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MINIREVIEWS

Psychotropic drug abuse in pregnancy and its impact on child neurodevelopment: A review

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Abstract

Substance abuse by women of child-bearing age and fetal in utero drug exposure has increased in the number of infants born with health issues. Prenatal exposure to psychoactive substances can lead to neurological and neurodevelopmental deficits later in life. Useful data concerning the effects of psychoactive drugs on fetal neurodevelopmental status are sparse. Understanding the neurodevelopmental consequences of prenatally drug-exposed children has become a pressing global concern. The aim of this review is to gather current evidence and information on neurodevelopmental outcomes of in utero drug exposure. A literature search was performed on the PubMed, Scopus, and Google Scholar databases using the terms "psychotropic drugs", "neurodevelopmental consequences", "prenatal drug exposure", and "pregnancy". Available studies on in utero drug exposure were reviewed and found to support the idea that some degree of health issues are present in fetuses and children. Different psychoactive substances have profound neurodevelopmental consequences, such as structural brain changes, poor attention span, Down syndrome, attention deficit hyperactivity disorder, autism spectrum disorder, imbalances in neurotransmitter levels, and many structural deficits. The pervasive use of psychoactive drugs in women of child-bearing age is an important health concern. Further scientific efforts are needed to investigate the effect of prenatal exposure to psychoactive drugs on children.

Key Words: Psychotropic drugs; Pregnancy; Prenatal substance exposure; Brain; Neurodevelopmental outcomes; Fetus

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Core Tip: Use of psychotropic drugs during pregnancy is thought to contribute to the pathophysiology of neurodevelopmental disorders in children. In utero, drug exposure is related to different factors such as drug dose, its chemical structure that influences the entrance of the drug to the fetus body, drug distribution and elimination. However, neurodevelopmental consequences like autism, Down syndrome and structural deficits are the results of in utero drug exposure. Evidence from previous studies confirmed that in utero drug exposure played a key role in the etiology of neurological problems later in life, providing information and insights for preventing substance abuse in women.

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INTRODUCTION

Addiction to drugs is defined as the repeated use of addictive substances that cause a set of physiological and behavioral effects. The repeated use of drugs, cravings, and withdrawal symptoms after stopping drug use are among the most important typical symptoms of addiction[1]. The prevalence of the non-medical and recreational use of drugs and substances among women remains at a level comparable to that of men[2]. Alongside the increasing trend of drug abuse, there has been a corresponding rise in the use (and abuse) of licit or illicit drugs in women of child-bearing age[3]. Drug use among pregnant women may result in several medical complications, both for the mother and her child. There are many critical variables involved in the effects of drugs of abuse on fetal brain development. These variables include the duration, timing, and magnitude of exposure, as well as how much of the drug enters the fetus blood and central nervous system (CNS). As the amount of absorbed drug is not equal along different routes of drug administration (oral, inhalation, smoking, and injection), their effects on a fetus's vital organs and fetal toxicity also differ[1]. Human research on pregnant mothers using illicit drugs has demonstrated associations between substance use and pregnancy loss[1].

There are several issues regarding drug abuse during pregnancy and its impact on child neurodevelopment. There are some practical difficulties in studying human embryos during in utero drug exposure. Drug-dependent mothers often use multiple drugs from different categories with various pharmacologic properties. This situation renders it challenging to study the effect of a single drug on the fetus's neurodevelopment in isolation. Other factors, such as the mother's hormones and blood glucose level, also influence the child's neurodevelopment[4]. However, studies based on self-reports of illicit drug use during pregnancy are subject to an underrepresentation bias [5].

Prenatal drug exposure is a rising global phenomenon with significant variability across countries[6]. Fetal brain development takes place during pregnancy. The first trimester of pregnancy is a particularly important period of development[7]. Exposure to drugs and substances early in life has long-lasting adverse effects on brain structure and function[5]. Embryonic exposure to drugs and addictive substances can change the cellular morphology of cortical neurons. Previous reports have confirmed that the cerebral cortex is greatly affected by drugs. The architecture of neurons, receptor function, and the synaptic plasticity of many inhibitory and excitatory neurons in the marginal system of the midbrain cortex are altered by drug use[8]. Prenatal exposure to drugs is one of the important issues that impact the CNS development of a fetus and, subsequently, his/her future behavior. Experimental and animal studies offer evidence that prenatal neurodevelopmental insults continue to involve fetal, neonatal, infant, and childhood CNS development[9]. Understanding the relationship between prenatal drug exposure and its effects on children's neurodevelopmental outcomes is a problematic task for researchers[10]. Associations between prenatal drug exposure and neurodevelopmental consequences in children are complicated because of confounding factors such as the type of drug used and its dose, environmental circumstances, and individual genetic profiles. Such circumstances limit researchers' ability to

understand the connection between in utero drug exposure and late childhood consequences[9].

Previous studies focused on the fetal health consequences of individual drug classes. The aim of this review is to summarize the effects of different categories of substances abused by pregnant women and their effects on children, including a detailed description of neurodevelopment difficulties.

DRUG PHARMACOKINETICS DURING PREGNANCY

Numerous factors play important roles in fetal exposure to drugs including drug dose, maternal drug pharmacokinetic parameters, drug distribution and elimination in the fetus body. However, three main factors determine a drug's transfer rate from placenta to fetus body; drug lipophilicity, the pH gradient across the placenta, and drug's protein-binding properties[11]. Non-ionized, low molecular weight and lipid-soluble drugs are freely absorbed from the placenta to the fetus body. Two important factors are responsible for drug equilibration between maternal and fetal blood compartments; concentration gradient (fetal/maternal drug ratio) and the placental blood flow[11]. The metabolic power of the fetus for the metabolism of drugs and substances administered to the mother is not completed during the first 3 mo of fetus life, resulting in the exposure of the fetus to high quantities of drugs[11]. Physiologic changes during pregnancy affect several pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion of drugs[11]. The first pharmacokinetic parameter, absorption, decreases during pregnancy as a result of gastric emptying time reduction as well as the small bowel drug transit time[11]. There is an escalation of maternal plasma volume during pregnancy, which can be increased by 50% during the last trimesters of pregnancy, thus leading to lower plasma concentration of drugs[11,12]. Most psychotropic substances have a lipophilic chemical structure and show a greater volume of distribution during pregnancy[12]. It is important to mention that hormonal induction or inhibition of metabolic processes plays an important role in pharmacokinetic changes of psychoactive substances during pregnancy[12].

PSYCHOACTIVE DRUGS AND SUBSTANCE CLASSIFICATIONS

Cannabis and synthetic cannabinoid receptors agonists

Cannabis consists of the flowering or fruiting tops of the cannabis plants — its *sativa*, *ruderalis,* and *indica* subspecies contain a number of chemical substances. The most predominant substance with psychoactive properties is *delta*-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids are cannabidiol (CBD) and cannabinol (CBN). The term "cannabis" is defined as different products obtained from the cannabis plant.

Marijuana, also known as cannabis, is obtained from plants of the *cannabis* genus that are members of the Cannabaceae family. The pharmacologically active ingredients of marijuana are the phytocannabinoids that interact with cannabinoid receptors. Tetrahydrocannabinol (THC) and cannabidiolic acid are two products of cannabinoids. There are many slang and street names for marijuana, including herb, weed, hashish, ganja, and grass. THC is the active ingredient of resin produced from the leaves and buds of female plants. The cannabis plant contains about 500 chemical compounds, 100 of which are structurally and chemically related to THC. These compounds, together with THC, are called cannabinoids[13]. CB1 and CB2 are two known cannabinoid G protein-coupled receptors. CB1 is found on axons and nerve terminals in the CNS[14]. Meanwhile, CB2 receptors are mostly expressed on immune cells[14]. Two active components of the cannabis plant (THC and CBD) are CB1 and CB2 receptor agonists. CB1 receptor agonists mediate decreased neuronal signaling across synapses[13]. Dried leaves of cannabis plant is shown in Figure 1.

Common routes of administration of cannabis products: Marijuana inhalation is the fastest route by which THC enters systemic blood circulation. Marijuana inhalation can be performed through smoking, dabbing, or vaporization. Different oral preparations, including drops, cakes, tinctures, candies, snacks, and drinks, are produced as oral marijuana. Rectal and vaginal suppositories are also made from oils and waxes that contain marijuana[15].

Figure 1 Dried leaves of cannabis plant.

Marijuana pharmacokinetics in pregnancy: Maternal use of marijuana has a high frequency due to the perception that marijuana is safe and can be used during pregnancy[16]. Human and animal studies have demonstrated that THC rapidly crosses the placenta and that its concentration in fetal blood correlates with that in maternal blood. A placenta's normal physiology and transport mechanisms are affected by marijuana. The permeability of the placental barrier to licit and illicit drugs increases due to CBD exposure, thus enhancing fetal exposure to other drugs and poisons. Other human studies have confirmed that prenatal exposure to cannabis reduces blood flow that is essential to supply the placenta. After oral administration, the amount of THC absorbed exceeds 90%. However, due to first-pass hepatic metabolism, its bioavailability is limited to less than 20%. In contrast, after marijuana smoking, THC bypasses the first-pass hepatic metabolism, resulting in highly irregular bioavailability. However, its concentration reduces due to losses through sidestream smoke, absorption by cigarette butts, and pyrolysis[17,18].

Effect of cannabis use in pregnancy and childhood outcomes: Studies on the effects of marijuana in pregnancy are confounded by nutritional inadequacy and multi-substance abuse that can show synergistic effects[19]. Animal and human studies on the effect of THC in fetal brains have demonstrated structural brain changes, especially in the nucleus accumbens[20,21]. One previous study showed that marijuana use was significantly associated with stillbirth, spontaneous preterm birth, and decreased birth weight[22]. Cannabis use was evidenced by tetrahydrocannabinolic acid positive screens in umbilical cord homogenate. This result was confounded by concurrent maternal tobacco use[23].

Prenatal marijuana use has a high prevalence as a recreational drug or to alleviate nausea and morning sickness. Babies exposed to prenatal cannabis suffer from problems associated with neurological development. These problems are manifested as changing responses to visual stimuli, shivering, and high-pitched cry[24]. Memory and skill gap problems are other important difficulties among school-aged children exposed to cannabis in the prenatal phase[25]. Neurologic tests and intelligence quotient (IQ) estimation manifested variable degrees of impairment in visual memory, perception, and language comprehension in different periods of children's lives. Children also suffered from poor sustained attention and high hyperactivity and impulsivity[26].

A study conducted in Hawaii showed that many birth defects, including Down syndrome, cardiovascular issues, arm and hand defects, and orofacial clefts, are more prevalent among children exposed to cannabis during gestation[27]. Another study in Canada confirmed that congenital defects were more common in territories where cannabis is smoked more often than in other territories[28]. Concerningly, the elevated rates of acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), rhabdomyosarcoma, and neuroblastoma in the pediatric population suggest further implications of cannabinoid-induced genotoxicity[27].

Synthetic cannabinoid receptor agonists: Synthetic cannabinoid receptor agonists are designed substances with structural features that allow binding to cannabinoid receptors. These substances mimic the effects of cannabis but are not licensed for medical use. In an experimental study conducted to evaluate the effect of synthetic cannabinoid receptor agonists on cortical and sub-cortical brain areas across postnatal

development, it was concluded that the administration of synthetic cannabinoid receptors has a disparate effect on neural morphology in adult and adolescent rats. Their results suggest that neural circuits in the adolescent brain may be more vulnerable to drugs[29].

Opium, opiates, and opioids

Opium is defined as the coagulated juice obtained from the plant *Papaver somniferum*.

There are a number of alkaloids with psychoactive properties which can be extracted from opium. Morphine, codeine, thebaine, papaverine, and noscapine are the major alkaloids in opium. Heroin (diacetylmorphine, diamorphine) is a semi-synthetic opiate obtained from the acetylation of morphine.

Opioids' mechanism of action: The pharmacologic properties of morphine, heroin, and other opiates are mediated through the activation of opioid receptors. There are different types of opioid receptors. Among them, μ (mu) receptors mediate analgesic and behavioral effects[30].

Opioids refer to opiates and their synthetic congeners, which can be synthetic or semi-synthetic. Their pharmacologic properties are similar to those of morphine. Synthetic derivatives of opioids have different chemical structures and can be extremely potent. Fentanyl derivatives, methadone, and buprenorphine are classified as synthetic opioids[30].

Opioid use during pregnancy and its outcomes: The prevalence of opioid use among women of child-bearing age has increased dramatically. In utero exposure to opioids can have a direct effect on neuronal development[10]. Before environmental confounding factors influence child neurodevelopment, neurological changes can be observed shortly after birth in opioid-exposed infants[31]. Along with adverse neonatal outcomes associated with prenatal opioid exposure (stillbirth, premature delivery, and reduced gestational age), brain growth and poor neurodevelopmental outcomes are important health issues[32].

However, maternal confounding factors, such as the concomitant use of alcohol and cigarettes, and multi-drug use during pregnancy (and their effects on neurodevelopmental outcomes), should not be neglected[33]. Damage to the central and peripheral nervous systems of fetuses is the leading adverse effect of opioids use in pregnancy [8]. The most significant consequences of opioid exposure on fetal neural development are neural tube defects and neonatal abstinence syndrome[8]. Incomplete closure of neural tube during 4 or 5 wk of embryonic neural tube development is a congenital malformation caused by opioids. It is demonstrating as anencephaly, encephalocele, and spina bifida[8,34]. Opioids can change connections and sizes between different parts of the brain, including the basal ganglia, thalamus, and cerebellar white matter. Also, the myelination process in developing oligodendrocytes is altered as a result of the effect of opioids on the fetus brain[35]. Opioid-exposed children suffer from lower cognitive and psychomotor scores and poor social-emotional consequences during infancy and preschool age. Preschool- and school-age children exposed to opioids during the prenatal period tend to have below-average IQ scores and language development and skills, as well as high attention problem scores. Results of previous findings strengthen the idea that opioid-exposed children suffer from a wide variety of long-term neurodevelopmental disorders. These problems were seen among infants born to opioid-dependent mothers taking methadone[3]. According to previous studies, methadone-exposed infants exhibit a more dysregulated pattern of neurobehavioral disorders at the time of birth in comparison to unexposed infants[3,36].

Prescription opioids are used as pain relievers and as substitutes for opioids in drug rehabilitation programs. However, these groups of substances are commonly abused by women of child-bearing age[8]. Methadone is a highly lipophilic substance with a low molecular weight. It readily crosses the placenta and reaches the embryo. Experimental and animal model studies have demonstrated that methadone has a profound impact on a child's neuronal development and brain function. It has been confirmed that methadone has deleterious effects at the critical stages of neuronal myelin formation[4,37]. Stoetzer *et al*[38] indicated that methadone disrupts locomotor activity. Methadone and other opioids have a negative influence on ion channels, thereby altering neuronal network activities. Methadone disrupts the integrity of human cortical organoids in a dose- and stage-dependent manner. Methadone also antagonizes NMDA receptors in human cortical organoids[4].

It has been confirmed that poor attention, regulation, and quality of movement result from in utero methadone exposure. Methadone-exposed infants suffer from excitability, regulation, signs of stress, abstinence, neurological deficits, and intel-

lectual disabilities later in life. Results of follow-up studies in children at 24 mo of age revealed that distinct neurobehavioral profiles, such as poor cognitive and motor development, persist over the first 4.5 years of a child's life[3,4]. However, there was no difference between infants prenatally exposed to methadone in comparison with unexposed infants at the gestational age.

Stimulants

Amphetamine-type stimulants: The term amphetamine-type stimulants (ATSs) refers to a group of substances that are mostly synthetic. The principal members are amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). ATSs have stimulatory effects on the CNS, as they interfere with the dopamine, norepinephrine, and serotonin systems[30].

