health warning labels reduced consumers' perception of the healthfulness of less healthful products while increasing their perceived disease risk from eating unhealthful products[88].

Mandatory health warning labels on foods containing ingredients with allowable heavy metal residues would direct parent purchasing behaviors away from unhealthful food products in the United States free market system. Movement away from the consumption of these foods could lead to significant reductions in child heavy metal exposures. Without any changes in United States food safety law, however, unabated dietary exposures to inorganic mercury and lead will continue to occur because of the adulterated American food supply. Autism and ADHD prevalence will continue to rise as transgenerational epigenetic inheritance becomes the norm.

CONCLUSION

The American food supply is contaminated with allowable heavy metals in specific food ingredients. Americans continue to be exposed to inorganic mercury and lead over time which can impact the national epigenome. The United States Congress has confirmed heavy metal exposures are occurring in American children due to contaminants in the food supply. We are seeing sustainable and alarming increases in autism and ADHD prevalence with cases doubling or tripling in one generation. Congress may act now to mandate the health warning label on foods containing food ingredients with allowable heavy metal residues before child intellectual development and learning erodes any further.

FOOTNOTES

Author contributions: Dufault RJ developed and wrote the original and revised manuscripts, compiled, and analyzed the dataset for table 2, created figure 3, obtained and verified public use of figure 1; Crider RA compiled and analyzed the dataset for table 1, created figure 2, provided comments on both manuscripts; Deth RC provided input on oxidative stress for revision; Schnoll R provided input on zinc metabolism and title for revision; Gilbert SG provided input on ethical considerations for revision; Lukiw WJ provided input on concurrent exposures to heavy metals for revision; Hitt AL provided insights on plant based animal product alternatives for revision; and all authors have read and approved the final manuscript.

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

Country/Territory of origin: United States

ORCID number: Renee J Dufault 0000-0002-8299-3768; Raquel A Crider 0000-0003-2217-1356; Richard C Deth 0000-0002-7717-7037; Roseanne Schnoll 0000-0002-5051-550X; Steven G Gilbert 0000-0002-0087-3974; Walter J Lukiw 0000-0001-5500-4402; Amanda L Hitt 0000-0001-5903-4131.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Clinical Pediatrics

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

World J Clin Pediatr 2023 March 9; 12(2): 38-44

DOI: 10.5409/wjcp.v12.i2.38

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Clinical and Translational Research

Factors associated with subsequent surgery after septic arthritis of the knee in children

Jennifer Marie O'Donnell, Ernest Ekunseitan, Ishaan Swarup

Specialty type: Orthopedics

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
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Carrozzo A; Muthu S, India

Received: December 1, 2022
Peer-review started: December 1, 2022
First decision: December 13, 2022
Revised: January 13, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 9, 2023

Jennifer Marie O'Donnell, Orthopaedic Surgery, University of California San Francisco, San Francisco, CA 94143, United States

Ernest Ekunseitan, Medical School, University of California San Francisco, San Francisco, CA 94143, United States

Ishaan Swarup, Pediatric Orthopaedic Surgery, UCSF Benioff Children's Hospital, Oakland, CA 94609, United States

Corresponding author: Ishaan Swarup, MD, Assistant Professor, Pediatric Orthopaedic Surgery, UCSF Benioff Children's Hospital, 747 52nd Street, Oakland, CA 94609, United States. ishaan.swarup@ucsf.edu

Abstract

BACKGROUND

Septic arthritis of the knee in children is a challenging problem. Surgical debridement is an established treatment, but there is a paucity of literature on long-term prognosis.

AIM

To determine the rates and factors associated with return to surgery (RTS) and readmission after index surgical debridement for septic arthritis of the knee in children.

METHODS

This is a retrospective cohort study that utilizes data from the Healthcare Cost and Utilization Project (HCUP). We included patients between ages 0 to 18 years that underwent surgical debridement for septic arthritis of the knee between 2005 and 2017. Demographic data included age, gender, race, hospital type and insurance type. Clinical data including index admission length of stay (LOS) and Charlson Comorbidity Index (CCI) were available from the HCUP database. Descriptive statistics were used to summarize the data and univariate and multivariate analyses were performed.

RESULTS

Nine-hundred thirty-two cases of pediatric septic knee were included. This cohort was 62.3% male, with mean age of 9.0 (± 6.1) years. Approximately 46% of patients were white and approximately half had Medicaid insurance. Thirty-six

patients (3.6%) required RTS at a minimum of 2 year after index surgery, and 172 patients (18.5%) were readmitted at any point. The mean readmission LOS was 11.6(± 11.3) d. Higher CCI was associated with RTS (P = 0.041). There were no significant associations in age, gender, race, insurance type, or type of hospital to which patients presented. Multivariate analysis showed that both increased CCI (P = 0.008) and shorter LOS (P = 0.019) were predictive of RTS.

CONCLUSION

Septic arthritis of the knee is an important condition in children. The CCI was associated with RTS at a minimum of 2 years after index procedure. No association was found with age, gender, race, insurance type, or hospital type. Shorter LOS and CCI were associated with RTS in multivariate analysis. Overall, risk of subsequent surgery and readmission after pediatric septic knee arthritis is low, and CCI and shorter LOS are predictive of RTS.

Key Words: Septic arthritis; knee; Orthopaedic surgery; Infection; Osteomyelitis; Debridement

Core Tip: Septic arthritis of the knee is an important condition in children. The Charlson Comorbidity Index and shorter length of stay during index admission were associated with return to surgery after index procedure. No association was found with age, gender, race, insurance type, or hospital type. Risk of subsequent surgery and readmission after pediatric septic arthritis of the knee is low; however, presence of comorbidities and shorter length of stay are predictive of subsequent surgery.

Citation: O'Donnell JM, Ekunseitan E, Swarup I. Factors associated with subsequent surgery after septic arthritis of the knee in children. *World J Clin Pediatr* 2023; 12(2): 38-44
URL: https://www.wjgnet.com/2219-2808/full/v12/i2/38.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i2.38

INTRODUCTION

Septic knee occurs in children at a rate between 5 and 12 per 100000[1,2]. This pathological invasion of the joint in children can place patients at risk for osteomyelitis, recurrent joint infection, and sepsis. Septic arthritis is often diagnosed clinically in pediatric patients, or can be diagnosed and treated based on arthrocentesis. Timely diagnosis and management is critical to decrease the risk of damage to articular cartilage and the joint[3]. Acute septic arthritis is typically of hematogenous origin in children. It is more common in boys and the most common causative agent is *Staphylococcus aureus*, with methicillin-resistant strains on the rise[4].

Treatment is typically comprised of antibiotics as well as surgical irrigation and debridement, either *via* arthroscopy or arthrotomy, which is typically determined by surgeon preference. Long-term sequelae of septic arthritis in children can include persistent infection, growth disturbance, chondrolysis, and degenerative arthritis[5]. However, it is important to note that complications such as symptomatic osteoarthritis develop slowly, and longer follow-up is required to detect all possible sequelae[6]. The rate of these sequelae has been cited at 10% among all patients with septic arthritis of the knee, and is increased when diagnosis and treatment are delayed[7]. To our knowledge, there are no studies investigating the need for subsequent surgery for these issues after septic arthritis of the knee.