Amphetamines mechanism of action: Amphetamine and methamphetamine affect neurotransmitter levels through various mechanisms. The mechanism of ATSs is mainly based on direct interactions with neurons and the information transmitted between them. Each specific substance has its own mechanism of action, but the basic principles remain the same. ATSs increase neurotransmitter concentrations in neuron synapses. On the other hand, ATSs are also classified as non-catecholamine sympathetic drugs that do not have catecholamine chemical structures and do not influence receptors[1]. Once methamphetamine enters the CNS, it releases noradrenaline, dopamine, and serotonin, and it mediates an increase in monoamine concentrations in neuronal cytosols and synapses. Neurotransmitter reabsorption inhibition is another mechanism by which ATSs increase neurotransmitter concentrations in neuronal synapses. Monoamine oxidase (MAO) is an enzyme involved in the degeneration and inactivation of monoamines. The methyl group on the alpha carbon in methamphetamine structure inhibits MAO activity, resulting in an increased monoamine concentration[1]. The combination of these processes stimulates the CNS. Methamphetamine acts mainly *via* interference with dopaminergic and serotonergic neuronal response pathways. In other words, methamphetamine can be classified as a non-catecholamine sympathetic substance[1].

Methamphetamine pharmacokinetics: Methamphetamine is absorbed freely through the gastrointestinal tract. It passes through the blood-brain barrier (BBB) with greater ease than its less lipophilic analogues, such as amphetamine. Methamphetamine is widely distributed throughout the body. It is metabolized differently in various animal species. In the human body, a substantial amount of methamphetamine is excreted unchanged *via* urine as a parent drug. Hydroxymethamphetamine is one of the methamphetamine metabolites that is formed *via* hydroxylation in the liver and excreted in the urine. The other metabolite is amphetamine, which is produced as a result of the N-demethylation of methamphetamine[1].

Neurotoxic effects of methamphetamine: The neurotoxic effects of methamphetamine occur as a result of highly reactive free radical production due to dopamine auto-oxidation. Also, vesicular pool storage depletion to the cytoplasmic compartment in dopaminergic neurons induces intraneuronal oxidation, which is one of the primary causes of dopamine terminal injury[39]. In conclusion, the imbalance among the vesicular, cytoplasmic, and extracellular dopamine pools is important in the neurotoxic action of methamphetamine. After long-term exposure to methamphetamine, dopaminergic receptors are degraded, dopamine production decreases, and withdrawal symptoms arise[40].

Different parts of the brain responsible for pleasure, motor control, and addiction are connected to each other by dopaminergic and serotonergic pathways. Monoamine transporters, such as dopamine, serotonin, and norepinephrine transporters, aid methamphetamine's entrance to the neuron body. Methamphetamine displaces monoamine pools in vesicular and intracellular compartments, and it facilitates the release of monoamines into the synaptic space[41].

Methamphetamine is a neurotoxic substance that can cause striatal nerve terminal degeneration. Dopamine extracellular concentrations are elevated *via* the migration of dopamine from intracellular pools to the extracellular space induced by methamphetamine. Methamphetamine exerts its neurotoxic effect *via* the auto-oxidation of dopamine into highly reactive free radicals[1,39,41]. The primary cause of dopamine terminal injury is the redistribution of dopamine from vesicular stores to the cytoplasmic compartment, which causes intraneuronal oxidation[1,39]. In methamphetamine-addicted subjects and long-term users, reduced dopamine production and a loss of dopaminergic receptors trigger the need to increase the dosage of the abused substance[40]. Methamphetamine-induced hyperthermia is mediated by dopamine

receptor overactivation. However, as dopamine stores deplete over time, serotonin starts to play the main role. Methamphetamine reduces forebrain serotonin concentrations causing depression and sleep disorders.

Methamphetamine use during pregnancy and its outcomes: Women are more sensitive to methamphetamine than men. Unfortunately, methamphetamine use among pregnant women has increased. Pregnancy has an important effect on a woman's sensitivity to drugs. In addition to malnutrition in addicted pregnant women, sensitivity to some drugs, such as cocaine, increases, sometimes causing sudden fetal death[42,43]. Methamphetamine's concentration peak, distribution volume, and biological half-life are affected by physiological changes and altered body water volume during pregnancy. Many factors change in the placenta throughout pregnancy. The placenta's cellular membrane, protein binding, nutrient and oxygen transfer capacity, blood flow rate, and drug permeability to the fetus are strongly affected by drug use[1]. Previous studies have confirmed that methamphetamine passes the placental barrier easily. It was also shown that half of the methamphetamine concentration can be detected in the fetal blood circulatory system when compared to maternal blood[44,45]. Methamphetamine is mainly metabolized in the liver, but the enzymatic system in the fetal liver is not yet able to handle large amounts of drugs. After repeated exposure to methamphetamine, high drug concentrations can be found in fetal plasma[44]. Due to the oxidant activity of methamphetamine and reactive oxygen species production, antioxidant levels are decreased in the embryo during maternal methamphetamine use, resulting in oxidative damage to lipids, proteins, and DNA[46].

Previous studies demonstrated that methamphetamine decreases dopamine and noradrenaline levels, followed by an increase in synaptic activity that produces neurotoxic effects on the CNS. Cui *et al*[47] showed that methamphetamine combined with monoamine neurotransmitters can disturb fetal brain development.

Issues regarding methamphetamine exposure during the prenatal period are associated with impaired neurological development[48]. Infants suffering from prenatal exposure to methamphetamine show neurobehavioral development manifestations, such as poor movement, electroencephalogram (EEG) changes, elevated stress levels, and physical tension[48,49]. Other studies confirmed low birth weight, stillbirth, and intrauterine growth retardation in methamphetamine-exposed children[50]. Fetus brain structure can also be affected by methamphetamine. Previous studies offer evidence of decreased volumes of subcortical structures such as the putamen, globus pallidus, caudate nucleus, and hippocampus; smaller striatum; and fewer dopamine (D2) receptors due to prenatal methamphetamine exposure[51]. However, these children do not suffer from language problems or low IQ[52]. Young school-aged children exposed to methamphetamine during their prenatal life exhibit problems related to adapting with their peers and cognition. They show anxiety, emotional instability, aggression, and personality disorders such as attention deficit hyperactivity disorder (ADHD)[53].

Coca and cocaine

Cocaine is obtained from the plant *Erythroxylon coca*. It consists of different kinds of alkaloids, including cocaine (the main psychoactive substance of coca leaves), benzoylecgonine, and ecgonine[30]. Cocaine exerts its stimulant activity by affecting the brain's dopamine, norepinephrine, and serotonin neurotransmitter systems. However, cocaine's effect on the level of dopamine is more pronounced than that of methamphetamine and amphetamine[30].

Cocaine's mechanism of action: Cocaine binds to monoamine transporters in the fetal brain. Animal model studies have described decreased dopaminergic, beta-adrenergic, and serotonergic receptor expressions in the embryonic brain following prenatal cocaine exposure[5].

Long-term repercussions of cocaine exposure have been found in GABA and glutamate neurotransmitters systems, resulting in an increase in the numerical density and anatomical alterations of glutamatergic neurons. These changes suggest alterations in neocortical connectivity that can cause behavioral and cognitive deficits [5,54].

Cocaine use during pregnancy and its outcomes: Recent studies report that cocaine use among pregnant women continues to be a public health concern. Fetal cocaine exposure during pregnancy disrupts brain monoamines, especially dopamine, during a critical stage of brain development. Animal-based and experimental studies permit rigorous and hypothesis-driven explorations of the effect of prenatal cocaine exposure

on brain development. There are some confounding factors in the human-based studies, such as multi-drug use. Multi-drug use is common among cocaine users. They often use alcohol, nicotine, and marijuana with cocaine[5].

Prenatal cocaine exposure can affect early brain development. It causes fetal growth retardation, seizure, respiratory distress, cerebral malformation, and, in some instances, sudden infant death syndrome. An infant's behavioral profile correlates with the timing of cocaine exposure. Cocaine exposure during the first and second trimesters causes abnormal reflexes, but its exposure during the second and third trimesters induces reductions in motor maturity and muscle tone[5]. Other consequences of prenatal cocaine exposure are disrupted arousal regulation, attention, emotional reactivity, and reward systems[5]. Children exposed prenatally to cocaine have shown specific language and cognitive deficits, behavioral problems, and impaired social development[5,55]. Abnormal brain development can be exhibited as decreased head circumference and microcephaly as a result of high levels of prenatal cocaine exposure. In fact, head circumference is a good predictor of neurobehavioral deficits in prenatal cocaine-exposed children. Magnetic resonance imaging (MRI) of brains revealed size reductions in cortical and subcortical structures, including a smaller caudate, corpus callosum, and pallidum. In contrast, the amygdala's size increases[56]. Significant reductions in the volume of cortical gray matter, thalamus, and putamen resulted from in utero cocaine exposure[57]. Brain wave activity changes and seizures are other outcomes of prenatal cocaine exposure. Prenatal cocaine-induced seizures continue throughout the child's initial months of life and, in some cases, even after 6 mo, suggesting long-term neurodevelopmental consequences of early life cocaine exposure[58].

Previous studies have confirmed that cocaine- or heroin-exposed infants are impacted by a combination of drugs (known as cocktails) with a variety of pharmacologic properties[7,59]. Cocaine users often use other substances, such as alcohol and tobacco, simultaneously[7].

Hallucinogens

Hallucinogens are naturally occurring or synthetic substances that induce hallucinations and distortions in consciousness and perception, thinking and feeling, often accompanied by some degree of auditory or visual hallucinations. They are also known as "psychedelics," and they produce synaesthesia and alter the user's perception of reality. Hallucinogenic agents fall into different chemical groups, including tryptamine (lysergic acid diethylamide or LSD and psilocin) and phenethylamines (mescaline, the main psychoactive component of peyote cactus). Hallucinogens mediate their hallucinogenic activity through interactions with serotonin receptors. LSD is one of the most potent hallucinogenic substances. It is derived from lysergic acid, an alkaloid found in a fungus named *Claviceps purpurea.* LSD's mechanism of action is similar to those of other hallucinogens. LSD exerts its hallucinogenic effect *via* its agonistic activity at the serotonin receptor 5-HT_{2A}. Serotonin is a neurotransmitter with biogenic properties. It acts as a neurotrophic agent in neuronal development processes such as neurogenesis and neuronal differentiation[60]. It has been shown that each agent that alters serotonergic signaling is linked to neurodevelopmental disorders such as autism spectrum disorder (ASD), ADHD, depression, and schizophrenia. Previous studies have demonstrated that normal placental structure and function are associated with equilibrium in serotonin signaling[61]. In fact, deficient placental serotonin levels are correlated with fetal growth restriction, anxiogenic behavior, and ASD[61].

Alcohol

Alcohol pharmacokinetics during pregnancy: Alcohol is absorbed readily from the placenta into the fetal bloodstream. Prenatal alcohol exposure begins with the dispersion of alcohol through the placenta to the fetal compartment. The chemical structure of ethanol enables rapid diffusion across the placental barrier and dispersion throughout the body water. The time needed to obtain an equilibrium between fetal and maternal alcohol concentration is one to two hours. Alcohol dehydrogenase is the enzyme responsible for ethanol metabolism in the mother, placenta, fetus, and neonates, though this occurs with different concentrations and activities. Available studies showed that the metabolic capacity of a fetus for ethanol oxidation is limited and that the majority of ethanol metabolism takes place in the maternal body to clear ethanol from the fetal-maternal unit. Small amounts of ethanol can be excreted unchanged through pulmonary excretion and in fetal urine, which can accumulate in amniotic fluid. It has been shown that the reuptake of amniotic fluid by the fetus has a

dramatic effect on the duration of fetal exposure to alcohol[62].

Alcohol (ethanol) use in pregnancy predisposes developing fetuses to health risks and is linked to adverse prenatal outcomes and fetal alcohol spectrum disorder (FASD)[63]. Many pregnancies are unintended. Therefore, a fetus may unintentionally be predisposed to alcohol in utero during critical embryonic development stages. Some health issues of alcohol use during pregnancy are miscarriage, preterm labor, stillbirth, and intrauterine growth restriction[64,65]. Women are more sensitive to alcohol than men due to their greater alcohol absorption and slower metabolism rate. Therefore, women exhibit higher blood alcohol levels than men upon drinking equal amounts of alcohol[63]. There are some varieties in response to alcohol in the fetal and neonatal stages. Several factors, such as the clearance rate of alcohol in the body, genetic variability, fetal developmental sensitivity, time (critical stages of organ formation), duration of alcohol and multi-drug use, influence the dose-response relationship between the amount of alcohol consumed during pregnancy and child health outcomes.

Alcohol use during pregnancy and its outcomes: Intrauterine alcohol exposure is associated with various fetal structural anomalies, including renal, cardiac, and craniofacial malformations. Children sometimes have complications with vision, hearing, short palpebral fissures, smooth philtrum, and a thin vermilion border of the upper lip as the most important craniofacial structural impairments[66]. Children with FASD may show abnormal facial features; low height and/or weight; and CNS complications such as small head circumference, poor attention and coordination, and hyperactive behaviors.

New psychoactive substances: New psychoactive substances (NPSs) are designer analogues of licit or illicit drugs designed for recreational use. The rapid growth in the global production of NPSs poses a considerable public health risk. These substances have spread in the market under names such as “legal highs”, “research chemicals”, and “bath salts”[67]. However, little is known about the adverse effects, health issues, and psychological properties of these new emerging substances. Safety data on the effect of prenatal exposure to NPSs, their toxicity, and their carcinogenic potential are either not available or limited[68]. Previous studies have pointed out that prenatal exposure to some classes of NPSs represents a risk to fetal health since several newborn outcomes such as neonatal abstinence syndrome have been correlated with these substances[69].

Synthetic cathinones have beta-keto-phenethylamine chemical structures. Their structure and mechanism of action are similar to those of ATS. Mephedrone, 3,4-methylenedioxypyrovalerone (MDPV), and methylone are classified as synthetic cathinones. It has been reported that mephedrone exposure during the gestational phase boosts the risk of low birth weight and stillbirth. Salimi *et al*[70]’s study on animal models showed that repeated use of mephedrone induces hippocampal damage, resulting in learning and memory process impairment. Table 1 shows different psychotropic drugs that are commonly used during pregnancy.

CONCLUSION

Pregnancy evolves a myriad of physiological variations in body organs that result in unavoidably significant changes in drug delivery to the fetus. Notably, many licit and illicit psychoactive drugs are designed to reach the brain and penetrate human barriers such as the BBB and the placenta (thus reaching the fetus body).

Substance use during pregnancy is associated with an increased risk of neurodevelopmental disorders. Drugs may have subtle outcomes in the late fetal development period when the main organs are formed. Some of these harmful consequences are altered brain formation, imbalanced neurotransmitter volume, changes in receptor expression, and unusual fetal growth patterns. Taken together, findings from previous studies suggest that being born to a drug abuser is a reliable indicator for later neurodevelopmental issues.

Further research is needed on the amount and timing of substance use during pregnancy and childhood health consequences. As NPSs are not categorized as controlled substances in many countries, the effects of prenatal exposure to these psychoactive chemicals and their neurodevelopmental outcomes are obscure and should be considered further.

Table 1 Commonly used psychotropic drugs during pregnancy

Drug classification	Drugs	Common forms	Routes of administration
Cannabis	Marijuana Hashish Synthetic cannabinoid receptor agonists	Greenish-gray mixture of dried different parts of cannabis plant; resin (hashish) or sticky, black liquid (hash oil)	Smoking, dabbing, or vaporization; Eaten (drops, cakes, tinctures, candies, snacks, and drinks); Suppositories
Narcotics	Opium Heroin Synthetic opioids (methadone, tramadol, buprenorphine)	Sticky brown gum; White or brownish powder, or black substance known as "black tar"; Colorful methadone and tramadol tablets with imprinted logos, capsules, powder, liquid	Injected, smoked, snorted; Swallowed
Stimulants	Amphetamine-type stimulants (Amphetamine, Methamphetamine, Ecstasy) Cocaine	White powder, crystal or shiny blue-white "rocks"; Colorful ecstasy tablets with imprinted logos, capsules; White powder and rock crystal cocaine	Snorted, smoked, injected, swallowed
Hallucinogens	LSD, psilocin mescaline (peyote)	Decorated squares of absorbent paper that LSD has been added to, Tablet, capsule, clear liquid; small pills (dots); Peyote cacti	Swallowed, absorbed through mouth tissues (paper squares); Mixed in food or brewed as tea
Alcohol	Ethyl alcohol	Alcoholic beverages with different alcohol content	Ingested

LSD: Lysergic acid diethylamide.

Limitations

The majority of the previous studies focused on early neurodevelopment, thereby limiting assessment of long-term impacts of prenatal drug exposure.

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MINIREVIEWS

Sickle cell nephropathy: A review of novel biomarkers and their potential roles in early detection of renal involvement

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Abstract

Whether the underlying mutations are homozygous, heterozygous, or co-inherited with other hemoglobinopathies, sickle cell disease is known to afflict the kidneys, leading to the clinical entity known as sickle cell nephropathy (SCN). Although common, SCN remains diagnostically elusive. Conventional studies performed in the context of renal disorders often fail to detect early stage SCN. This makes the quest for early diagnosis and treatment more challenging, and it increases the burden of chronic kidney disease-related morbidity among patients. Novel diagnostic tools have been employed to overcome this limitation. In this study, we discuss various biomarkers of SCN, including those employed in clinical practice and others recently identified in experimental settings, such as markers of vascular injury, endothelial dysfunction, tubulo-glomerular damage, and oxidative stress. These include kidney injury molecule-1, monocyte chemoattractant protein-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, and cation channels, among others. Furthermore, we explore the potential of novel biomarkers for refining diagnostic and therapeutic approaches and describe some obstacles that still need to be overcome. We highlight the importance of a collaborative approach to standardize the use of promising new biomarkers. Finally, we outline the limitations of conventional markers of renal damage as extensions of the pathogenic process occurring at the level of the organ and its functional subunits, with a discussion of the expected pattern of clinical and biochemical progression among patients with SCN.

Key Words: Sickle cell disease; Sickle cell nephropathy; Chronic kidney disease; Kidney injury molecule-1; Monocyte chemoattractant protein-1; N-acetyl-B-D-glucosaminidase

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Core Tip: This study discusses the expected clinical and biochemical progression among patients with sickle cell nephropathy, the utility of various biomarkers, and the limitations of conventional biomarkers. Novel biomarkers used in combination have been demonstrated to have a higher diagnostic yield as compared to that of individual markers, necessitating a collaborative approach in the standardization and utilization of promising biomarkers such as kidney injury molecule-1, monocyte chemoattractant protein-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, cation channels, and endothelial dysfunction.

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INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy with a global burden of more than 30000 newborns per year. SCD is a broad term used to describe a variety of recognized mutations, including homozygous mutations, heterozygous mutations, and mutations co-inherited with other hemoglobinopathies. The resultant erythrocyte abnormalities instigate a host of sequelae with multi-organ repercussions. The pathogenesis involves vaso-occlusive events, ischemic end-organ damage, reperfusion injury, endothelial dysfunction, vasculopathies, and oxidative stress, among other contributing factors[1]. The disease process is further complicated by an increased predisposition to infections. This is linked to impaired splenic function, micronutrient deficiencies, and sluggish circulation combined with regions of infarction, which act as favorable foci for infections. In addition, therapeutic interventions such as blood transfusions and lines for vascular access predispose patients to blood-borne infections, siderophilic organisms, and catheter-related infections[2]. Notably, chronic transfusion programs are linked to iron overload and endocrine dysfunction with a profound effect on growth and sexual maturation, which is particularly relevant to the pediatric population.

SCD can affect the kidneys through multiple pathways outlined below. The resultant entity, known as sickle cell nephropathy (SCN), typically presents during early childhood. Unfortunately, prompt diagnosis of early SCN is difficult. Therefore, it is necessary to discover new diagnostic biomarkers to facilitate the diagnosis of early stage SCN, enabling timely treatment and reducing related morbidity and mortality.

In this review, we discuss biomarkers of SCD, explore the applications of novel biomarkers for diagnostic and therapeutic approaches, and outline the limitations of conventional markers of renal damage.

PATHOPHYSIOLOGY

The pathogenesis of SCN is multifaceted and involves the effects of different components on different regions of the kidney. The extent of these effects depends on the disease chronicity and severity.

Altered hemodynamics at the level of the glomerulus and the resulting hyperfiltration have been attributed to various biochemical properties of sickling, including local factors such as the release of vasorelaxants and global factors such as increased cardiac output in chronic anemia, leading to increased renal blood flow. Consistent with Brenner's hyperfiltration theory, these changes have been described as precursors to structural changes ranging from endothelial hyperplasia and mesangial proliferation to glomerular sclerosis[3]. These glomerular changes lead to the onset of proteinuria[4].

At the level of the medullary nephron, the same conditions that contribute to normal physiology pertaining to the exchange of solutes and the control of urinary concentrations have deleterious effects on red blood cells that are prone to sickling.

The concentration gradient created by the "countercurrent" system is paramount to the unique ability of mammalian kidneys to concentrate urine. The countercurrent system is jeopardized by fast transit states; therefore, low renal blood flow in the medulla contributes to the osmolarity gradient. Combined, these factors create a climate of relative hypoxia and hyperosmolarity within the medulla[5]. Among susceptible individuals, these conditions promote red blood cell (RBC) sickling.

Wang *et al*[6] examined this phenomenon on a molecular level using SCD-mice and non-SCD mice to further study the medullary changes and their link to concentration defects. The SCD-mice exhibited elevated urinary vasopressin levels and increased abundance of aquaporin 2, urea transporter A1, and epithelial Na channels-beta subunit. The mice were shown to concentrate urine under water-replete conditions in a vasopressin-dependent compensatory mechanism. However, under water-restricted conditions, the medullary concentration ability among SCD-mice was significantly compromised as compared to the non-SCD population, with changes in urinary osmolarity equal to 28% and 104%, respectively.

Dehydrated RBCs lose solutes through a K-Cl cotransporter, a Ca^{2+}-activated K^+ channel (Gardos channel), and uniquely through the nonselective "P_{sickle}" channel that is activated by conditions of low oxygen tension[7]. Widespread RBC adhesion and inflammation within the vasa recta ensure that hemolysis causes the release of free hemoglobin, which sequesters nitric oxide and causes an overall increase in vascular tone[5]. Consequently, juxtamedullary nephrons are impaired, and defective countercurrent exchange mechanisms fail to reabsorb free water. This produces the early findings of SCN, including nocturia, polyuria, and an increased susceptibility to volume depletion. Additionally, these features are particularly problematic among this patient population because volume loss can precipitate vaso-occlusive crises as well as prerenal acute kidney infection (AKI), complicating the original renal insult.

Long-term tubular compromise is accompanied by concentration defects, impaired distal tubular function with renal tubular acidosis, and compensatory increases in proximal convoluted tubule function. The cascade of damage and the factors leading to its acceleration are shown in Figure 1.

In addition to the events described above and their consequences, pathogenesis may be aggravated by the presence of renal cysts, which have been reported to occur more frequently in patients with SCD and in younger patient groups than in the general population[8]. Other pathological changes, such as renal amyloidosis, have been described in case reports and have been shown to be resistant to interventions such as hydroxyurea and angiotensin converting enzyme inhibitors[9].

A summary of pathogenic changes and modifying factors were shown in Figure 1.

CLINICAL FEATURES AND PROGRESSION

As previously described, hyposthenuria is an early constituent of the temporal continuum of the SCN. Its presence is reflective of chronic complications and the cause of acute decline from baseline function. Previously, a negative correlation between the degree of hyposthenuria and fetal hemoglobin has been reported, and a positive correlation with age has been observed. Similar to the general population, patients with SCD in the pediatric age group may experience nocturnal enuresis, which may be partly due to delayed maturation. Unlike in patients without SCD, this otherwise nonalarming presentation is compounded by nocturnal polyuria owing to hyposthenuria as well as the potential effects of cerebral vasculopathy on bladder control. Although most patients outgrow this phenomenon, up to 10% of individuals may continue to experience this phenomenon as high school students, resulting in severe effects on psychosocial well-being[10].

Glomerular hyperfiltration is another relatively early finding. Hyperfiltration occurs with glomerular filtration rates (GFRs) of 1.50-2.34 mL/s/1.73 m^2 or more and is commonly observed early in infancy or in children with SCD[11]. Moreover, hyperfiltration can be followed by progressive declines in the estimated GFR (eGFR), as demonstrated in approximately one-third of adult patients with SCD[12]. Two widely cited clinical trials, BABYHUG and HUTSLE, confirmed this pattern with high GFR values among entrants from ages 9 to 12 mo and showed a progressive increase in short-term follow-up. The latter study further demonstrated that high GFR values persisted into early adulthood. By the fourth decade of life, however, renal clearance deteriorates and GFR exhibits a declining pattern[11].

Hyperfiltration with eGFR values greater than 2.17-2.34 mL/s/1.73 m^2 is linked to microalbuminuria (3.39-33.90 mg/mmol)[11]. Microalbuminuria is estimated to affect

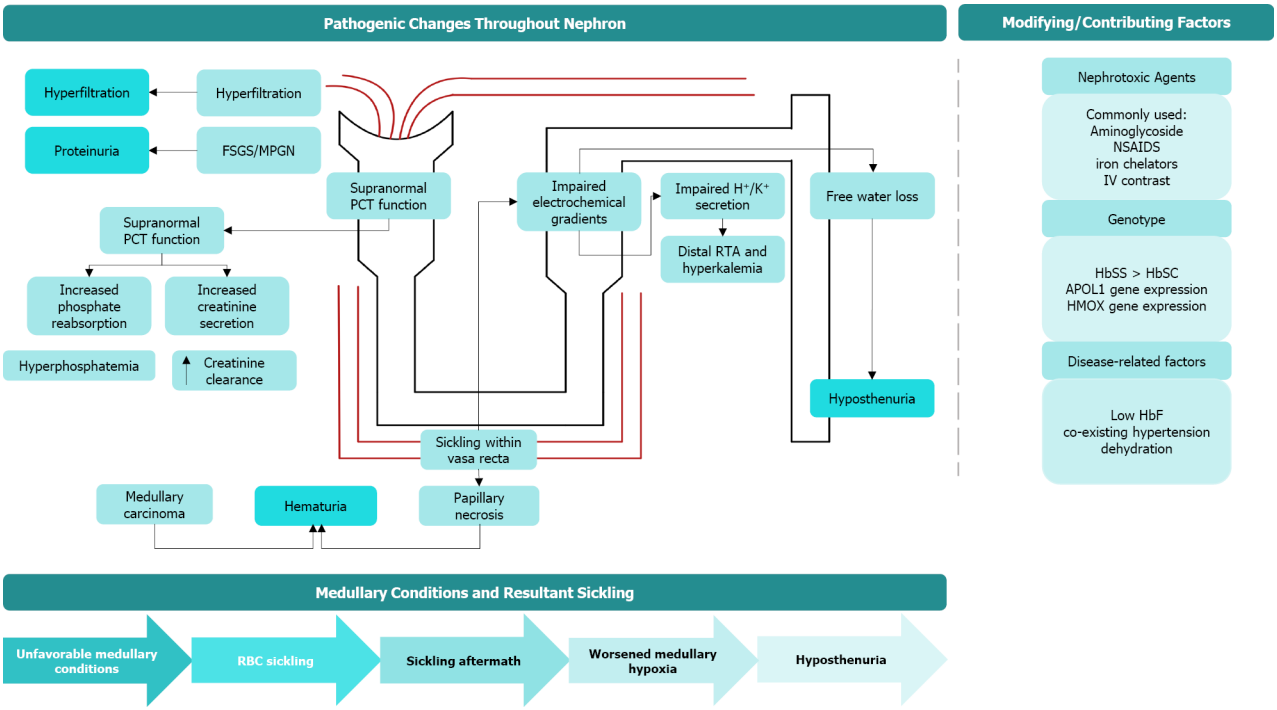

Figure 1 Summary of pathogenic changes and modifying factors. FSGS: Focal segmental glomerulosclerosis; MPGN: Membranoproliferative glomerulonephritis; PCT: Proximal convoluted tubule; RTA: Renal tubular acidosis; NSAIDs: Nonsteroidal anti-inflammatory drugs; IV: Intravenous; HbSS: Classic sickle cell; HbSC: Hemoglobin C sickle cell; APOL1: Apolipoprotein L1 gene; HMOX: Heme oxygenase 1 gene; HbF: Fetal hemoglobin; RBC: Red blood cell.

20%-35% of patients during adolescence, and progressive glomerular changes in response to a hemodynamic environment persist with age, eventually leading to macroalbuminuria (> 33.90 mg/mmol) in 60% of adult patients[13]. Glomerular changes that result in increased permeability to proteins have been described as products of chronic glomerular capillary hypertension. Furthermore, Roy *et al*[14] demonstrated that angiotensin II signaling contributes to glomerulopathy, independent of hemodynamic changes and hyperfiltration, thereby acting as a biomarker of glomerular damage in SCD, with or without hyperfiltration[12]. Another study proposed that inflammatory processes are responsible for the development of proteinuria, demonstrating a correlation between the levels of inflammatory mediators and albumin/creatinine ratios (ACR) in urine[15].

Niss *et al*[12] recognized that although the association between SCN and albuminuria is well established, there is a gap in our understanding of the progression of albuminuria with age. Their longitudinal study of 303 patients with SCD estimated that the progression of albuminuria occurs at a rate of 0.4 mg/mmol per year and suggested an ACR of 11.3 mg/mmol as a surrogate of persistent proteinuria among affected patients.

Hematuria

Hematuria, either microscopic or macroscopic, is reported in 13%-30% of patients with SCD, correlating positively with increased age and male sex[11,16]. Additionally, hematuria can be attributed to vaso-occlusive events and micro-infarctions, resulting in ischemic parenchymal injury and papillary necrosis. Capillary congestion in the medulla also contributes to the process by causing RBC leakage into the renal tubules [13]. Although normally asymptomatic, this process can produce abdominal colic and back pain when extensive. A less common yet more worrisome etiology to consider in the setting of hematuria among patients with SCD is medullary cell carcinoma, which may present during early childhood or adulthood[17].

Hypertension

Generally, blood pressure values among patients with SCD appear to be lower than those in the medically free population. This is attributed to unbalanced fluid losses and possibly to a reduction in systemic vascular resistance[13]. Paradoxically, when present, hypertension has been shown to be predictive of poorer outcomes with increased incidences of both AKI and chronic kidney disease (CKD)[18]. The term

"relative systemic hypertension" has been employed to describe relative elevations in blood pressure among patients with SCD. Relative systemic hypertension is observed in 45% of patients and is defined as a systolic blood pressure of 16.0-18.5 kPa and diastolic blood pressure of 9.3-11.9 kPa.

Novelli *et al*[19] demonstrated through a large cohort of 661 patients that pulse pressure has a higher yield than systolic and diastolic blood pressures in predicting long-term outcomes related to SCD vasculopathy. Thus, pulse pressure is also independently associated with proteinuria and elevated serum creatinine levels.

CKD and end-stage renal disease

The aforementioned pathogenic components accumulate over time and culminate in end-stage renal disease (ESRD). Some modifying factors, also described in Figure 1, increase the likelihood of patients succumbing to CKD. ESRD has been linked to risk factors such as older age, hypertension, proteinuria, hematuria, and deteriorating anemic state[16]. Notably, Yeruva *et al*[18] reported a 2-3-fold increase in the incidence of CKD in patients with SCD when compared with patients without SCD, based on a study performed over a 6-year period. Statistical variations between different studies have been noted and have been linked to discrepancies in the definition of renal failure as well as the different equations used to estimate GFR. These differences may lead to underestimation of the reported incidence and prevalence of renal impairment.