This outcome has been similarly studied in septic arthritis of the hip in children[8-10]. Livingston *et al* [8] found that presence of left shift or higher C-reactive protein pre-operatively, higher post-operative temperature, and positive cultures were associated with increased risk for repeat surgery. As such, we hypothesize that similar preoperative risk factors may exist for recurrent septic arthritis of the knee.

The purpose of this study was to determine the incidence of patients that require any subsequent surgery after septic arthritis of the knee initially managed with irrigation and debridement. We also assess risk factors for subsequent surgery after septic arthritis of the knee. We hypothesized that in this database, demographic factors such as age, race, or ethnicity would have no effect on increased risk, and that clinical factors such as medical comorbidities would carry increased risk of subsequent surgery.

MATERIALS AND METHODS

Data collection

This study was reviewed by the Institutional Review Board and exempt as a database study. Data were collected from the Healthcare Cost and Utilization Project database from the states of California and Florida. Inclusion criteria were patients age 0 to 18 years, who underwent knee irrigation and debridement for septic arthritis from 2005 to 2017 and had at least two years of follow-up data.

Demographic data including age, sex, ethnicity, race, insurance, and state were collected for all patients. Clinical data included length of stay (LOS), type of hospital (pediatric, academic, county), and significant comorbidities. The Charlson Comorbidity Index (CCI) was utilized as a composite measure to capture the occurrence of major comorbidities[11-13]. The CCI is a validated tool and accounts for age and comorbidities such myocardial infarction, heart failure, liver or kidney disease, diabetes, and cancer [11]. Our primary outcome of interest was any surgical procedure after index irrigation and debridement of the knee, including those that occurred during the index or subsequent hospital admissions. Secondary outcomes included readmission and length of stay for re-operation.

Statistical analysis

Descriptive data are expressed as means ± standard deviation, or for categorical variables as percentage with counts. Differences among outcome groups and categorical variables were tested by chi-square test. Differences between continuous variables were analyzed using student's *t*-test. Pearson's correlation was used to analyze association between all studied parameters. The values $P < 0.05$ were considered statistically significant. Multivariate logistic regression analysis was then performed using any variables with $P < 0.10$ in univariate analysis, which was established *a priori*. Statistical analysis was done using Stata 17 (StataCorp LLC, College Station, TX, United States).

RESULTS

A total of 932 cases of septic arthritis of the knee were identified over the study period. Table 1 displays the demographic characteristics of this cohort. At the time of index admission for septic arthritis, the median age was 9.0 ± 6.1 years and 62% of patients were male. Approximately, 2% of patients were of Asian race, 26% were Hispanic, 22% were Black, 46% were white, and 3% identified as other race. Thirty percent of patients were seen at a county hospital, 13% were seen in an academic hospital, and 15% were seen in a children's hospital. Forty-nine percent of patients were state- insured and 41% were privately insured. The majority (58.5%) of admissions were emergent. The mean LOS for the index hospitalization was 9.3 ± 12.0 d, with a median of 6 d. The mean CCI of patients was 0.26 ± 0.73, with a range from 0 to 8.

In total, 36 (3.9%) of these patients underwent subsequent surgery at a median of 11.5 d after index debridement (range 1-1641 d). Readmission was for a mean of 11.6 d (± 11.3 d). The most common readmission diagnosis was pyogenic arthritis, and the most common subsequent surgery code was knee arthrotomy. There were no significant differences in demographics, payor type or presenting hospital between patients that did or did not undergo a subsequent knee-related procedure. In univariate analysis, CCI at the time of initial treatment was significantly higher in the cohort who underwent subsequent surgery ($P = 0.041$). Shorter length of stay at the time of index admission trended towards significance as well and was therefore included in the subsequent multivariate analysis ($P = 0.066$). Multivariate analysis showed that both increased CCI ($P = 0.008$) and shorter LOS ($P = 0.019$) were predictive of subsequent surgery.

DISCUSSION

This retrospective database study demonstrated that in a population of 932 children who underwent initial surgical irrigation and debridement for septic arthritis of the knee, subsequent surgery was undertaken in 3.9% ($n = 39$) of them. Higher index CCI and shorter LOS were significantly associated with the group requiring repeat irrigation and debridement.

In the literature, it has been shown that in septic hip arthritis, risk factors for repeat debridement include methicillin-resistant *Staphylococcus aureus* infection, higher inflammatory markers and higher fevers. There are few similar studies that have looked at septic knee arthritis, and none have looked at the rates among a large patient population. We utilized a multi-state database to examine similar trends in septic knee arthritis in children. The current study shows that majority of patients with septic arthritis of the knee managed with surgical debridement do not require any subsequent surgery. However, baseline comorbidities and shorter LOS at the time of index admission may be associated with need for subsequent surgery.

Table 1 Cohort characteristics

Characteristics	Total	No return to surgery	Return to surgery	*P* value
n	932	896 (96.1)	36 (3.9)	
Age	8.96 6.07	8.90 6.09	10.47 5.53	0.129
Sex, % male	581 (62.3)	557 (62.2)	24 (66.7)	0.709
Race, %				0.366
Asian	19 (2.0)	17 (1.9)	2 (5.6)	
Black	185 (19.9)	181 (20.2)	4 (11.1)	
Hispanic	220 (23.6)	208 (23.2)	12 (33.3)	
White	382 (41.0)	367 (41.0)	15 (41.7)	
Native American	3 (0.3)	3 (0.3)	0 (0)	
Other	26 (2.8)	26 (2.9)	0 (0)	
County hospital, %	282 (30.3)	271 (30.3)	11 (30.6)	0.968
Academic hospital, %	120 (12.9)	113 (12.6)	7 (19.4)	0.230
Children's hospital, %	138 (15.0)	134 (15.1)	4 (11.4)	0.551
Insurance				0.716
Commercial	380 (40.8)	366 (40.9)	14 (38.9)	
Medicaid	460 (49.4)	444 (50.0)	16 (44.4)	
Other	67 (7.2)	62 (6.9)	5 (13.9)	
Self pay	19 (2.0)	18 (2.0)	1 (2.8)	
No charge	5 (0.5)	5 (0.6)	0 (0)	
Admission type				0.646
Elective	221 (23.8)	211 (24.7)	10 (27.8)	
Urgent	157 (16.9)	149 (16.7)	8 (22.2)	
Emergent	544 (58.5)	528 (58.9)	16 (44.4)	
State				0.268
CA	383 (41.1)	365 (40.7)	18 (50)	
FL	549 (58.9)	531 (59.3)	18 (50)	
Length of index stay	9.3 12.0	9.4 12.1	5.7 6.1	0.066
Charlson Comorbidity Index	0.26 0.73	0.25 0.73	0.5 0.81	0.041[a]

[a]Significant.