Compared with patients with non-SCD CKDs, patients in this category may experience rapid deterioration of kidney function, posing unique challenges in the area of renal replacement therapy. One issue is vascular access for hemodialysis in patients with frequent hospital admissions and compromised peripheral access[16]. More major issues revolve around the higher rates of mortality due to dialysis-related complications. Finally, although renal transplantation is the optimal therapeutic approach for patients with ESRD, patients with SCD perform poorly on transplant waiting lists[20]. If successful in obtaining a kidney, however, prognostic outcomes post-transplant are similar to those with ESRD due to other etiologies[21].

Furthermore, patients with SCD and renal failure display higher propensities for developing chronic restrictive pulmonary disease, leg ulcers, and stroke than those with intact kidney function.

Conventional renal studies and their limitations in SCN

Routine follow-up protocols currently implemented in SCD follow-up utilize conventional renal studies to diagnose SCN. These include blood pressure assessments, urinalyses, metabolic panels featuring creatinine, and selective imaging based on these findings. The eGFR values are often extrapolated from creatinine-based equations. Creatinine levels, under the influence of muscle mass and hydration status, have limitations in the general population. Among patients with SCD, such limitations are compounded by the effects of hyperfiltration and hypersecretion into the renal tubules. Thus, the rate of creatinine clearance may be misleading in the early stages of the disease. This is exemplified in numerous studies. For example, Asnani *et al*[22] reported that serum creatinine only started rising after the GFR level decreased below 0.84 mL/s. A similar conclusion was made by Guasch *et al*[23], who showed that serum creatinine levels started to rise once the GFR fell below 0.5 mL/s.

The discrepancy between estimated and measured GFRs among patients with SCD is one of the factors hindering our understanding and management of SCN[24]. Current estimating equations vary in the SCN setting[25]. The CKD epidemiology equation produced estimates that were comparable to the measured GFR values, according to Arlet *et al*[26] and Asnani *et al*[27]. Additionally, a study by Asnani *et al*[25] compared eGFR values among 98 patients against values measured using 99m-Tecnetium diethylenetriamine pentaacetic acid nuclear renal scans and showed that the creatinine-based modification of diet in renal disease formula overestimated GFR values by a mean of 1.18 mL/s. The creatinine-based EPI formula yielded improved concordance rates between measured and estimated values, with a mean overestimation of 0.69 mL/s.

Another formula used to estimate GFR, specifically among the pediatric population, is the Schwartz formula, which considers the height and enzymatically measured serum creatinine levels of the patients. In a study of the effects of hydroxyurea on infant renal capacity, a double-blinded randomized controlled trial, BABYHUG, compared the estimated GFR as per the Schwartz formula with quantitative GFR measurements in 176 infants. The age of the infants ranged from 9 to 19 mo. The results showed that this formula markedly overestimated GFR and was found to be useful only in children with low GFRs. Considering the natural history of the disease and the late decrease in GFR, CKD may need to be redefined in SCN using criteria for

a decline in estimated GFR from baseline. This would require a consistent method of routine GFR measurements, starting from a predetermined baseline age[24].

Another limitation pertaining to GFR measurements among patients with SCD is its influence on poor nutritional status, which could lead to eGFR underestimation and hence, premature CKD determination[28].

Cystatin C-based GFR

Cystatin C is a non-glycosylated low-molecular-weight protein produced by all nucleated cells. Its production rate increases during inflammatory events, and the protein undergoes renal metabolism, which is characterized by free filtration at the glomerulus followed by reabsorption by tubular epithelial cells[29]. Relative to creatinine clearance, cystatin C is described as a superior marker for GFR because it is not affected by height, sex, diet, and muscle bulk[30]. Its renal handling is also advantageous in that unlike creatinine, it is not secreted by tubules.

Asnani *et al*[31] corroborated this finding in a study examining 98 subjects with SCD, which presented a significant correlation between serum cystatin C and measured GFR, serum creatinine, urine ACR (r = 0.79), and systolic blood pressure.

Tantawy *et al*[32] reported the sensitivity and specificity of serum cystatin C at 91% and 90%, respectively. These values were superior to those of serum creatinine, with a sensitivity of 79% and a specificity of 85%. Another study conducted by Economou *et al*[33] concluded that 36% of patients with chronic hemolytic anemia showed high serum cystatin C levels.

The implications of these findings have been explored in the domain of management and monitoring of patient responses to hydroxyurea because patients managed with hydroxyurea have been shown to have relatively low cystatin C levels [32]. Additionally, the utility of cystatin C in SCD has been shown to extend to extrarenal complications as well as SCN, with a positive correlation between cystatin C levels and carotid intima-media thickness[32].

Alternatives to both creatinine and cystatin have also been explored. For example, beta-trace protein (BTP) is a low-molecular-weight glycoprotein that is easily filtered by the glomerulus with very little or no tubular reabsorption. In 1997, Hoffmann *et al* [34] discovered increased levels of serum BTP among hemodialysis patients and suggested that BTP is a potential diagnostic marker for renal disease.

Beta-2-microglobulin, a constituent of class I major histocompatibility molecules, has also been explored as a surrogate for GFR estimation. This protein was found to be strongly correlated with measured GFR values. However, its values may fluctuate in response to inflammatory processes and lymphoproliferative diseases. Moreover, to date, only Inker *et al*[35] reported a GFR equation based on a combination of BTP and Beta-2-microglobulin. Unfortunately, this equation did not show any advantages over equations combining creatinine and cystatin C in a variety of populations.

Estimated GFR formulas employed in sickle cell nephropathy were shown in Table 1.

NOVEL BIOMARKERS

As previously discussed, findings from conventional renal studies, otherwise referred to as first-generation biomarkers, have numerous shortcomings. Owing to the kidney's functional reserve, elevations in blood urea nitrogen and creatinine are not appropriately reflective of early renal damage or impending AKI. The limitations of this well-recognized hindrance expand beyond the scope of SCN. The collaborative InnoMedPredTox project, for example, explores biochemical alternatives to conventional renal studies in the interest of detecting nephrotoxicity to determine pharmaceutical safety[36]. Fortunately, the demand for novel biomarkers is coupled with great strides in biomedical capabilities and high-throughput omics.

Validating new diagnostic biomarkers requires the fulfillment of certain criteria and the consideration of a variety of logistics, including diagnostic yield *vs* cost effectiveness. The following criteria were established by the Predictive Safety Testing Consortium Nephrology Working Group in their quest to identify novel biomarkers that could be employed in the early detection of nephrotoxicity. The principles of their criteria, listed in Table 1, may be extrapolated to satisfy the context of SCN[37]. An exception to this may be the point labeled "2," which is less applicable to nonpharmacological settings. Applying these principles to the context of SCD, the ideal biomarker for SCN should predate clinically apparent findings, creatinine elevation, microalbuminuria, and compromised GFR. This is key in the process of early intervention to halt

Table 1 Estimated glomerular filtration rate formulas employed in sickle cell nephropathy

Formula	Equation
CKD-EPI (Cr)	F with Cr ≤ 62 μmol/L (≤ 0.7 mg/dL): 144 × (creatinine/0.7) - 0.329 × 0.993 age (× 1.159 if Black); F with Cr > 62 μmol/L (> 0.7 mg/dL): 144 × (creatinine/0.7) - 1.209 × 0.993 age (× 1.159 if Black) M with Cr ≤ 80 μmol/L (≤ 0.9 mg/dL): 141 × (creatinine/0.9) - 0.411 × 0.993 age (× 1.159 if Black); M with Cr > 80 μmol/L (> 0.9 mg/dL): 141 × (creatinine/0.9) - 1.209 × 0.993 age (× 1.159 if Black)
MDRD	175 × creatinine - 1.154 × age - 0.203 × 0.742 (if female)
Schwartz	0.413 × [height (cm)/creatinine]
CKD-EPI (Cystatin C)	Cystatin C ≤ 0.8 mg/L: 133 × (cystatin C/0.8) - 0.499 × 0.996 age (× 0.932 if female); Cystatin C > 0.8 mg/L: 133 × (cystatin C/0.8) - 1.328 × 0.996 age (× 0.932 if female)

CKD-EPI: Chronic kidney disease epidemiology; Cr: Creatinine; F: Female, M: Male; MDRD: Modification of diet in renal disease.

the progression of CKD. Furthermore, oscillations in values in response to injury and recovery may be ideal for monitoring disease progression and response to therapy. Noninvasive accessibility to biomarkers in urine or plasma samples is another point that must be fulfilled for increased convenience in clinical settings. Localization of kidney injury may shed light on the pathogenic process and aid in a targeted treatment approach. However, some markers discussed below are indicative of global changes, as opposed to localized insults.

Ideal features of biomarkers used to detect drug-induced kidney toxicity were listed in Table 2.

Jerebtsova *et al*[38] recognized that despite considerable efforts being dedicated to the discovery and validation of novel biomarkers of renal damage there have yet to be groundbreaking discoveries that are clinically applicable. The authors also cited shortcomings in proteomic technology over the past decade as a reason for this and discussed logistic issues in the domain of sample collection, result reproducibility, and validation tools, leading to a proposal of the roles of new proteomic technology in bypassing previous limitations. The authors also suggested that, although urine samples are readily available, one must consider the impact of concentration defects on the urinary concentrations of the studied biomarkers.

A summary of studies of novel biomarkers were listed in Table 3.

Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed by renal cells after exposure to injurious stimuli[13]. Its relationship with diabetes, nephrogenic medications, and ischemia has been well established in animal models and cohort studies. Elevated values have been shown to acutely herald inflammation and chronic fibrosis. Moreover, its urinary excretion parallels tissue levels[39]. In one experimental study conducted by InnoMedPredTox, rats were exposed to nephrotoxic agents, and among other biomarkers, urinary KIM-1 was subsequently quantified by polymerase chain reaction, enzyme-linked immunosorbent assay, and immunohistochemistry. KIM-1 expression was found to correlate with histopathological alterations occurring at the level of the outer cortex, even in the setting of normal kidney function. This revealed the potential applications of KIM-1 as an early and sensitive noninvasive marker of renal injury[36]. Currently, KIM-1 is used as a biomarker for predicting chemo-induced nephrotoxicity. In a cross-sectional study examining AKI in adult patients undergoing cardiac surgery, elevated values were predictive of postoperative AKI[40].

The hypoxic, proinflammatory conditions of the kidney in SCD imply the applicability of this utility to the context of SCN. Sundaram *et al*[41] and Niss *et al*[12] demonstrated a positive correlation within their samples with albuminuria and ACR as endpoints, respectively. Although both of these studies confirmed the sensitivity of the biomarker, questions regarding the diagnostic yield of KIM-1 have been raised. For example, KIM-1 is expressed in the liver, spleen, and kidneys and plays roles in immune tolerance and viral uncoating; genetic polymorphisms may affect its expression and therefore the efficacy of intracellular tracking.

Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP-1) is a powerful chemotactic agent induced by proinflammatory cytokines. This protein is involved in recruiting monocytes/

Table 2 Ideal features of biomarkers used to detect drug-induced kidney toxicity

	Features
(1)	Identifies kidney injury early (before renal reserve is dissipated and levels of serum creatinine increase)
(2)	Reflects the degree of toxicity, in order to characterize dose dependence
(3)	Displays similar reliability across species, including humans
(4)	Localizes to the site of kidney injury
(5)	Tracks the progression of injury and recovery from damage
(6)	Is well characterized with respect to the limitations of its capacities
(7)	Is accessible in readily available body fluids or tissues

macrophages to areas of renal damage. Macrophages are well-established fibrogenic agents in the setting of chronic inflammation. Similarly, renal fibrosis and ESRD-related histopathological changes are expected to be expedited by this chemokine[42]. These findings have been corroborated by animal models and clinical studies examining this agent in the setting of lupus nephritis and diabetic nephropathy[43, 44]. Additionally, MCP-1 is produced by tubules and glomeruli, and its urinary excretion is proportional to its tissue concentration.

The application of MCP-1 to SCN was first reported by Laurentino *et al*[13], and the findings were further confirmed by Belisário *et al*[15] in 2020. Other contributions by Belisario and colleagues showed a positive correlation between MCP-1 levels and ACR as well as between inflammatory mediators and RAS molecules.

N-acetyl-B-D-glucosaminidase

N-acetyl-B-D-glucosaminidase is a lysosomal enzyme that is synthesized by proximal tubular epithelial cells and liberated into the urine in the context of proximal tubular injury[45]. Other authors have verified its potential in predicting the onset of diabetes among patients with diabetes. Sundaram *et al*[41] obtained similar results when exploring the potential of N-acetyl-B-D-glucosaminidase as an early marker of SCN. Their results demonstrated elevations in N-acetyl-B-D-glucosaminidase activity, even among patients without microalbuminuria, highlighting its possible role in early detection.

Ceruloplasmin and orosomucoid

To identify potential biomarkers with elevations predating the onset of albuminuria, Jerebtsova *et al*[46-48] employed mass spectrometry in the analysis of 20 non-albuminuric urine samples. The samples were further subdivided according to the presence or absence of urinary hemoglobin. Of the 270 proteins identified, 18 extracellular proteins were shown to be significantly upregulated or downregulated in hemoglobinuric samples. Further analysis of ceruloplasmin showed that this protein was positively correlated with hemoglobinuria. Further associations with proteins linked to iron metabolism were explored because the samples showed increased ceruloplasmin, transferrin, and ferritin to creatinine ratios in urinary samples when compared with healthy controls. As an extension of this study, orosomucoid, a major acute-phase protein, was also studied as a potential biomarker. Its relationship with other kidney disorders, including diabetic nephropathy and lupus nephritis, has already been demonstrated. Moreover, orosomucoid was found to be correlated with urinary ceruloplasmin values and CKD progression.