The rate of subsequent surgery after index irrigation and debridement for septic arthritis of the knee is low. There may be several reasons for this finding. In cases of septic arthritis of the knee, joint aspiration is more readily accessible as a bedside procedure, and therefore an aspirate sample is obtained faster and treatment with antibiotics may be initiated sooner in the hospital course. The knee is also a larger joint without the tenuous vascularity as is noted in the hip. Most cases of septic arthritis of the knee are methicillin-sensitive *Staphylococcus aureus*, or other less virulent organisms such as Kingella which overall portend a more benign clinical course. Overall, these findings help to counsel patients that most will not require any subsequent surgery after initial irrigation and debridement.

The choice between arthrotomy and arthroscopy is actively studied in the literature[14]. One study suggests that arthrotomy was associated with reduced repeat surgeries and faster recovery[15]. However, additional research is needed. All these factors from microbiology to method of debridement can contribute to the success of the surgery in eradicating infection. One consequence of inadequate treatment is need for repeat surgery[16].

Comorbidities are an established risk factor for infections such as septic arthritis[17,18]. Additionally, greater comorbidities have been shown to contribute to poor outcomes after septic arthritis in adults [17]. The CCI has been used to quantify comorbid conditions in pediatric patients, and our study shows

that pediatric patients with comorbidities are at risk for requiring subsequent surgery after index irrigation and debridement. This information may be useful in counseling patients and families regarding the risk for subsequent surgery, and it may also help clinicians in determining postoperative management after index debridement.

Additionally, a shorter LOS was associated with a need for subsequent surgical management. A shorter LOS is likely associated with a shorter course of IV antibiotics and presumably less postoperative observation. Shorter courses of IV antibiotics have been associated with persistent infection and it is important to ensure appropriately clinical and laboratory improvement prior to transitioning to oral antibiotics for discharge[19]. This data is also helpful for healthcare systems to provide clinical pathways, which have been shown in previous studies to reduce the risk for readmission[20]. It should be noted, however, that our length of stay was long with mean of 9 d, and the standard deviation was wide.

This study found no significant differences across socioeconomic factors such as insurance type or hospital where patients were hospitalized. This is reassuring given the obvious disparities in healthcare; however, the number of subsequent surgeries in our cohort is low. Further study using data from more sources and including direct measures of patient socioeconomic status, such as household income, are needed to confirm this finding. Furthermore, sex and race were not significantly associated with subsequent surgery. However, it is important to note that the majority of our patients were male, which is consistent with the epidemiology of septic arthritis[17].

Limitations in this study include the retrospective nature of this database study, and the limited clinical data available. We did not have available data such as time to diagnosis, pre-operative inflammatory markers, microbiology results, or post-operative vital signs. Similarly, we are unable to determine the specific reasons or diagnosis codes for subsequent surgery such as growth disturbance or joint degeneration, or comorbidities such as osteomyelitis. Also, the data available are not able to determine with specificity between open and arthroscopic index procedures. We intend to study future cohorts with more clinical data available and explore the variables which best predict need for repeat surgeries in similar populations. Additionally, it is possible that some patients may have sought care elsewhere; however, this study utilized a large database and provides a baseline assessment of risk for subsequent surgery. Lastly, we only included patients that underwent a subsequent procedure and not all hospitalizations. It is likely that readmissions may be more common than the rate of subsequent surgery reported in this study; however, the goal of this study was to determine the rates of significant outcomes such as subsequent surgery after index septic arthritis of the knee.

Few patients require subsequent surgery after irrigation and debridement for septic arthritis of the knee. However, patients with comorbidities and shorter LOS at index admission are risk factors for subsequent surgery. Additional research is needed to determine the appropriate length of stay for patients with septic arthritis of the knee in order to optimize patient care and minimize the need for repeat surgery.

CONCLUSION

In conclusion, this retrospective database study demonstrated that in a population of 932 children who underwent initial surgical irrigation and debridement for septic arthritis of the knee, subsequent surgery was undertaken in 3.9% (n = 39) of them. Higher index CCI and shorter LOS were significantly associated with the group requiring repeat irrigation and debridement.

ARTICLE HIGHLIGHTS

Research background

Septic arthritis in children is a challenging clinical problem and carries with it many long-term sequelae. Repeat surgeries are sometimes necessary to eradicate infection. Understanding the rate of repeat irrigation and debridement in this population, and the risk factors associated, can help to focus clinical interventions and future studies.

Research motivation

Septic arthritis of the knee can be a serious clinical problem, and affects children and their families greatly. Understanding further the rate and risk of requiring multiple surgeries can help surgeons in counseling of these patients and their families.

Research objectives

To determine the rate of repeat irrigation and debridement in children who undergo surgical washout of the knee. Secondarily, the aim is to highlight any significant risk factors associated with repeat surgery.

Research methods

This is a retrospective cohort study that utilizes data from the Healthcare Cost and Utilization Project (HCUP). We included patients between ages 0 to 18 years that underwent surgical debridement for septic arthritis of the knee between 2005 and 2017. Demographic data included age, gender, race, hospital type and insurance type. Clinical data including index admission length of stay and Charlson Comorbidity Index (CCI) were available from the HCUP database. Descriptive statistics were used to summarize this data. Univariate and multivariate analyses were performed with all variables with $P < 0.10$ on univariate analysis.

Research results

Nine-hundred thirty-two patients were included in this retrospective database study. In total, 36 (3.9%) of these patients underwent subsequent surgery after surgical irrigation and debridement for septic arthritis of the knee. In univariate analysis, CCI at the time of initial treatment was significantly higher in the cohort who underwent subsequent surgery ($P = 0.041$). Shorter length of stay at the time of index admission trended towards significance as well and was therefore included in the subsequent multivariate analysis ($P = 0.066$). Multivariate analysis showed that both increased CCI ($P = 0.008$) and shorter LOS ($P = 0.019$) were predictive of subsequent surgery.

Research conclusions

In conclusion, this retrospective database study demonstrated that in a population of 932 children who underwent initial surgical irrigation and debridement for septic arthritis of the knee, subsequent surgery was undertaken in 3.9% ($n = 39$) of them. Higher index CCI and shorter LOS were significantly associated with the group requiring repeat irrigation and debridement.

Research perspectives

Future research in this area should include prospective studies of septic arthritis of the knee in children, and can follow patients long-term for sequelae of disease. This study was limited as a retrospective database study to the clinical data available.

FOOTNOTES

Author contributions: O'Donnell JM, Ekunseitan E, and Swarup I all contributed to this work; O'Donnell JM and Swarup I designed the research study; O'Donnell JM and Ekunseitan E performed the research; O'Donnell JM analyzed the data; O'Donnell JM wrote the manuscript; Ekunseitan E and Swarup I edited and reviewed the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: This study was exempt by the local institutional review board.

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

Data sharing statement: The authors will make available all data which are also part of a publicly available database.

Country/Territory of origin: United States

ORCID number: Jennifer Marie O'Donnell 0000-0002-9509-506X; Ishaan Swarup 0000-0003-3481-3408.