Nephrin

Nephrin is a transmembrane protein that exhibits podocyte cytoskeletal structural integrity. Its presence in the urine is indicative of damage localized to the glomerulus. At the molecular level, various factors are associated with functional disruption of nephrin and have been linked to various glomerulopathies, systemic lupus erythematosus, preeclampsia, and hyperglycemia. Its use as a biomarker of early pathological changes has been studied in these disorders with variable results[49]. A study conducted at a tertiary center in Malawi was the first to explore this biomarker among patients with SCD. The results showed that nephrin-to-creatinine urinary ratios were significantly associated with albuminuria. A cutoff value of 622 ng/mg was identified as predictive of albuminuria with a sensitivity of 96% and a specificity of 64%[50]. The

Table 3 Summary of studies of novel biomarkers

Ref.	Study design	Sample size	Endpoints	Finding(s)	Criteria fulfillment
KIM-1					
Sundaram *et al* [41]	Cross-sectional (United States)	116 (ages 5-65 yr, mean age: 18 yr)	MiA: UACR 3.39-33.90 mg/mmol MaA: UACR > 33.90 mg/mmol	KIM-1 detectable in all SCD samples, increased with MiA (P = 0.005), further increased with MaA (P = 0.0015)	Early detection (MiA); reflects severity; localized damage to PCT; detected in urine
Niss *et al*[12]	Prospective longitudinal, mean FU 23 mo (United States)	303 (2-64 yr, mean age: 21 yr)	Albuminuria: Urine albumin ≥ 11.3 mg/mmol)	KIM-1 linked to baseline and persistent albuminuria with P < 0.001	Applicable to larger samples
MCP-1					
Laurentino *et al* [13]	Prospective cohort (Brazil)	50(33.2 ± 10.2 yr)	ELISA, urine sample	Increased urinary MCP-1 in SCD (SSHU: 168.2 ± 90.1 and SS: 231.4 ± 123.7) P < 0.0001 relative to the control group (42.1 ± 27.6)	Reflects oxidative stress; localized damage to PCT + glomerulus; detected in urine
Belisário *et al* [15]	Prospective longitudinal, mean FU 1.1 yr	213 (1.6-19yr)	ELISA	Increased urinary MCP-1 positively related to ACR with P < 0.0001	Positively correlated with other biomarkers; detected in urine
Ceruloplasmin					
Jerebtsova *et al* [46]	Cross-sectional cohort	54	Hemoglobinuria: Hgb/CRE > 0.8 ng/mL CKD stage: Stage 0: eGFR > 1 mL/s/1.73 m^2; Stage 1: eGFR > 1.5 mL/s/1.73 m^2; Stage 2: eGFR 1-1.49 mL/s/1.73 m^2; Stage 3: eGFR 0.5-0.99 mL/s/1.73 m^2; Stage 5: eGFR < 0.25 mL/s/1.73 m^2	CP significantly (31 ×) higher among samples with hemoglobinuria with $P = 1.8 \times 10^5$; Urinary CP/CRE, TF/CRE, and Ftn/CRE were all significantly higher than in non-SCD controls; CP/CRE (only) positively correlated with CKD stage (n = 34, P = 0.0008); ROC analysis: Sensitivity, 68.75%; specificity, 95.65%	Reflects iron handling defects in SCN; high sensitivity/specificity; detected in urine
Orosomucoid					
Jerebtsova *et al* [47]	Cross-sectional cohort	54	Hemoglobinuria: Hgb/CRE > 0.8 ng/ mL and CKD stage	ORM significantly higher among samples with hemoglobinuria with $P = 8.4 \times 10^3$; ORM positively correlated with CKD stage (n = 34, r = 0.51, P = 0.0014); ROC analysis: Sensitivity, 87.1%; specificity, 86.6%	Acute-phase protein; high sensitivity/specificity; detected in urine
Jerebtsova *et al* [48]	Cross-sectional cohort	51 HbSSand 15 HbSC	Hemoglobinuria: Hgb/CRE > 0.8 ng/ mL and CKD stage	PORM significantly higher among HbSS population with UORM/CRE; positively correlated with CKD progression (P = 0.0013); ROC analysis: Sensitivity, 60%; specificity, 78.26%	Acute-phase protein; high sensitivity/specificity; detected in urine
Nephrin					
Heimlich *et al* [50]	Prospective cohort	101 [median age: 9 yr (IQR: 4-11 yr)]	Urine albumin: Creatinine ≥ 3.39 mg/mmol	Urinary NCR higher in HbSS than in HbAA; NCR significantly associated with albuminuria (odds ratio = 1.002, 95% confidence interval: 1.001-1.003, P = 0.0003); at an NCR cut-off value of 622 ng/mg: R (albuminuria × 45.9); at NCR ≥ 622 ng/mg: Sensitivity, 96%; specificity, 64%	Reflects glomerular injury; localized damage to glomerulus; detected in urine; modest specificity, PPV; high sensitivity and negative predictive value
Cation Channels					
Brewin *et al*[51]	Prospective cohort (Brazil)	112 (10.7 ± 4.1 yr; 4-19 yr)	Hyperfiltration: GFR > 2.34 mL/s/1.73 m^2; microalbuminuria: > 3 mg/mmol	eGFR, modestly positively correlated with Gardos channel and Psickle (r = 0.234, P = 0.002) and (r = 0.326, P = 0.005), respectively; ACR, positively correlated with Gardos channel (r = 0.246, P = 0.013) and Psickle (r = 0.207, P = 0.033) activity; KCC activity, negatively associated with ACR (r = 0.334, P = 0.007),	Reflects RBC permeability; detected in RBC samples; strong predictor of microalbuminuria

				suggesting renoprotection	
Endothelial Injury					
Youssry *et al* [53]	Prospective cross-sectional (Egypt)	47	PCR, blood samples	Urinary NCR higher in HbSS than in HbAA NCR significantly associated with albuminuria (odds ratio = 1.002, 95% confidence interval: 1.001-1.003, P = 0.0003); at NCR cut-off value of 622 ng/mg: R (albuminuria × 45.9); at NCR ≥ 622 ng/mg: Sensitivity, 96%; specificity, 64%	Reflects glomerular injury; localized damage to glomerulus; detected in urine; modest specificity, PPV; high sensitivity and negative predictive value

ACR: Albumin/creatinine ratio; CP: Ceruloplasmin; CP/CRE: Ceruloplasmin/creatinine ratio; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; ELISA: Enzyme-linked immunosorbent assay; Ftn/CRE: Ferritin/creatinine ratio; FU: Follow-up; Hgb/CRE: Hemoglobin/creatinine ratio; Hgb/CRE: Hemoglobin/creatinine ratio; IQR: Inter-quartile range; KIM-1: Kidney injury molecule-1; KCC: KCl co-transporter; MaA: Macroalbuminuria; MiA: Microalbuminuria; MCP-1: Monocyte chemoattractant protein-1; NCR: Nephrin/creatinine ratio; ORM: Orosomucoid; PCR: Polymerase chain reaction; PCT: Proximal convoluted tubules; PORM: Plasma ORM; PPV: Positive predictive value; ROC: Receiver operating characteristic; RBC: Red blood cell; SCD: Sickle cell disease; SS: Sickle cell disease patients not taking hydroxyurea; SSHU: Sickle cell disease patients taking hydroxyurea; TF/CRE : Transferrin/creatinine ratio; UACR: Urine albumin/creatinine ratio; UORM: Urinary orosomucoid.

authors concluded that nephrin may have applications in predicting glomerulopathy and its progression.

Cation channels

The pathophysiology of SCN has been widely described with reference to the microenvironment of the kidney and its promotion of sickling. However, the molecular pathogenesis of cellular damage has not been thoroughly evaluated. One of the more novel approaches for understanding SCD pathology involves examination of the cation transport system and its role in promoting solute loss, subsequent dehydration, and sickling[7]. Brewin *et al*[51] investigated the potential application of this principle to the early detection of SCN. Radioactive rubidium (86Rb+) was used to measure the activity of the K-Cl cotransporter, Ca^{2+}-activated K^+ channel (Gardos channel), and P_{sickle} channel among patients with SCD. According to their findings, the Gardos channel and P_{sickle} channel were both positively correlated with eGFR and ACR. Although these findings have not yet been confirmed in larger cohorts, detecting changes at the level of altered cellular permeability may prove valuable in determining the prognosis prior to the onset of renal damage. Furthermore, pharmacological interventions targeting these channels offer a potential focus for targeted treatment in the future.

Endothelial dysfunction

Endothelial dysfunction is thought to be related to SCN. Mediators such as endothelin-1 (ET-1) and soluble fms-like tyrosine kinase-1 have been studied as contributors to pathogenesis, possible diagnostic markers, and even targets for therapeutics. In an experimental animal study, Heimlich *et al*[50] studied ET-1, an established strong vasoconstrictor, proliferative, and proinflammatory molecule that elicits the production of reactive oxygen species in the pathway, leading up to SCN and oxidative damage. These results confirmed the role of ET-1 in humanized sickle cell mice, demonstrating elevated mRNA expression of *ET-1* and its receptor *ETA*.

Furthermore, Saleh *et al*[52] confirmed the increased binding to the aforementioned receptor within the renal vasculature and showed that antagonism of this receptor is linked to decreased urinary protein and nephrin excretion. This has already been established in animal models dedicated to the study of diabetic nephropathy. Closely related to this principle, an Egyptian study explored the effects of SCD on the production of soluble fms-like tyrosine kinase-1, an anti-angiogenic vascular endothelial growth factor receptor and found that its overexpression was linked to vascular dysfunction[53].

Further studies

Future studies extrapolated from animal-based findings can pave the way for future biomarkers to be explored. For example, a study by Ofori-Acquah *et al*[54] that was targeting SCD mice exhibited that SCD mice had marked deficiency of the protein hemopexin. This biological event in turn leads to a compensatory response, which is an increase in the protein a-1-microglobulin, as discussed above.

The results found a strong correlation between hemopexin deficiency and the induction of AKI in SCD mice under hemolytic stress. Human studies that explore this protein as a biomarker, among others should also be contemplated in the future[54].

CONCLUSION

Because of its devastating effects on patient mortality, morbidity, and quality of life, SCN has become a major research target. Approaches to both management and diagnosis have not yet been optimized, despite rigorous efforts from investigators in the field. Multiple authors have cited a lack of longitudinal studies as the primary limitation in the standardization and validation of their findings. Most of our current understanding of SCN stems from cross-sectional studies as opposed to large-sample cohorts with prospective follow-up of long-term renal performance. However, according to electronic databases of clinical trials, studies assessing novel parameters and their responses to interventions are underway.

Furthermore, several authors have demonstrated that the diagnostic yield of combinations of novel biomarkers may exceed that of individual markers, necessitating a collaborative approach in the standardization and utilization of promising biomarkers. As highlighted earlier, the lack of efficient renal studies is not a problem exclusive to SCN. Rather, first-generation renal studies should be supplemented with newer investigations detecting impeding, rather than irreversible, losses of renal reserve. This highlights the importance of follow-up studies documenting the performance of the abovementioned biomarkers in larger populations, for extended durations, and their fluctuations in response to interventions and crises.

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MINIREVIEWS

Hereditary pancreatitis: An updated review in pediatrics

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Abstract

Hereditary Pancreatitis (HP) has emerged as a significant cause of acute, acute recurrent and chronic pancreatitis in the pediatric population. Given that it presents similarly to other causes of pancreatitis, a positive family history and/or isolation of a gene mutation are vital in its designation. Inheritance patterns remain complex, but mutations involving the PRSS1, SPINK1, CFTR and CTRC genes are commonly implicated. Since being first described in 1952, dozens of genetic alterations that modify the action of pancreatic enzymes have been identified. Among children, these variants have been isolated in more than 50% of patients with chronic pancreatitis. Recent research has noted that such mutations in PRSS1, SPINK1 and CFTR genes are also associated with a faster progression from acute pancreatitis to chronic pancreatitis. Patients with HP are at increased risk of developing diabetes mellitus, exocrine pancreatic insufficiency, and pancreatic adenocarcinoma. Management follows a multi-disciplinary approach with avoidance of triggers, surveillance of associated conditions, treatment of pancreatic insufficiency and use of endoscopic and surgical interventions for complications. With significant sequela, morbidity and a progressive nature, a thorough understanding of the etiology, pathophysiologic mechanisms, diagnostic evaluation, current management strategies and future research considerations for this evolving disease entity in pediatrics is warranted.

Key Words: Hereditary pancreatitis; Acute pancreatitis; Acute recurrent pancreatitis; Chronic pancreatitis; Pancreatitis; Pediatrics

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Core Tip: Herediatry Pancreatitis is associated with the inheritance of pathologic genetic mutations. Recent work in pediatrics has isolated genetic variants responsible for early onset and rapidly progressive disease. Early identification of at risk patients and timely referral to appropriate tertiary centers has the ability to limit health care cost and substantial sequelae of this aggressive disease continuum. Further research is warranted to better define preventative management strategies.

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INTRODUCTION

Acute pancreatitis (AP) in pediatrics is on the rise, with incidence rates now similar to that of the adult population[1]. In many children AP is self-limiting with a largely uncomplicated course[2]. However, single center reports have noted that as much as 35% of patients experience recurrent attacks with development of chronic pancreatitis (CP)[3]. Pediatric CP is associated with a high disease burden and complications, necessitating multiple hospitalizations, procedures, psychiatric comorbidities and days away from school, all impacting negatively on the quality of life (QOL) of affected patients[4].

In pediatrics, the rapid progression from the initial episode of AP to CP is striking, with a median time of 3.79 years[5]. Such an aggressive disease continuum calls for a closer analysis of the etiologies involved in childhood pancreatitis. Alcohol and cigarette smoking are well established risk factors for acute recurrent pancreatitis (ARP) and CP in adults, but these are uncommon among children. Risk factors in the pediatric setting are more varied and include; infections, systemic illness, trauma, pancreatic ductal anomalies, metabolic disease, biliary/obstructive causes and hereditary factors such as gene mutations[4,6]. With the implementation of more widespread genetic testing, mutations in pancreatitis related genes have now been demonstrated to be commonly implicated in both pediatric ARP and CP[4].

Historically, herediatry pancreatitis (HP) was grouped and defined as pancreatitis in association with highly penetrant germline mutations, with particular reference to *cationic trypsinogen (PRSS1)* gene defects. Pancreatitis associated with the inheritance of other genetic variants in a non-autosomal dominant manner were termed as familial pancreatitis[7]. However, these designations have changed as more pancreatitis related gene mutations have been discovered and complex inheritance patterns have been characterized. Some have adopted the definition that HP describes patients with pathologic genetic variants predisposing them to the development of pancreatitis. Such a definition would therefore, also encompass genetic mutations inherited in both an autosomal recessive or complex pattern, namely those of the serine *protease inhibitor Kazal type 1 (SPINK1)* and *cystic fibrosis transmembrane conductance regulator (CFTR)* genes[8].

Recent work in pediatrics has implicated particular gene mutations in early onset and rapidly advancing disease[5,9]. This together, with several unique features, and a significantly increased risk of pancreatic carcinoma, places HP as a disease process under intense debate and study. In this regard, we aim to review the historical perspectives, clinical features, genetics, diagnostic evaluation, current management strategies and future research considerations for this evolving disease entity in pediatrics.

HISTORICAL PERSPECTIVES

The emergence of HP as a unique entity was first noted in 1952, wherein, the authors reported the pedigree of six family members (four definite and two probable),

spanning three generations with repeated episodes of pancreatitis. Age of onset ranged from 5 to 23 years of age, with clinical features and complications seeming to occur in an autosomal dominant inheritance pattern[10]. Since, more than 100 families with HP have been reported. In 1996, an exceptional family genealogy was studied between 1800 and 1993, involving 249 members across eight generations. Such a series yielded 63 definite and 17 probable cases of HP. Importantly, this report confirmed an autosomal dominant pattern of inheritance with variable penetrance[11]. Later that year, Whitcomb and colleagues, discovered the first genetic mutation associated with the HP phenotype; an arginine to histidine substitution at codon 122 of the *PRSS1* gene, further designated as the *R122H* variant[12]. Since, dozens of mutations of the *PRSS1* and other genes associated with HP have been identified.

EPIDEMIOLOGY

True prevalence rates of HP may be difficult to determine given infrequent genetic testing outside of specialized centers[13]. The prevalence has been estimated to be 0.3 per 100,000 persons in France[14], but, this, along with worldwide estimates are likely under representations of actual figures.

Germline mutations are common in both pediatric ARP and CP. In a recent cross-sectional study of a multinational, pediatric cohort, 48% of patients with ARP and 73% of CP patients were noted to have at least one gene mutation implicated in HP. Having said that, not all patients in this study underwent testing for pancreatitis-associated gene mutations, and in those who did, the genetic panel was rarely comprehensive, making the true impact of childhood HP likely more significant than reported[4].

CLINICAL FEATURES

HP generally presents as an acute episode of pancreatitis, manifested by significant abdominal pain, nausea and vomiting, with amylase and/or lipase levels more than 3 times the upper limit of normal. If abdominal imaging is warranted features consistent with AP can be noted; typically acute interstitial pancreatic edema, peripancreatic inflammation, fluid collections or pancreatic/peripancreatic necrosis[15]. Given inherent genetic mutations, patients are predisposed to recurrent episodes of AP. In particular, pediatric patients experience a rapid progression from the initial episode of AP to CP, with a median time of 3.79 years being described. Children with pathogenic *PRSS1* mutations progress at a faster rate to CP, as compared to patients without *PRSS1* variants (median time to CP: 2.52 *vs* 4.48 years; $P < 0.05$)[5]. Such an aggressive disease process leads to chronic parenchymal and ductal changes (Figures 1 and 2). These include hyperechoic foci with and without shadowing, main pancreatic duct calculi, lobularity with honeycombing, cystic changes, duct dilation, hyperechoic duct margins, dilated side branches and hyperechoic stranding. The Rosemont Criteria can be used to categorize such imaging findings, however its use in pediatrics has not been validated[15,16].