S-Editor: Chang KL
L-Editor: A
P-Editor: Chang KL

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World Journal of Clinical Pediatrics

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

World J Clin Pediatr 2023 March 9; 12(2): 45-56

DOI: 10.5409/wjcp.v12.i2.45

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Vaccination coverage in children with juvenile idiopathic arthritis, inflammatory bowel diseases, and healthy peers: Cross-sectional electronic survey data

Elizaveta Makarova, Aygul Khabirova, Natalia Volkova, Tatiana Gabrusskaya, Natalia Ulanova, Larisa Sakhno, Maria Revnova, Mikhail Kostik

Specialty type: Pediatrics

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, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chen K, China; Poddighe D, Kazakhstan

Received: December 4, 2022
Peer-review started: December 4, 2022
First decision: January 9, 2023
Revised: January 25, 2023
Accepted: February 13, 2023
Article in press: February 13, 2023
Published online: March 9, 2023

Elizaveta Makarova, Larisa Sakhno, Maria Revnova, Department of Polyclinic Pediatrics, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia

Aygul Khabirova, Mikhail Kostik, Department of Hospital Pediatrics, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia

Natalia Volkova, Tatiana Gabrusskaya, Natalia Ulanova, Department of Pediatric GI, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia

Corresponding author: Mikhail Kostik, MD, PhD, Full Professor, Professor, Department of Hospital Pediatrics, Saint-Petersburg State Pediatric Medical University, Lytovskaya 2, Saint-Petersburg 194100, Russia. kost-mikhail@yandex.ru

Abstract

BACKGROUND

Patients with immune-mediated diseases, such as juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) are at increased risk of developing infections, due to disease-related immune dysfunction and applying of immunosuppressive drugs.

AIM

To evaluate vaccine coverage in patients with IBD and JIA, and compare it with healthy children.

METHODS

In the cross-sectional study we included the data from a questionnaire survey of 190 Legal representatives of children with JIA (n = 81), IBD (n = 51), and healthy children (HC, n = 58). An electronic online questionnaire was created for the survey.

RESULTS

There were female predominance in JIA patients and younger onset age. Parents of JIA had higher education levels. Employment level and family status were similar in the three studied groups. Patients with JIA and IBD had lower vaccine coverage, without parental rejection of vaccinations in IBD, compare to JIA and

healthy controls. The main reason for incomplete vaccination was medical conditions in IBD and JIA. IBD patients had a lower rate of normal vaccine-associated reactions compared to JIA and HC. The encouraging role of physicians for vaccinations was the lowest in JIA patients. IBD patients had more possibilities to check antibodies before immune-suppressive therapy and had more supplementary vaccinations compared to JIA and HC.

CONCLUSION

JIA and IBD patients had lower vaccine coverage compared to HC. Physicians' encouragement of vaccination and the impossibility of discus about future vaccinations and their outcomes seemed the main factors for patients with immune-mediated diseases, influencing vaccine coverage. Further investigations are required to understand the reasons for incomplete vaccinations and improve vaccine coverage in both groups, especially in rheumatic disease patients. The approaches that stimulate vaccination in healthy children are not always optimal in children with immune-mediated diseases. It is necessary to provide personalized vaccine-encouraging strategies for parents of chronically ill children with the following validation of these technics.

Key Words: Vaccines; Juvenile idiopathic arthritis; Inflammatory bowel diseases; Vaccine coverage; Immune-mediated diseases

Core Tip: Juvenile idiopathic arthritis and inflammatory bowel disease patients had lower vaccine coverage compared to healthy children. Physician's encouraging to vaccination and impossibility to discus about future vaccinations and their outcomes seemed the main factors for patients with immune-mediated diseases, influenced the vaccine coverage. Further investigations required to understand the reasons for incomplete vaccinations and improve the vaccine coverage in both groups, especially in rheumatic disease patients. The approaches that stimulate vaccination in healthy children are not always optimal in children with immune-mediated diseases. It is necessary to provide personalized vaccine-encouraging strategies for parents of chronically ill children with following validation of these technics.

Citation: Makarova E, Khabirova A, Volkova N, Gabrusskaya T, Ulanova N, Sakhno L, Revnova M, Kostik M. Vaccination coverage in children with juvenile idiopathic arthritis, inflammatory bowel diseases, and healthy peers: Cross-sectional electronic survey data. *World J Clin Pediatr* 2023; 12(2): 45-56
URL: https://www.wjgnet.com/2219-2808/full/v12/i2/45.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i2.45

INTRODUCTION

Patients with immune-mediated diseases, such as juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD), are at increased risk of developing infections, due to disease-related immune dysfunction and applying of immunosuppressive drugs[1,2]. Additional factors of increased infection risk include disease activity, malnutrition, surgical interventions, and concomitant chronic diseases, such as obesity, diabetes mellitus, atopic dermatitis, asthma, and others[3-5].

Biologic therapy with and without immune suppressors can reliably control inflammatory activity in many patients with immune-mediated diseases, including JIA and IBD. Tumor necrosis factor inhibitors - adalimumab and infliximab, with or without azathioprine, methotrexate, and sulfasalazine uses in IBD [6]. Etanercept, adalimumab, tocilizumab, abatacept, and tofacitinib with and without methotrexate applied in JIA[7]. Infections are the most common complications associated with biological treatment and immune suppressors. The main infectious, associated with immune-mediated diseases are pneumococcus, influenza, varicella-zoster virus, and measles[8-10]. Immune-compromised patients may have a more severe course of infections, requiring hospital admissions, using intravenous antibiotics and intravenous immunoglobulin lead to withdrawal of current therapy with following disease flare and non-achievement of the remission[11,12]. These above-mentioned factors may influence a child's overall health and long-term therapy outcomes[13].

Vaccination is a well-known and effective tool, which allows for reducing the frequency and severity of infectious episodes, and indirectly might reduce the risks of disease flare and failure to achieve remission, and significantly improve disease course and outcomes[14].

Several studies assessed reasons for low vaccine coverage from a medical point of view, but studies from a parental point of view are limited.

Our study aimed to assess the parental-related reasons for incomplete vaccination.

MATERIALS AND METHODS

Ethical statement

The study was approved by the Ethical Committee of the Saint-Petersburg State Pediatric Medical University (Protocol №3 from 01/03/2021). There were no violations of patients' rights according to the Declaration of Helsinki. The study was completely anonymous.

Study design and population

In the cross-sectional study, we included the data from questionnaire surveys of 190 Legal representatives of children, with JIA (n = 81), IBD (n = 51), and healthy children HC (n = 58). The electronic survey was disseminated through the parental social network for IBD and JIA in Saint-Petersburg and the North-West part of the Russian Federation from January 2022 to March 2022. The group of HC was collected with portable electronic devices in one of the city's schools and kindergartens with the exclusion of children with chronic diseases if it was reported in the survey. All parents of patients with IBD and JIA who were invited to participate responded to the survey. Initially, 58 out of 152 guardians of HC who had been asked to participate in the survey answered.