All in all, the clinical spectrum of pancreatic disease noted with pediatric HP closely resembles other etiologies of ARP and CP, albeit, at a faster rate of progression with particular phenotypes. There are however, a few notable distinguishing features. HP tends to have an earlier presentation. Variants of the *PRSS1, chymotrypsin C (CTRC) and carboxypeptidase A1 (CPA1)* genes are associated with early disease onset, particularly before 10 years of age[9,14]. Additionally, there is some evidence to suggest that a maternal pattern of inheritance confers earlier disease onset as compared to a paternal pattern of inheritance[17]. At this time there is no compelling evidence to indicate that patients with HP develop exocrine or endocrine insufficiency at a faster rate[13]. However, given an earlier progression to CP in certain HP phenotypes, such a protracted disease course with ongoing pancreatic parenchymal damage and atrophy, may represent a contributory factor to the rapid development of exocrine pancreatic insufficiency and diabetes noted in children with ARP[5].

HP in the adult setting confers an increased risk of pancreatic cancer, with a lifetime risk of at least 40% for developing carcinoma of the pancreas among HP adults[17]. Of note environmental factors, namely tobacco smoking and alcohol consumption may act as confounders in this population. Further analysis controlling for smoking did reveal a relative risk of approximately 7% for the development of pancreatic cancer among adults with a *PRSS1* gene mutation[18]. To the best of our knowledge, the risk of pancreatic cancer in childhood CP, let alone pediatric HP, remains unknown[19].

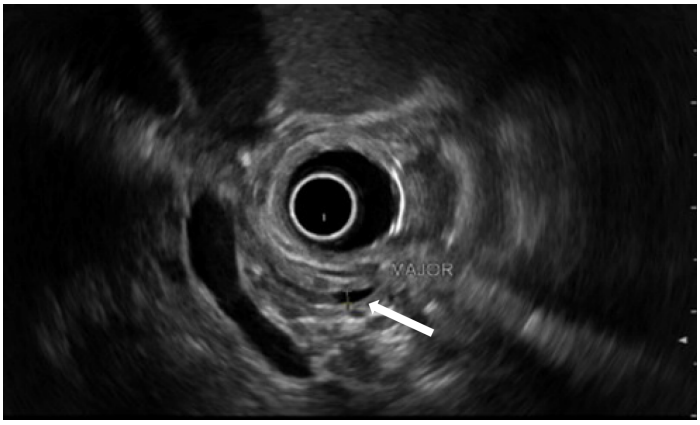

Figure 1 Radial endoscopic ultrasound in a 13 year old male with SPINK1 and CTRC gene mutations demonstrating pancreatic duct dilatation (arrow) in addition to chronic parenchymal changes: Honeycombing with lobularity, non-shadowing hyperechoic foci, cystic changes and hyperechoic duct margins.

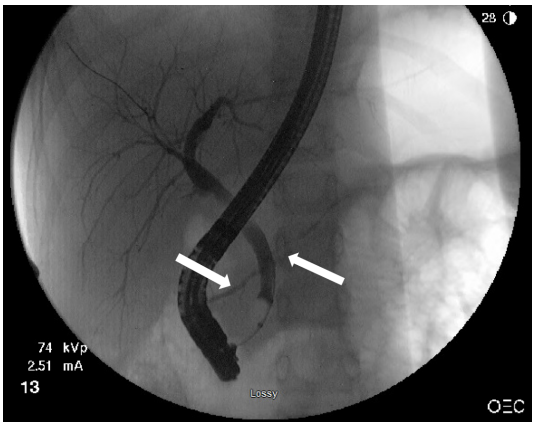

Figure 2 Endoscopic retrograde cholangiopancreatography in a 10 year old male with a CFTR gene mutation and pancreas divisum demonstrating contrast entering the dorsal pancreatic duct (arrows) from the common bile duct during a balloon occlusion cholangiogram. This occurred due to a fistula between the common bile duct and pancreatic duct secondary to repeated episodes of acute pancreatitis.

PANCREATITIS RELATED GENE MUTATIONS

It was not until 1996 that the first pancreatitis related gene variant, the *R122H* mutation of the *PRSS1* gene was discovered. Since then, numerous pathogenic mutations of the *PRSS1* and additional genes have been identified[12]. Other notable genes associated with HP include, *SPINK1, CFTR, CTRC, CPA1, calcium-sensing receptor (CASR)* and *claudin*-2. In many instances, HP seems to involve a complex interplay of genetic and environment factors that causes an imbalance in protease regulation leading to pancreatic parenchymal injury. From recent analyses, these genetic mutations have been grouped and classified into disease causing or modifiers of disease[7,20-22]. The following section describes the inheritance pattern and proposed mechanism of action of the major pancreatitis related variants implicated in HP. A summary of this information has also been provided (Table 1).

PRSS1

Pathogenic variants of *PRSS1* have been isolated in >60% of large families afflicted with HP, spanning numerous generations[7]. Although dozens of *PRSS1* mutations have been identified, *R112H, N29I and A16V* are the most common disease causing variants. These are all inherited in an autosomal dominant manner. *R122H* (80% penetrance, 78% of mutations) and *N29I* (93% penetrance, 12% of mutations) together are estimated to account for approximately 90% of *PRSS1* HP cases[14,23].

The *R122H* mutation has been classified as a gain of function mutation that prevents autolysis of trypsin, which increases trypsin stability, thereby allowing for enhanced enzyme activation and pancreatic digestion[24]. Similarly, *N29I* mutation results in

Table 1 Prominent pathogenic pancreatitis related gene variants

Pathogenic gene (Variant)	Inheritance pattern	Mechanism of action
PRSS1 (R122H)	Autosomal dominant	Impaired autolysis of trypsin
PRSS1 (N29I)	Autosomal dominant	Increased autoactivation of trypsin
PRSS1 (A16V)	Autosomal dominant	Possible increase in trypsin activation
CFTR (R75Q)	Autosomal recessive	Impaired zymogen secretion
Disease modifiers		
SPINK1 (N34S)	Autosomal recessive	Decreased trypsin inhibition
CTRC (A73T, V235I, R253W, K247_R254del)	Autosomal dominant or multigeneic	Impaired lysis of trypsin

increased autoactivation of trypsin, also allowing for unchecked pancreatic autodigestion[25]. As a result, *R122H and N29I* mutations generally follow a similar clinic presentation. On the other hand, the mechanism by which the *A16V PRSS1* gene variant cause disease remains incompletely understood. Some evidence suggest that the *A16V* mutation increases the secretion of the *CTRC* protein, ultimately leading to a fourfold increase in activation of trypsin[26].

SPINK1

The *SPINK1* gene encodes an acute phase reactant that functions as a trypsin inhibitor. Pathogenic *SPINK1* mutations are loss of function mutations leading to decreased trypsin inhibition, predisposing to pancreatitis[27]. The *N34S* variant is the most common haplotype reported globally. In the majority of cases *SPINK1* mutations are inherited in a heterozygous form and require other genetic and/or environmental factors to effect pancreatitis. As such, they are better considered as disease modifiers [28].

CFTR

Mutations in the *CFTR* gene are also associated with HP. One would readily associate the F508-delta variant with the typical multisystem cystic fibrosis syndrome. Such a variant is rarely associated with HP, but rather inheritance of a milder variant in an autosomal recessive manner, such as the *R75Q* mutation has been implicated with recurrent attacks of AP[29]. The presence of the *R75Q* mutation is associated with at least a 40 fold increased probability of developing pancreatitis when compared to the general population[30]. Bicarbonate secretion is essential for the release of pancreatic zymogens. A dysfunctional variant such as the *R75Q* mutation, leads to failure of acinar cell alkalization. As such, zymogens are not released, and once protease activation ensues, autodigestion of surrounding pancreatic tissue occurs leading to episodes of AP[22].

CTRC

The *CTRC* gene encodes for chymotrypsin C, a protease involved in trypsin regulation. Loss of function mutations in this gene, impair tyrpsin lysis and reduce the protective function against developing CP. Numerous CTRC gene variants, including *A73T, V235I, R253W*, and *K247_R254del* act by this mechanism. Such variants do not seem to be causative of HP when found in isolation, but are rather seen in concert with other genetic mutations (*SPINK1* or *CFTR*) or environmental factors[31,32].

Other genetic mutations

There are several less studied genetic variants that appear to contribute to HP. One example is the *CASR* gene, which encodes for a plasma membrane calcium sensing receptor involved in regulation of intracellular calcium levels and thereby, trypsin stability[33]. Another notable genetic variant involves the *CPA1* gene. This gene encodes for carboxypeptidase A1, which also functions as a pancreatic protease. Pathogenic defects of CPA1 are believed to confer a propensity towards developing HP through trypsin misfolding and aggregation, cumulating in increased endoplasmic reticulum stress[34]. The *CLND2* gene is located on the X chromosome and encodes claudin-2, which mediates sodium and water transport in the proximal pancreatic duct. From the results of a genome wide susceptibility study, mutations of the *CLND2* gene appear to mediate an atypical distribution of claudin-2, and consequently

increase the risk of alcohol induced pancreatitis, particularly in males[35,36].

DIAGNOSTIC EVALUATION

The investigation of HP typically begins with an extensive history to delineate previous episodes of acute pancreatitis, as well as an extended family history of clinical symptoms, aimed at identifying possible inheritance patterns. Diagnostic criteria for AP, ARP and CP in the pediatric population follow those outlined by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium. Once 2 of the following 3 are met AP is diagnosed; suggestive abdominal pain, serum amylase or lipase at least 3 times the upper limit of normal and/or characteristic imaging findings. If a patient has normalization of amylase and lipase levels and symptoms, or complete resolution of pain for at least 1 mo in between episodes of AP, this is termed ARP. CP is diagnosed when imaging findings of chronic pancreatic injury is noted along with at least one of; typical abdominal pain, endocrine or exocrine insufficiency[13,15].

Abdominal imaging studies may be required to assess for radiographic features of acute or chronic pancreatitis. In the pediatric setting such a radiologic workup generally begins with non-invasive cross-sectional imaging, mainly computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasonography (EUS) can be considered if the aforementioned studies fail to establish a diagnosis, etiology or adequately outline the extent of disease. Use of endoscopic retrograde cholangiopancreatography (ERCP) solely for diagnostic purposes in pediatrics is discouraged, mainly due to procedure related risks and similar diagnostic capabilities of MRCP in children[37].

When HP is suspected genetic testing to identify pathogenic pancreatitis related gene variants may be warranted. Criteria have been proposed to assist in determining which patients should undergo genetic evaluation (Table 2). Once the patient satisfies at least one of these, testing is recommended[38,39]. The decision to test children, whether symptomatic or asymptomatic can have considerable psychosocial impact not only for patients, but also their families. Consequently, it is recommended, that such testing and interpretation of results is best done with the assistance of an experienced genetics provider[21,40].

MANAGEMENT

HP can present at any juncture of the pancreatitis continuum. Generally children are brought to specialist medical attention and subsequently diagnosed after experiencing repeated episodes of AP. As with AP resulting from other etiologies, management generally involves early aggressive fluid hydration with appropriate monitoring, adequate pain control and early enteral nutrition. Invariably patients experience repeated pancreatic insults and complications necessitating further medical care, endoscopic and surgical procedures[13]. Given the early and aggressive nature of disease associated with pancreatitis related gene variants[5,9,14] we aim to examine the role that preventative measures and other therapeutic modalities can have in the management of HP among children.

Preventative measures

Substantial alcohol consumption is a well described predisposing factor for AP and subsequent progression to eventual CP among adult studies[41,42]. Similarly, data from the adult population has demonstrated that tobacco use is associated with pancreatic disease progression and development of pancreatic calcifications in a dose-dependent manner[42,43]. Expert consensus strongly recommend that pediatric providers caution their patients against the use of tobacco and ethanol due to the negative short and long-term effects on pancreatic health [19].

Inflammatory processes that underlie the pathophysiology of CP involves antioxidant depletion and oxidative stress. Supplementation of antioxidants has been proposed as a mechanism to prevent CP progression and the development of exocrine pancreatic insufficiency (EPI). To date, insufficient data exists to recommend antioxidant supplementation in children with CP for such indications[19,44].

Studies from the adult population have also implicated truncal obesity as a risk factor for severe AP, mainly due to the pathogenic role that peripancreatic or intrapan-

Table 2 Criteria Necessary for Genetic Testing of Pancreatitis related Gene Variants

Criteria necessary
Documented pancreatitis in a child without a definite cause
Acute recurrent pancreatitis without an identifiable etiology
Idiopathic chronic pancreatitis in patients younger than 25 years old
Family history of idiopathic chronic pancreatitis or acute recurrent pancreatitis
Relatives with known pancreatitis related gene mutations
Patients eligible for participation in approved study protocols

creatic fat plays in the development of pancreatic necrosis [45]. Interestingly, overweight or obese children have been found to be less likely to develop CP compared to children with a normal BMI. Obese children generally also experience their first episode of AP later than their non-obese counterparts. However, research examining the effects of BMI on CP outcomes in pediatrics remains limited and the current expert consensus recommendation is for pediatricians to recommend a balanced, healthy diet and lifestyle for their patients afflicted with CP [19].

Unfortunately, aside from these lifestyle modifications, there remain no novel therapeutic agents available for preventing repeated episodes of AP and the eventual progression to CP in patients with HP. In this regard, present treatment strategies are focused on managing the natural history of HP as opposed to preventing or delaying disease progression. Further research is warranted to better define 'optimal' preventative management in this population.

Medical management

Pediatric patients with progressive pancreatic disease are at risk for a number of sequelae which are best managed with a multidisciplinary approach. Given the significant postprandial abdominal pain and discomfort associated with ARP and CP, many patients are at risk of macro- and micronutrient deficiencies. With the help of a clinical dietician, growth and nutritional status should be carefully evaluated at every clinic visit (at least every 6-12 mo). Dietary education should also be provided to prevent obesity and malnutrition[19,44].

In a recent report of data analyzed among pediatric patients with ARP, it was noted that 18% and 7.7% developed EPI and diabetes mellitus respectively within 6 years of the initial AP attack[5]. EPI can be subclinical or present with steatorrhea, poor growth and nutritional deficiencies, particularly of fat-soluble vitamins. These patients should be provided with pancreatic enzyme replacement therapy, along with monitoring of fat-soluble vitamin levels at least every 12-18 mo. Screening for endocrine pancreatic insufficiency should be done at least yearly with a HbA1c and fasting glucose level. Should these values be outside the reference range, referral to a pediatric endocrinologist is indicated[19].

Pediatric CP is associated with a considerable disease burden, impairing quality of life and significantly disrupting childhood educational activities. These children can require frequent emergency room visits, hospitalizations and absences from school, mainly for management and control of chronic, severe pain[46]. In this regard, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition pancreas committee has set forth a number of recommendations to address pain management in pediatric patients with CP. These recommendations stress the importance of working alongside physical therapists, psychologists and pain specialists to institute a multi-modal approach to pain management. Before immediately using a non-opioid to opioid analgesic 'step-up' approach, neuromodulators, cognitive behavioral therapy and physical therapy should be considered as adjunctive measures for pain management[19].

Endoscopic therapy

As the sequalae of HP progress, endoscopic interventions may become necessary. As previously noted, EUS can play a diagnostic role if conventional cross-sectional imaging modalities fail to establish an etiology or disease extent. Among adults, therapeutic EUS is increasingly being considered as a first therapy for pancreatic walled off necrosis, and psuedocysts[47]. Though conservative measures should always be considered for pediatric pancreatic fluid collections, expert consensus from

the pancreas committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommend EUS intervention when endoscopic drainage is indicated.