Survey

An electronic online questionnaire was created for the survey, containing 62 questions for parents of children with IBD, 55 questions for parents of children with JIA, and 37 questions for parents of healthy children. The majority of questions were identical for all three groups, some questions were equal for IBD and JIA and the remaining questions were disease-specific. The survey is in the Supplementary material.

Data collection

We collected the following information: (1) Patient's demography: gender, type of disease, disease onset, age of inclusion; (2) Parental demography: gender of respondent, education, family status, and employment status; and (3) Information about vaccines: the coverage with obligatory and additional vaccines, reasons for incomplete vaccinations.

Statistical analysis

The sample size did not initially calculate. Descriptive statistics are reported in terms of medians and interquartile ranges for continuous variables and absolute frequencies and percentages for categorical variables. Missing data were not included in the analyses. We used a non-parametric statistic because all variables had non-normal distribution. To check whether the distribution was normal or not, we used the Kolmogorov-Smirnov test and distribution graphs. Pearson's χ^2 test or Fisher's exact test in the expected frequencies < 5 was used to compare the categorical variables. A comparison of two quantitative variables was carried out using the Mann-Whitney test. Bonferroni's correction test was applied to avoid multiple comparisons. The software Statistica (release 10.0, StatSoft Corporation, Tulsa, OK, United States) was used for data analysis, P value < 0.05 was considered to indicate a significant difference.

RESULTS

Patients and parental demography

A total of 190 individuals participated in the survey. The IBD group consisted of 51 patients, 39 (76%) with Crohn's disease and 12 (24%) with ulcerative colitis. The JIA group represented 81 parents, including systemic JIA (n = 10; 12.3%), RF positive or negative polyarthritis (n = 23; 28.4%), persistent or extended oligoarthritis (n = 38; 46.9%), enthesitis-related arthritis (n = 3; 3.7%), psoriatic (n = 4; 4.9%) and undifferentiated arthritis (n = 3; 3.7%). There was a female predominance in JIA patients (n = 43; 54% *vs* n = 24; 47% and n = 28; 49% for IBD and HC, respectively) and younger onset [4.7 (0.8; 16.0) *vs* 10.9 (1.0; 17.0) years for IBD] age and age of inclusion [7.8 (2.0; 18.0) years *vs* 13.6 (2.7; 17.0) and 11.3 (3.0; 17.0) for IBD and HC, respectively] in the present study. Mothers were the main survey respondents, with a lower part in JIA (88.2%) compared to IBD (96.1%) and HC (98.3%). Parents of JIA had higher education levels - 81.5% compared to 64% (IBD) and 77.6% (HC). Employment level and family status were similar in the three studied groups. Data are presented in Table 1.

Russian national vaccination schedule and specific additional recommended vaccinations

The 2021 Russian national vaccination schedule included vaccinations against hepatitis B virus (HBV),

Table 1 Demographic characteristics of survey respondents

Parameters	Parents of IBD patients (*n* = 51)	Parents of JIA patients (*n* = 81)	Parents of HC (*n* = 58)	*P* value
Patients characteristics				
Age of inclusion in the study, years, Me (25%; 75%)	13.6 (2.7; 17.0)	7.8 (2.0; 18.0)	11.3 (3.0; 17.0)	0.00006
Gender, females, *n* (%)	24 (47)	43 (54)	28 (49)	0.0000001
The onset of the disease, years, Me (25%; 75%)	10.9 (1.0; 17.0)	4.7 (0.8; 16.0)	NA	0.0000001
Parental status				
Gender of representative, females, *n* (%)	49 (96.1)	71 (88.2)	57 (98.3)	0.022
Education level, *n* (%) -secondary school -higher education - academic degree	18 (36) 33 (64) 0 (0)	11 (13.6) 66 (81.5) 3 (4.9)	13 (22.4) 45 (77.6) 0 (0)	0.019
Level of employment, *n* (%) -working -self-employed - unemployed -receiving welfare support	32 (62.7) 5 (9.8) 8 (15.7) 6 (11.8)	48 (59) 8 (9.9) 12 (14.8) 13 (16,3)	37 (65) 11(18.5) 9 (16.5) 0 (0)	> 0.050
Family status, *n* (%) - Married - Divorced - Widow/widower - Single parent	43 (85.2) 4 (8.6) 1 (1.2) 2 (5)	66 (80.4) 9 (11.8) 3 (3.9) 3 (3.9)	46 (79.3) 11 (19.0) 1 (1.7) 0 (0)	0.327

IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

tuberculosis, pneumococcus infection, poliomyelitis, diphtheria, tetanus, whooping cough, and measles - mumps - rubella (MMR)[21]. In addition, Haemophilus influenzae type B is recommended for all children from 3 mo (before 2021 it was voluntary and just for the risk group). Varicella-zoster virus (VZV) vaccination can be performed voluntarily, recommended for children after 1 year with negative VZV history. Influenza vaccination should be performed annually in children after 1 year. Vaccination against meningococcal, hepatitis A and tick-borne encephalitis are not recommended routinely for healthy children but can be performed voluntarily. Vaccinations against influenza (annually), pneumococcal, Haemophilus influenzae, Meningococcal, and hepatitis B infections are strongly recommended for IBD and JIA patients.

Assessment of vaccine coverage

Patients with JIA (*n* = 65; 79.9%) and IBD (*n* = 42; 82.3%) had lower vaccine coverage compared to HC (*n* = 52; 91.4%, *P* = 0.320). At least one episode of vaccine-associated reaction (low-grade fever, injection site reactions) was meant with a similar rate by parents in 40 (49.3%) JIA patients and 27 (46.6%) HC, and two times rarely in IBD (*n* = 13; 26.1, *P* = 0.02) patients. Fever after vaccination was reported by parents of JIA patients more frequently (33.3%) than by parents of IBD patients (21.6%) and HC (24.1%). Injections site reactions rate was the lowest in IBD children (3.9%) compare to JIA (16.1%) and HC (22.4%).

Reasons for incomplete vaccination

Temporary medical conditions (active stage of diseases, acute respiratory infections, high dose corticosteroids, and biologic therapy for live vaccines) were noted as the main reason for missing or delayed vaccinations in IBD (*n* = 9; 17.6%) and JIA patients (*n* = 14; 17.3%) with the same rate (Figure 1). No cases of parental rejection of vaccinations in IBD compared to JIA (*n* = 2; 2.5%) and HC (*n* = 3; 5.2%) were reported by respondents. A small proportion of JIA (*n* = 6; 7.4%) and IBD (*n* = 5; 10.9%) patients continue vaccinations after disease onset. Only a third part of immune-compromised patients: 23 (28.4%) of JIA and 16 (32%) of IBD patients' parents had the opportunity to discuss perspectives related to following vaccination with their attending physician. IBD patients (*n* = 22; 43.2%) had more frequent opportunities to measure levels of anti-vaccine antibodies before immune-suppressive therapy than JIA patients (*n* = 24; 29.6%). Among encouraging vaccination factors the role of attending physicians was the leading in IBD patients (*n* = 42; 84%), compared to JIA patients (*n* = 56; 69.1%) (Figure 2).

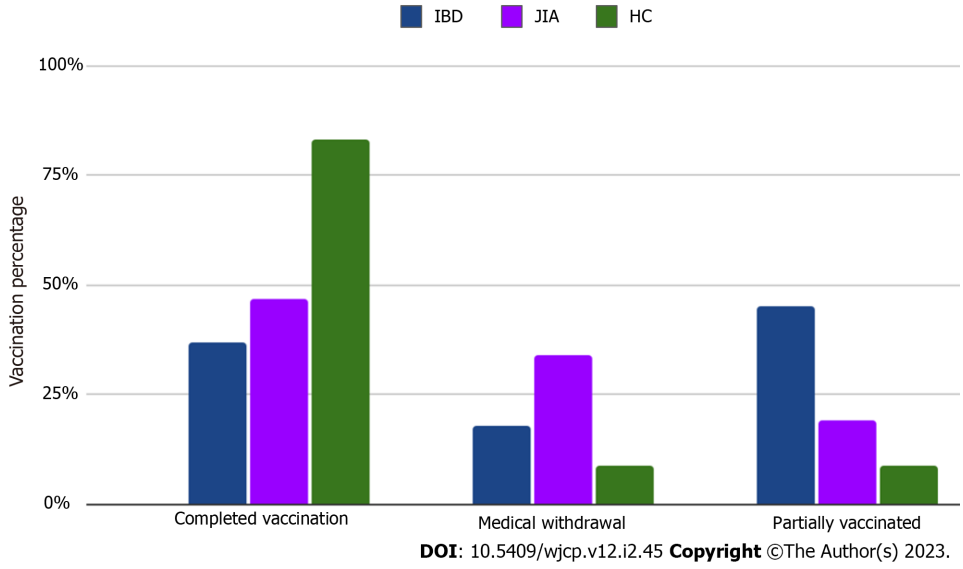
Patients with both immune-mediated diseases had a lower rate of supplementary vaccines, compared to HC, with an exception for the pneumococcal vaccine, which was more frequently used in IBD patients (data are in Table 2 and Figure 3).

According to parental opinion, lack of discussion about the safety of vaccines and future disease-related perspectives was the main factor, in the restraining of active vaccination. Vice versa, encouraging manner of attending physicians to vaccinate was meant by parents as a factor, that stimulated vaccination.

Table 2 Vaccine coverage of survey respondents

Parameters	Parents of IBD patients (*n* = 51)	Parents of JIA patients (*n* = 81)	Parents of HC (*n* = 58)	*P* value
Vaccine status				
Completed vaccination according to the national calendar, *n* (%)	42 (82.3)	65 (79.9)	52 (91.4)	0.320
Temporary medical contraindications for vaccination (postponed vaccination), *n* (%)	9 (17.6)	14 (17.3)	2 (3.4)	0.000001
Refused to be vaccinated, *n* (%)	0 (0)	2 (2.5)	3 (5.2)	0.00001
Vaccine-associated reactions: No reaction Fever Injection site reactions	38 (74.5) 11 (21.6) 2 (3.9)	41 (50.6) 27 (33.3) 13 (16.1)	31 (53.5) 14 (24.1) 13 (22.4)	0.020
Continued vaccination after diagnosis, *n* (%)	5 (10.9)	6 (7.4)	NA	0.505
Had an opportunity to discuss vaccinations with the attending physician, *n* (%)	16 (32)	23 (28.4)	NA	0.716
Control of anti-vaccine antibodies before immunosuppressive treatment, *n* (%)	22 (43.2)	24 (29.6)	NA	0.147
Factors encouraged vaccination, *n* (%) - Personal beliefs - Doctor's advice - Internet / Media - Parents' forums - Others	10 (20) 42 (84) 2 (4) 2 (4) 2 (4)	25 (30.8) 56 (69.1) 8 (9.9) 9.9 (12.3) 5 (6.4)	40 (70.9) 19 (34.5) 7 (12.7) 1 (1.8) 6 (10.9)	0.010
Additional vaccines, *n* (%), against - tick-borne encephalitis - influenza - meningococcus - pneumococcus - varicella	8 (9.8) 6 (11.7) 8 (16.0) 29 (56.8) 6 (12.7)	3 (3.7) 9 (11.1) 8 (9.8) 23 (29.4) 7 (6,2)	8 (14.5) 20 (35.1) 21 (36.8) 27 (48.9) 17 (30.2)	0.003 0.002 0.0000001 0.000004 0.000002

IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.



DOI: 10.5409/wjcp.v12.i2.45

Figure 1 Vaccination coverage according to the National Preventive Immunization Calendar. IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

DISCUSSION

In this study vaccine coverage and parental point of view on vaccination in patients with immune-mediated disease, (IBD and JIA) and HC were demonstrated.

Vaccine prophylaxis recommendations have been around for years, but the problem of low vaccination rates among these patients is still relevant. For children with rheumatic diseases, the major national and international medical societies, including the American College of Rheumatology and the European League of Associations for Rheumatology, as well as for children with IBD, including ECCO Guidelines, have recommended expanded vaccinations including pneumococcal, varicella-zoster, influenza and human papillomavirus (HPV) in addition to the common vaccines (hepatitis B, pertussis,

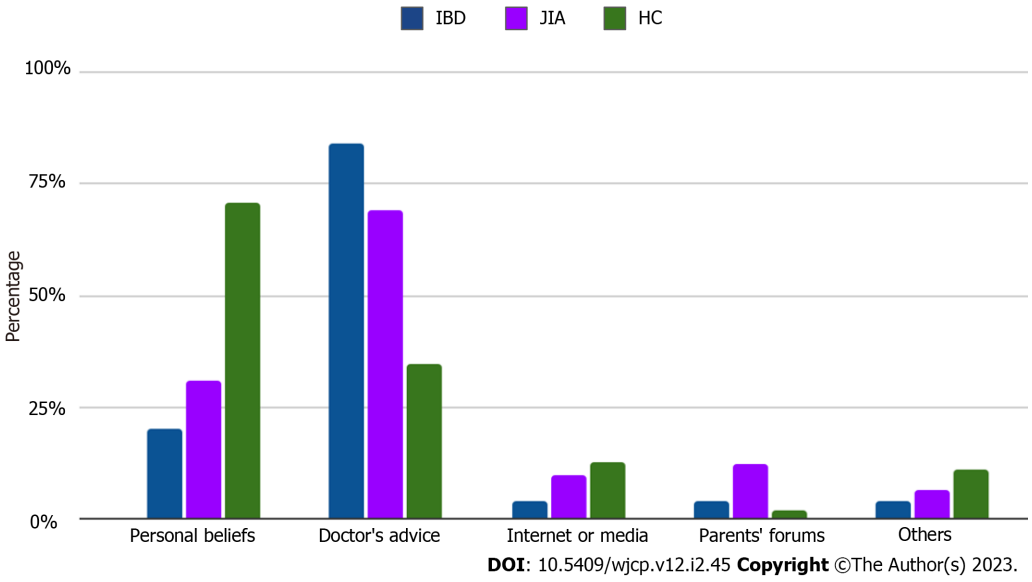


Figure 2 Sources influenced the parental decision on vaccination. IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