Given associated procedural risks, ERCP use solely for diagnostic purposes is discouraged. However, therapeutic benefits have been derived among children with pancreatic duct stenting and removal of pancreatic calculi. Such patients have experienced improvement in symptoms and reduction in pancreatitis episodes[48,49].

Special considerations apply when undertaking these advanced endoscopic procedures in pediatrics. Theapeutic EUS, and in particular ERCP should only be undertaken after all the potential risks and possible need for multiple procedures are thoroughly discussed with caregivers. In addition, patients under 10-15 kg, may require specialized equipment not available in most centers. Primary physicians should consider referral to an appropriate tertiary center if therapeutic endoscopic procedures are required, as these procedures should ideally be done by endoscopists with ample experience in the pediatric setting.

Surgical therapy

Pancreatic necrotic collections and psuedocysts not amendable to endoscopic intervention may require surgical drainage[13]. Incapacitating CP that has failed medical and endoscopic therapy may benefit from conventional surgical approaches. A longitudinal pancreaticojejunostomy (Puestow procedure) can be utilized as a drainage procedure for an obstructed main pancreatic duct, whereas with involvement of the pancreatic head, a pancreaticoduodenectomy has proven some (Whipple procedure) benefit among adult patients[50,51]. Such procedures compromise islet cell yield and if undertaken, the remaining pancreatic tissue would still be subject to repeated insults. In this regard, its applicability to pediatric HP remains questionable [50,52,53]. Ultimately, pediatric patients with unremitting constant pain and grossly impaired quality of life proceed to total pancreatectomy with islet autotransplantation (TPIAT). Unfortunately this procedure commits the patient to lifelong pancreatic enzyme replacement therapy and a high likelihood of becoming insulin dependent, however, it has demonstrated improved quality of life and substantial pain relief. No formal criteria exist for which pediatric patients should proceed to TPIAT, so this decision should ideally involve a multidisciplinary team of pediatric pain specialists, surgeons, endocrinologists, gastroenterologists and dietitians[50,53,54].

CONCLUSION

HP has emerged as a significant cause of AP, ARP and CP in the pediatric setting. Given that it presents similarly to other causes of pancreatitis, a positive family history and/or isolation of a pathogenic pancreatitis related gene mutation are vital in its designation. Since the discovery of the first genetic mutation associated with the HP phenotype in 1996, dozens of other genetic defects have been identified, with varying inheritance patterns. More recent work among pediatric patients has associated particular variants with early onset and rapid progression, potentially making pediatric HP an aggressive disease with significant sequelae and substantial burden. Primary care physicians can play a vital role in identifying at risk patients with careful screening, and providing timely referral to tertiary centers adept at genetic testing and managing the continuum of pediatric pancreatitis. This model has the ability to limit health care cost and reduce the negative psychosocial effects on patients and families. Further work should focus on analyzing the impact that genetic and other risk factors have on the natural history and progression of pediatric pancreatitis, so that preventative interventions can be implemented to limit debilitating disease.

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ORIGINAL ARTICLE

Basic Study

Levels of vocational satisfaction, burnout and compassion fatigue of health professionals working in pediatric clinics

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Author contributions: Koyuncu O and Arslan S performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript and aided in interpreting the results and worked on the manuscript; all authors discussed the results and commented on the manuscript.

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Abstract

BACKGROUND

Burnout and compassion fatigue are affecting the quality of professional life.

AIM

To investigate the levels of vocational satisfaction, burnout, and compassion fatigue and factors that may be related to health professionals working in children's clinics.

METHODS

The study sample was in the west of Turkey. Data were collected using the questionnaire form and the quality of life scale for employees.

RESULTS

The findings obtained in this study showed that the level of vocational satisfaction of female health professionals and the burnout level of male health professionals were higher. The professional satisfaction of the doctors was lower than that of the nurses and midwives, and the mean score of burnout and fatigue was high.

CONCLUSION

Further studies are needed on this topic to help improve the factors that may affect the professional quality of life of health professionals.

Key Words: Health professionals; Professional life quality; Professional satisfaction; Burnout; Compassion fatigue

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

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Core tip: The right of health professionals to choose the clinic where they work; the fact that they do not constantly change the places where they work; a low number of night shifts; and adequate numbers of personnel have positive effects on the quality of professional life. It has be suggested to improve the working conditions and make them more favorable, and to satisfy the working individuals economically and emotionally. Health professionals and managers should work together to create a healthy work environment, increase professional satisfaction, and prevent burnout and fatigue.

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INTRODUCTION

Vocational satisfaction may occur when employees evaluate their jobs[1-6]. It is crucial for hospitals and employees to know the level of satisfaction of working individuals in their professional lives and what parameters may influence them. Vocational satisfaction is one of the most significant factors that increase the productivity of working individuals by corporate metrics[5-7].

Some vocational groups require close contact with people. Intense emotional responses are observed in these individuals, as employees in these professions are in close contact with people for long periods. Health professionals are especially at risk concerning burnout, as they are exposed to high levels of stress due to their institutional structure and working conditions. It should not be forgotten that a high risk of burnout will have negative effects on the professional quality of life[1,8,9].

Compassion has been one of the virtues of all religions and societies since the start of recorded history and has been defined as the feeling of being related to pain and suffering in other individuals[4,10-12]. It is an indispensable and essential quality for health professionals. Negative feedback sent to health insurance companies related to patient satisfaction has recently increased. Thus, the concepts of compassion and compassionate care have started to attract more significance[10-15]. The concept of compassion is considered to be an excellent component in health professionals worldwide[4-12]. Recently, studies on compassionate care scales have been conducted and compassionate healthcare models have been created worldwide. We define compassionate care as a care model that can be shown as the quality level of hospitals; can create satisfaction for patients and their relatives; has no financial costs; accelerates recovery; and has positive physiological effects on patients[10-15].

It may be emotionally exhausting and traumatizing for health professionals to care for sick or dying children. In addition, the fact that parents experience this process one-on-one and under intense stress may be redirected to healthcare professionals as a separate trauma. Exposure to these traumas for a long time may cause many physical, psychological and emotional problems in healthcare professionals working in pediatric clinics[4,10,12,14]. This study aimed to investigate the level of vocational satisfaction, burnout, compassion fatigue and other potentially related factors in pediatric clinics.

MATERIALS AND METHODS

This research was a descriptive study to investigate the levels of vocational satisfaction, burnout, and compassion fatigue and other factors that may be related to health professionals working in children's clinics.

Population and sample

The study population worked in the Child Health and Disease Clinics of the Hospitals of Sakarya Province between 1 November and 15 December 2018 and who had direct contact with patients. The study was conducted on 128 healthcare professionals

working in children's clinics on the same date and who agreed to participate in this research.

Data collection tools and questionnaire

The data in this study were collected using the questionnaire form created by the researchers and the quality of life scale for employees (QoLSE).

There were questions regarding the sociodemographic (*e.g.*, gender, age, marital status, and educational status) and study characteristics that were thought to be related to professional quality of life, vocational satisfaction, burnout and compassion fatigue in the personal information form created by the researchers. QoLSE was developed by Stamm[16] to detect the symptoms of vocational satisfaction, burnout, and compassion fatigue, and a Turkish validity and reliability study was performed by Yeşil *et al*[17]. The scale is a self-report assessment tool consisting of three subscales and 30 items. Items 1, 4, 15, 17 and 29 needed to be reversed and calculated during the evaluation of the scores obtained from the scale. The items in the scale were evaluated on a six-digit chart ranging from never (0) to very often (5).

Data assessment

While the relationships between the scores obtained from the scale were evaluated using correlation analysis, the relationships between the sociodemographic and professional characteristics of the healthcare professionals and the scores obtained from the scale were evaluated by Mann–Whitney U test in binary groups and Kruskal–Wallis tests in more than two groups.

Ethical aspects of this research

Ethical principles and rules were followed during this research. To conduct this study, ethical approval from the Sakarya University Faculty of Medicine Ethics Committee was obtained (dated 142.07.2018 and numbered 142). The purpose of this study was explained to the health professionals included in the sample, and their written and verbal consent was obtained.

RESULTS

The average age of health professionals participating in this study was 31.54 years. The majority of them were women (84.4%), married (61.7%), nurses (64.8%), undergraduate graduates (47.7%) and had no children (53.1%) (Table 1). The rate of the health professionals who worked 3–5 years in child health and disease was 35.2%. It was seen that 57% of health professionals were assigned by the administrative supervisor, 78.1% of them were on duty, and 88.3% of them worked at the public hospital. A total of 85.2% of the health professionals participating in this study worked overtime in the last 6 mo. A total of 89% of the participants were partially or completely dissatisfied with their working conditions and the reasons for dissatisfaction included insufficiency of the main social facilities (31.3%), communication problems in the work environment (24.2%), and inappropriateness of physical conditions (21.1%). A total of 51.6% of the participants encountered child death in the clinic where they worked in the last 6 mo. Within the scope of this research, the average weekly working hours of health professionals was 51.80 (Table 2). A total of 19.04% of the researchers stated that their encounters with child deaths had positive effects in terms of gaining experience in intervention, and 66.6% of them stated that they had negative effects emotionally (sadness, pain, grief) within the scope of this research. It was seen that 42.85% of them were affected between 1 and 3 d when the duration of exposure was examined (Table 3). The mean scores of female healthcare professionals in QoLSE Vocational Satisfaction Sub-dimension, and the mean scores of the male healthcare professionals in QoLSE Burnout Sub-dimension were significantly higher than those of the females healthcare professionals ($P < 0.05$).

When examined according to occupations, doctors' Vocational Satisfaction Sub-dimension mean score was significantly lower than that of nurses and midwives ($P < 0.05$), while the Burnout Sub-dimension and Compassion Fatigue Sub-dimension mean scores were significantly higher ($P < 0.05$). In the comparison made by looking at the educational status of the health professionals participating in this study, the Vocational Satisfaction Sub-dimension average score of postgraduate graduates was significantly lower, while the Burnout Sub-dimension average score was significantly higher ($P < 0.05$). The mean score of the Vocational Satisfaction Sub-dimension of the employees with night shift work compared to other groups was significantly lower (P

Table 1 Distribution of health professionals by sociodemographic characteristics (*n* = 128)

Features	*n*	%
Age, mean ± SD (min–max)	31.54 ± 9.123 (19.0–64.0)	
Gender		
Male	20	15.6
Female	108	84.4
Profession		
Doctor	26	20.3
Nurse	83	64.8
Midwife	19	14.8
Marital status		
The married	79	61.7
Single	49	38.3
Having children		
No	68	53.1
1	29	22.7
2	25	19.5
≥ 3	6	4.7

< 0.05). In the comparison made according to the satisfaction of the health professionals with their working conditions, the Vocational Satisfaction Sub-dimension mean score of the dissatisfied people was significantly lower and the Burnout Sub-dimension mean score was significantly higher ($P < 0.05$) (Table 4).

DISCUSSION

It is stated that the low level of professional satisfaction of health professionals leads to a weakened relationship with their patients, negative attitudes towards their profession, or failure to fulfill their job-related responsibilities. However, to our knowledge, it has been reported that patients are more satisfied with the care and treatment of health professionals with high professional satisfaction[18-21]. Health professionals suffer from burnout syndrome and fatigue, which is the most important determinant of work quality of life[1,2,3,9,22,23]. Burnout and compassion fatigue in healthcare professionals may result in decreased patient satisfaction and unhealthy results[1,2,3,9,22,23].

Female healthcare professionals constitute 84.4% of the group that participated in our study. The reason for this is that there are more female healthcare professionals in the nurse and midwife vocational groups in Turkey[6,7,24]. In this study, the rate of participants whose educational status was undergraduate and graduate was 72.7%. The postgraduate education level was 25%. This ratio is between 3% and 21% in studies conducted in Turkey[5,6,7,18,24]. The reason why it is higher compared to other studies may be the increase in the number of nurses and midwives with undergraduate degrees and the participation of doctors in the study group.

A total of 57% of the health professionals participating in our study had been appointed by the administrative supervisor to the clinic where they worked and 78.1% of them worked night shifts. This may reduce the quality of professional life and cause burnout and compassion fatigue in health professionals. A total of 70.3% of the health professionals participating in this study worked in departments where the number of staff was not sufficient, and they had been on duty for 3 wk per month for the last 6 mo. They had to come to work several times and 85.2% worked although they were ill.

It has been determined that health professionals are not partially or completely satisfied with their working conditions. They expressed the reasons for dissatisfaction as insufficient social facilities (31.3%), lack of communication in the environment (24.2%) and inappropriateness of physical conditions (21.1%). It was also found that

Table 2 Distribution of healthcare professionals by work features (*n* = 128)

Features	*n*	%
Working time in child health and disease		
< 1 yr	32	25.0
1–2 yr	10	7.8
3–5 yr	45	35.2
≥ 6 yr	41	32.0
How did she/he settle in the clinic where she worked?		
By myself	37	28.9
My profession	18	14.1
By administration	73	57.0
How it works		
Continuous day	22	17.2
Seizure	100	78.1
Other[a]	6	4.7
Hospital worked		
Public hospital	113	88.3
Private hospital	15	11.7
Overtime work in the last 6 mo		
Yes	109	85.2
No	19	14.8
Satisfaction with working conditions		
Yes	14	10.9
No	52	40.6
Partially	62	48.4
Reasons for dissatisfaction		
Communication problems in the working environment	31	24.2
Inadequate social facilities	40	31.3
Incompatibility of physical conditions in the environment	27	21.1
Economic shortcomings	15	11.7
Failure to rise on duty	1	0.8
Other	14	10.9
Confrontation with child death in the clinic working in the last 6 mo		
Yes	66	51.6
No	62	48.4
Weekly average hours of operation mean ± SD (min–max)	51.80 ± 11.918 (32.0–120.0)	

[a]In some clinics, they work with an 8-h shift system or 08:00-00:00 and 16:00-00:00 h.

their professions did not satisfy or only partially satisfied them economically. In another study, inconveniences in the working system (42.8%), economic inadequacy (32.2%) and lack of social opportunities (25.4%) were the main reasons for dissatisfaction with occupational life[24]. The average weekly working hours of the health professionals participating in the study were 51.8. According to Eurostat data, the average weekly working hours of full-time employees in the EU-28 is 37.1[25]. This period is specified as 45 h in labor law, but is 51.8 h, which is above international

Table 3 Effects of health professionals participating in this research when they come against child deaths in the last six months (*n* = 42)

Features	*n*	%
Positive effects		
Gaining experience in intervention	8	19.04
Getting used to death	2	4.76
Negative effects		
Emotional (sadness, pain, grief)	28	66.6
Decreasing from professional motivation	4	9.52
Affected times		
< 1 d	10	23.80
1–3 d	18	42.85
3–10 d	5	11.90
> 10 d	9	21.42

standards, in many developing countries. It was found that 22% of working individuals had an average weekly working time of > 48 h in all countries in a study conducted by the International Labor Organization[25].

A total of 19.04% of the health professionals participating in this study stated that their encounters with child deaths had positive effects on gaining experience in intervention, and 66.6% stated that they had negative emotional effects (sadness, pain, grief). Given the duration of the effects, it was seen that 42.85% were affected between 1 and 3 d. This indicates that because doctors, nurses and midwives are working long hours, the negative effects of child mortality during working hours should be considered. We note that the negative effects of the event occurring in one shift may continue into the next shift. These negative effects affect the professional quality of life, burnout and compassion fatigue.