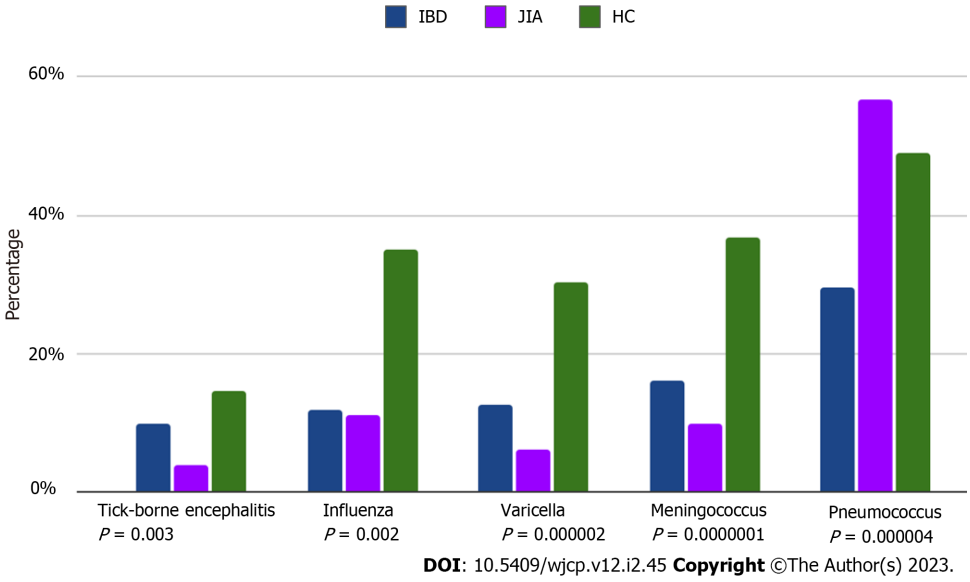


Figure 3 Vaccine coverage between the studied groups. IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

diphtheria, tetanus, measles, rubella) [4,5,15]. Despite the existing international recommendations and consensus of the European communities of pediatric gastroenterologists and rheumatologists according to vaccination, current studies note a low level of awareness of the necessity and safety of vaccination among both types of physicians and parents, which translates into lower vaccine coverage in patients with both inflammatory bowel disease and juvenile idiopathic arthritis[16-19]. At the same time, it has been proven that maintaining appropriate vaccination status in these patients is critical for optimizing treatment outcomes. Vaccination recommendations for IBD and JIA patients are available, however, the implementation rate remains suboptimal[20,21]. In real practice, only 82.9% of gastroenterologists reported as "very important" to perform the vaccinations recommended by the guidelines in patients with IBD according to A Survey of the Italian Group for the Study of Inflammatory Bowel Disease[22].

Vaccine coverage and incomplete vaccination

The main previously published reasons for incomplete vaccination were the fear of physicians, as primary care or specialists in the efficacy and safety of vaccinations, and fears of parents about disease flares after vaccinations[18,19,25,26]. The fear and concerns of the physicians about the role of vaccines in the flares of pediatric rheumatic diseases might lead to vaccine delays or schedule interruption or

neglect of some "non-important vaccinations, according to their opinion"[25-27]. Due to the relevant issue of the effect of vaccination on the outcome of immune-mediated diseases, several large-scale cohort studies have been conducted, with no convincing evidence that the activity of immune-mediated diseases can be increased by vaccination[28,29]. The risk of infections, missing treatment, disease flare, and non-achievement of the remission usually are not mentioned as factors, associated with incomplete vaccination. Incomplete vaccination in JIA and pediatric rheumatic disease patients were reported in several previous studies[18,19,30,31,32]. From the medical point of view, the main predictors of incomplete vaccination were polyarticular and systemic JIA categories and immunosuppressive medications[30,31,33]. In our previous study, the younger JIA onset age was associated with a higher proportion of omitted vaccines similar to the study of Minden *et al*[18], but some authors reported that preschool children had a similar rate of vaccine coverage as healthy peers[30,32,33].

Usually, decreased vaccine coverage correlated with patients' age and teens had more omitted vaccines than preschools[18,30,32,33]. In our study, the proportion of patients, who received vaccination against pneumococcus was the highest in the IBD subgroup. Professional GI medical associations recommended using this vaccine to prevent respiratory infections, ensuring the treatment was uninterrupted and maintained remission. Many GI physicians follow this recommendation and encourage this vaccination. We hope that this can become a bridge to other vaccinations in patients with immune-mediated diseases.

The diphtheria vaccination coverage was lower in JIA and IBD patients[31,34]. The lower seroprotection was associated with an increased level of immunosuppression both in JIA and IBD children[31,35]. Booster revaccinations against diphtheria increased the proportions of subjects with seroprotection and were safe for JIA patients[31,34,36]. Canadian Association of Gastroenterology Clinical recommends vaccination against diphtheria for IBD patients[37].

Patients with JIA and IBD may have lower vaccine coverage (40%-75.8%) and seroprotection against hepatitis B (50%-60.7%) according to the data of several studies[35,38,39]. The vaccine against hepatitis B (HB) is recombinant and may be recommended for vaccination to all immune-compromised children because of its safety and efficacy[40,41,42]. The Japanese College of Rheumatology and the Japanese College of Hepatology considered anti-HB vaccination for unimmunized patients with JIA as soon as JIA has been under control for 3 mo[41,42].

Safety and efficacy of vaccines

Vaccines are considered to be effective and safe. There is no evidence that vaccines increase the risk of developing immune-mediated conditions or exacerbating the existing IBD or rheumatic diseases in children[43-45]. There are no contraindications for the administration of inactive or live vaccines in patients who are not receiving immunosuppressive treatment[15,16]. Despite the higher risk of live vaccines in immune-mediated diseases patients there was no strong correlation between the type of omitted vaccines (live or non-live) and disease activity[30,33]. Sometimes patients with pediatric rheumatic diseases might have omitted non-live vaccines[30,33]. Contemporary EULAR recommendations for children (2021) and adults (2019) with rheumatic diseases allow using live-attenuated vaccines, especially booster doses of MMR and varicella zoster virus in patients with low-grade immune suppression[5,15]. The protective role of vaccines in immune-compromised children was successfully demonstrated in several studies. Compared to healthy children, morbidity and mortality from influenza and streptococcus pneumonia-associated pneumonia are higher among patients with immune-mediated diseases. According to Tinsley A. 2013, patients with IBD who got influenza are more likely to be hospitalized and develop viral pneumonia, although this disease can be prevented by vaccination[46]. Vaccine coverage against pneumococcus was 5% in the Australian pediatric IBD cohort, 18.6% in 430 pediatric IBD patients, from a multicentre study, and 50.3% in JIA patients from Switzerland without differences irrespective of immune-suppressive therapy[33,47,48]. In the study of pneumococcal and anti-Hib vaccination of non-systemic and systemic JIA patients was shown the decreasing number of episodes of acute respiratory infections different etiology[49]. No differences in response related to treatment and disease activity stage were observed. The vaccination against both infections was safe and not associated with following short-term flares[49,50].

Immunization barriers

There are a lot of barriers between primary care physicians and specialists (rheumatologists, gastroenterologists) in the immunization process of patients with immune-mediated diseases. In a survey of 178 pediatric gastroenterologists conducted by Lester R, 2015, a different view on immunization of IBD patients among gastroenterologists was reported[15]. The main problem was the inability to coordinate patient follow-up for dispensary and immunoprophylaxis between gastroenterologists and pediatricians. Only 28% of GI physicians believed that only primary care physicians were responsible for immunizations. In contrast, in a survey of general pediatricians, only 29% were ready to prescribe vaccination to their patients with IBD[17]. General pediatricians avoid vaccinating patients with a pediatric rheumatic disease without specialists' confirmation. In a recent Greece study, it was shown that 50% of primary care physicians required rheumatologist approval for vaccination[25].

Similar to our data, patients themselves identified a lack of information and fear of side effects as the main reasons for low vaccination rates[51,52].

Practicing gastroenterologists checked the immunization status in 63.5% of cases at the time of diagnosis and in 44.4% before initiating immunosuppressive therapy, according to the survey of 657 gastroenterologists from North America, and only 9% checked serology to assess the protection of IBD children from vaccine-preventable diseases[17]. A relatively small number of our respondents had an opportunity to discuss vaccines and diseases course perspectives and check the serology against vaccines to vaccine-preventable diseases. This point should be improved.

The discrepancy of factors, encouraging vaccination, between IBD and JIA patients was observed. The urging role of attending physicians was lower in JIA patients compared to IBD, but the role of the parent's forum was higher. The sum of the role of internet/media and parental forums in vaccination coverage JIA patients was higher 22.2% compare to IBD - 8% (P = 0.01). It might explain the fact that a survey for JIA patients was disseminated through the parental forum where one of the manuscript co-authors (Mikhail K) delivered several lectures about the efficacy and safety of vaccinations in the last two years. This educational effort was very effective: the vaccine coverage for MMR and diphtheria in JIA patients was 42% and 50% respectively in 2018 and now vaccine coverage (complete vaccination) has raised to 79.9% in 2022[31].

How we can improve vaccine coverage?

The international guidelines on the management of opportunistic infections and vaccine prophylaxis in patients with IBD were updated in 2021[14]. Regular surveys of vaccine status in patients with inflammatory bowel disease have been recommended, as well as mandatory vaccination against common vaccines: tetanus, diphtheria, and poliomyelitis. In addition, each patient with inflammatory bowel disease should be considered for additional vaccination with the following five vaccines: Varicella-zoster vaccine, HPV, annual influenza (trivalent inactivated vaccine), pneumococcal polysaccharide vaccine, and hepatitis B vaccine for all HBV seronegative patients[4,5,16].

Professional communities should provide more information about the safety and efficacy of vaccination in immune-compromised children and encourage applying modern recommendations in their practical work and discussions with families. Education and vaccine access in clinics lead to the growth of influenza vaccine coverage from 47% to 75% (education) and 89.5% (plus vaccine access)[53]. It was shown that even a single specialized infectious disease consultation with patients can improve patients' knowledge of vaccination and influence their decision to vaccinate from initial coverage of 16.1% for pneumococcus to 85.7% after intervention[51]. Educational programs for IBD children and their parents increased the coverage for vaccines against diphtheria-tetanus-poliomyelitis (92% *vs* 100%) and Haemophilus influenzae (88% *vs* 98%), hepatitis B (52% *vs* 71%), pneumococcus (36% *vs* 57%), and meningococcus C (17% *vs* 41%) (P < 0.05)[38].

Physicians' encouragement of vaccination and the impossibility to discuss future vaccinations and their outcomes seemed the main positive and negative factors that influenced vaccine coverage in immune-mediated diseases patients. Individual vaccine schedules based on the evaluation of vaccine status and serial anti-vaccine antibody assessment should be a reliable tool for increasing trust in vaccines and persuading parents to continue vaccinations, especially omitted ones. It is strongly recommended to implement educational algorithms and programs for parents and children, provided by the attending physicians or other care-given providers about the safety and efficacy of vaccines in children with immune-mediated diseases.

Limitations

The main limitation of this study related to the self-reported nature of results, assessment of parental outcomes, and inability to compare parental data with official medical records related to vaccination. We cannot be sure of the proper meaning of complete vaccination and parental knowledge of the national vaccine schedule, which makes some bias in the study results. The small sample size and lack of validated surveys make some bias.

CONCLUSION

JIA and IBD patients had lower vaccine coverage compared to HC. Physicians' encouragement of vaccination and the impossibility of discus about future vaccinations and their outcomes seemed the main factors for patients with immune-mediated diseases, influencing vaccine coverage. Further investigations are required to understand the reasons for incomplete vaccinations and improve vaccine coverage in both groups, especially in rheumatic disease patients. The approaches that stimulate vaccination in healthy children are not always optimal in children with immune-mediated diseases. It is necessary to provide personalized vaccine-encouraging strategies for parents of chronically ill children by following the validation of these techniques. Increasing immunization coverage and implementing advocacy events among special groups are required.

ARTICLE HIGHLIGHTS

Research background

Patients with immune-mediated diseases have incomplete vaccination.

Research motivation

There are no previous studies about parental view of the reasons of incomplete vaccination.

Research objectives

To evaluate the parental view about possible reasons of incomplete vaccination.

Research methods

An electronic survey for parents of immune-mediated disease patients and healthy controls was created and disseminated. The analysis of response was done.

Research results

Lower vaccine coverage in immune mediated patients was detected, compared to healthy controls. Medical conditions were the main medical reasons for incomplete vaccination in juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD). Less rate of vaccine-associated reactions was reported in IBD. Pediatric rheumatologists rarely explain the safety and benefits of vaccinations. Pediatric gastroenterology physicians frequently checked anti-vaccine antibodies and recommend more supplementary vaccines.

Research conclusions

Children with immune-mediated disease (IBD and JIA) have incomplete vaccination. The encouraging role of physicians and lack of discussion about the vaccines from physicians are factors, influencing completeness of the vaccination.

Research perspectives

Future studies on the effectiveness of educational programs supporting vaccinations may be planned.

FOOTNOTES

Author contributions: All authors were involved in the conception, drafting, and critical revision of the article, read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethical Committee of the Saint-Petersburg State Pediatric Medical University (Protocol №3 from 01/03/2021). There were no violations of patients' rights according to the Declaration of Helsinki. The study was completely anonymous.

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

Conflict-of-interest statement: All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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: Russia

ORCID number: Mikhail Kostik 0000-0002-1180-8086.

S-Editor: Wang LL

L-Editor: A
P-Editor: Wang LL

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