In this study, the average QoLSE Vocational Satisfaction Sub-dimension and QoLSE Burnout Sub-dimension scores of female healthcare professionals were significantly higher ($P < 0.05$). Similarly, Cañadas-De la Fuente *et al*[26] found that burnout syndrome was higher in male nurses. In Kılıç's[7] study, the mean scores of the female nurses' Traumatic Stress Symptoms Scale and QoLSE Burnout and Coordination Fatigue Sub-dimensions were significantly higher ($P < 0.05$) than those of male nurses.

When examined according to occupations, doctors' Vocational Satisfaction Sub-dimension mean score was significantly lower than that of nurses and midwives ($P < 0.05$), while the Burnout Sub-dimension and Compassion Fatigue Sub-dimension mean scores were significantly higher ($P < 0.05$). To our knowledge, there is not any research into this subject.

In the comparison made by looking at the educational status of the health professionals participating in this study, the Vocational Satisfaction Sub-dimension average score of postgraduate graduates was significantly lower, while the Burnout Sub-dimension average score was significantly higher ($P < 0.05$). In the study of Kılıç[7], the mean score of QoLSE Vocational Satisfaction sub-dimension of nurses trained at high school level was statistically higher than that of nurses at other education levels. Nurses who received their education at a master's level mean score of QoLSE Compassion Fatigue Sub-dimension was significantly higher than that of nurses at other education levels.

The mean score of the Vocational Satisfaction Sub-dimension of the employees who worked night shifts was significantly lower than in the other groups ($P < 0.05$). These conditions may decrease the quality of the professional life of the health professionals working night shifts and cause burnout and fatigue to be more frequent [7,18,27].

In this study, a significant negative correlation was found between the weekly average working hours of the health professionals and QoLSE Vocational Satisfaction Sub-dimension. A significant positive correlation was found between the weekly average working hours and the Burnout Sub-dimension. A weak positive correlation was found between the weekly average working hours and Compassion Fatigue Sub-dimension ($P < 0.05$). In this study, the professional satisfaction of nurses working > 40 h/wk was lower than that of nurses working ≤ 40 h/wk[5,17]. In a study by Marcum

Table 4 Distribution of the scores of health professionals scored from quality of life scale for employees sub-dimensions (*n* = 128)

Features of health professionals	QoLSE vocational satisfaction sub-dimension		QoLSE burnout sub-dimension		QoLSE mercy fatigue sub-dimension	
	mean ± SD	Med (min–max)	mean ± SD	Med (min–max)	mean ± SD	Med (min-max)
Gender						
Female	34.86 ± 9.0	35.0 (9.0-50.0)	17.58 ± 6.23	17.50 (2.0-36.0)	15.50 ± 6.86	14.0 (0.0-40.0)
Male	26.45 ± 10.91	25.50 (8.0-49.0)	23.10 ± 6.70	24.50 (9.0-36.0)	15.45 ± 6.93	15.0 (3.0-31.0)
P value[a]	**0.001**		**0.001**		0.911	
Profession						
Doctor	28.76 ± 9.30	29.0 (9.0-49.0)	23.50 ± 5.65	24.50 (9.0-36.0)	18.65 ± 7.23	17.0 (8.0-40.0)
Nurse	34.53 ± 9.53	36.0 (8.0-50.0)	17.20 ± 6.25	17.0 (2.0-36.0)	14.39 ± 6.63	13.0 (0.0-37.0)
Midwife	35.78 ± 9.86	36.0 (8.0-50.0)	16.94 ± 6.02	17.0 (7.0-26.0)	15.94 ± 6.15	16.0 (5.0-27.0)
P value[b]	**0.014**		**0.000**		**0.020**	
Education status						
Medical career high school	38.33 ± 9.55	40.0 (17.0-50.0)	17.47 ± 6.33	17.0 (6.0-26.0)	13.80 ± 7.59	15.0 (0.0-25.0)
Two-year degree	33.65 ± 9.69	35.50 (9.0-48.0)	18.90 ± 7.14	17.50 (10.0-36.0)	16.30 ± 8.12	13.50 (7.0-37.0)
Bachelor degree	34.15 ± 9.84	35.0 (8.0-50.0)	16.75 ± 6.07	17.0 (2.0-33.0)	14.44 ± 5.92	13.0 (3.0-27.0)
Master degree	30.09 ± 9.01	30.50 (9.0-49.0)	21.84 ± 6.27	22.0 (9.0-36.0)	17.78 ± 6.97	17.0 (8.0-40.0)
P value[b]	**0.039**		**0.007**		0.167	
Hospital worked						
Public hospital	32.38 ± 9.61	33.0 (8.0-50.0)	18.97 ± 6.33	19.0 (6.0-36.0)	15.46 ± 6.84	14.0 (0.0-40.0)
Private hospital	42.33 ± 5.80	44.0 (33.0-50.0)	14.46 ± 7.40	13.0 (2.0-27.0)	15.73 ± 7.11	17.0 (5.0-25.0)
P value[a]	**0.000**		**0.029**		0.716	
How it works						
Continuous day	41.59 ± 8.06	44.0 (18.0-50.0)	15.81 ± 5.79	15.0 (6.0-27.0)	14.04 ± 6.5	12.50 (5.0-27.0)
Night shift	31.75 ± 9.29	32.50 (8.0-50.0)	18.94 ± 6.30	19.0 (6.0-36.0)	15.67 ± 6.31	15.0 (0.0-37.0)
Other[a]	34.0 ± 9.71	36.0 (18.0-44.0)	19.83 ± 11.78	22.0 (2.0-33.0)	17.83 ± 14.37	12.0 (3.0-40.0)
P value[b]	**0.000**		0.109		0.514	
Satisfaction with working conditions						
Yes	38.14 ± 10.91	44.0 (19.0-50.0)	15.57 ± 6.0	17.50 (7.0-26.0)	15.0 ± 5.98	13.0 (7.0-25.0)
No	29.80 ± 11.01	29.50 (8.0-50.0)	21.03 ± 7.06	21.0 (6.0-36.0)	14.92 ± 7.99	15.0 (0.0-40.0)
Partially	35.64 ± 7.13	36.0 (14.0-49.0)	16.91 ± 5.58	17.0 (2.0-28.0)	16.08 ± 5.99	15.0 (6.0-28.0)
P value[b]	**0.020**		**0.009**		0.789	

[a]Mann–Whitney *U* test.
[b]Kruskal–Wallis test. QoLSE: Quality of Life Scale for Employees.

et al[28] of factors related to compassion fatigue and burnout in American nurses included age, years worked as a nurse, working environment, coping mechanisms and specialties.

In the comparison made according to the satisfaction of the health professionals with their working conditions, the Occupational Satisfaction Sub-dimension mean score of the dissatisfied professionals was significantly lower, and the Burnout Sub-dimension mean score was significantly higher ($P < 0.05$). It is crucial not to ignore employee satisfaction to ensure patient satisfaction. To achieve this satisfaction, managers need to take the necessary steps to improve working conditions.

CONCLUSION

The right of health professionals to choose the clinic where they work; the fact that they do not constantly change the places where they work; a low number of night shifts; and adequate numbers of personnel have positive effects on the quality of professional life. It may be appropriate to reduce overtime hours, and if not, overtime wages should be sufficient and regular to satisfy employees. It can be suggested to improve the working conditions and make them more favorable, and to satisfy employees economically and emotionally. The average weekly working hours can be 45, as stated in labor law. Health professionals who are met with child deaths should be given the necessary time to overcome the negative effects that they experience. Factors that help reduce compassion fatigue and burnout, as well as factors that allow staff and managers to be appreciated, will increase the quality of professional life. Health professionals and managers should work together to create a healthy work environment, increase professional satisfaction and prevent burnout and fatigue.

ARTICLE HIGHLIGHTS

Research background

Burnout and compassion fatigue are affecting the quality of professional life.

Research motivation

Doctors and nurses working in pediatric clinics caring for sick or dying children for a long time can develop compassion fatigue. This may affect their professional quality of life.

Research objectives

This study has been done to determine the levels of professional satisfaction, burnout and compassion fatigue of nurses and doctors working in pediatric clinics and related factors.

Research methods

This was a descriptive study.

Research results

The mean scores of female healthcare professionals in Quality of Life Scale for Employees (QoLSE) Vocational Satisfaction Sub-Dimension and the mean scores of the male healthcare professionals in QoLSE Burnout Sub-Dimension were significantly higher than those of the females ($P < 0.05$). When examined according to professions, the QoLSE Occupational Satisfaction Sub-Dimension mean scores of doctors were significantly lower than those of the nurses and midwives ($P < 0.05$), while the QoLSE Burnout Sub-Dimension and Empathy Fatigue Sub-Dimension mean scores of the doctors were higher ($P < 0.05$). In the comparison made according to the satisfaction of health professionals with their working conditions, the QoLSE Occupational Satisfaction Sub-Dimension mean score of the dissatisfied professionals was significantly lower and the QoLSE Burnout Sub-Dimension mean score was significantly higher.

Research conclusions

The working conditions of health professionals should be improved physically and socially, and time should be given to allow them to get rid of the negative emotions they have experienced after child deaths.

Research perspectives

In this context, it is essential to collect information that will improve the risk profile associated with burnout syndrome among health professionals working in the field of child health and diseases. Future research should focus on identifying the protection factors or positive aspects that enable healthcare professionals to successfully cope with burnout.

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ORIGINAL ARTICLE

Basic Study

Impact of stimulant medication on behaviour and executive functions in children with attention-deficit/hyperactivity disorder

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Abstract

BACKGROUND

Children with attention-deficit/hyperactivity disorder (ADHD) often exhibit behaviour challenges and deficits in executive functions (EF). Psychostimulant medications [*e.g.*, methylphenidate (MPH)] are commonly prescribed for children with ADHD and are considered effective in 70% of the cases. Furthermore, only a handful of studies have investigated the long-term impact of MPH medication on EF and behaviour.

AIM

To evaluate behaviour and EF challenges in children with ADHD who were involved in an MPH treatment trial across three-time points.

METHODS

Thirty-seven children with ADHD completed a stimulant medication trial to study the short- and long-term impact of medication. Children with ADHD completed three neuropsychological assessments [Continuous Performance Test (CPT)-II, Digit Span Backwards and Spatial Span Backwards]. Parents of children with ADHD completed behaviour rating scales [Behaviour Rating Inventory of Executive Functioning (BRIEF) and Behaviour Assessment System for Children-Second Edition (BASC-2)]. Participants were evaluated at: (1) Baseline (no medication); and (2) Best-dose (BD; following four-week MPH treatment). Additionally, 18 participants returned for a long-term naturalistic follow up (FU; up to two years following BD).

RESULTS

Repeated measure analyses of variance found significant effects of time on two subscales of BRIEF and four subscales of BASC-2. Neuropsychological assess-

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ments showed some improvement, but not on all tasks following the medication trial. These improvements did not sustain at FU, with increases in EF and behaviour challenges, and a decline in performance on the CPT-II task being observed.

CONCLUSION
Parents of children with ADHD reported improvements in EF and behaviours during the MPH trial but were not sustained at FU. Combining screening tools and neuropsychological assessments may be useful for monitoring medication responses.

Key Words: Attention-deficit/hyperactive disorder; Behaviour; Executive functions; Stimulant medications

Core Tip: Parents of children with attention-deficit/hyperactivity disorder reported improvements in executive function and behaviours during the methylphenidate trial, but these improvements did not sustain at the long-term follow up condition. Combining screening tools and neuropsychological assessments may be useful for monitoring psychostimulant medication responses as children enter their adolescent years.

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INTRODUCTION

Deficits in executive function (EF) skills and behaviour challenges are commonly reported in children with attention-deficit/hyperactivity disorder (ADHD)[1,2]. ADHD, a neurodevelopmental disorder, is highly prevalent (5%-7%) in school-aged children[3,4]. Symptoms of ADHD typically include developmentally inappropriate levels of inattention, or impulsivity, and hyperactivity[5].

Children with ADHD often exhibit challenges associated with behaviour as well as EF[2]. In the literature, EF is an umbrella term that refers to a complex range of cognitive abilities, including working memory, goal-directed planning, impulse control, cognitive flexibility, and self-monitoring[6]. There is presently no consensus in the literature regarding the exact definition of EF, with upwards of 18 different available definitions included across studies[7]. Nevertheless, it is accepted that EF represents a family of top-down cognitive processes that are needed to make judgments and decisions and initiate purposeful behaviour[8]. As well, EF challenges are known to impact children with ADHD academically and behaviourally, as well as with their interpersonal relationships[2,9,10]. For instance, EF challenges can impact or affect performance at school, including task initiation, organizing thoughts to complete written assignments, using problem-solving skills to complete math calculations, switching from one task to another, and keeping track of task completion[11]. At home, EF challenges can manifest as trouble initiating or completing house chores, inflexibility to changing routines, or difficulty regulating and modulating emotions [12]. Socially, EF challenges may result in continual interruption of others or difficulty engaging in appropriate reciprocal conversation[9].

The measurement of EF in children with ADHD is generally done through either performance-based neuropsychological measures or behaviour rating scales. Both the performance-based measures and rating scales are considered to be reliable measures of EF[1]. However, the relationship between performance-based and behaviour ratings of EF is less clear, especially when evaluating whether they measure the same underlying construct. Furthermore, children with ADHD exhibit variable EF performance on neuropsychological tests when measured in a lab setting[13]. The current

study included a combination of parent behaviour rating scales and neuropsychological measures to gain a more thorough understanding of EF challenges in children with ADHD.

Currently, psychostimulant medications [*e.g.*, methylphenidate (MPH)], along with behavioural interventions, are the most common treatment options for children with ADHD[14-17]. Stimulant medications are considered effective in about 70% of the cases[1,15], and the efficacy and safety of psychostimulants for the treatment of ADHD have been well documented[18]. Specifically, numerous research studies have consistently demonstrated that stimulants such as MPH improve executive and nonexecutive memory, reaction time, reaction time variability, and response inhibition in individuals with ADHD[18-20]. Short-term efficacy for pharmacological treatments is supported by all major evidence-based guidelines, including the Canadian ADHD Resource Alliance guidelines[15,16]. Conversely, findings related to the long-term impact of MPH, including the multimodal treatment of ADHD study (MTA), have been inconsistent with some studies finding sustained behavioural improvement following medication trials[21], while other studies failed to demonstrate long-term behavioural improvements[22,23].

Given that psychostimulant medications are commonly prescribed for children with ADHD[18], it is important to understand the developmental impact of these medications as children enter their adolescent years. Few studies to date have conducted a naturalistic follow up (FU) of children with ADHD who were part of a treatment trial [24,25]. Naturalistic FU studies are different from randomized controlled FU studies, as the participants are no longer part of the active treatment trial and follow what would be considered typical outpatient treatment through their healthcare professionals. As of spring 2021, no study to our knowledge has included parental behaviour rating scales and performance on neuropsychological assessments to evaluate the long-term naturalistic impact of stimulant medications use on behaviour, learning, and EF in children with ADHD.

The purpose of the present study was to investigate the short- and long-term (naturalistic FU) impact of stimulant medications in children with ADHD using both behaviour rating scales completed by parents and neuropsychological performance-based measures. The study aims to answer the following research questions:

(1) What are the changes in behaviour and EF as observed by parents of children with ADHD at baseline (BL; no medication) compared to best-dose (BD; MPH dose that was recommended by their primary care physician) condition (following a four-week trial of MPH treatment)?

(2) What are the changes in EF performance in children with ADHD at BL (no medication) compared to BD condition (following a four-week trial of MPH treatment)?

(3) What are the changes in EF and behaviour at the long-term FU (6 mo to 2 years following long-acting MPH treatment trial) as observed by parents?

(4) What are the changes in EF performance at the long-term FU (6 mo to 2 years following long-acting MPH treatment trial)?

MATERIALS AND METHODS

Participants

Children with ADHD: A total of 37 eligible participants with ADHD were included for analyses in the current study. Participants were excluded from the analyses if they did not return for the best-dose condition, were on medications at BL or did not meet the inclusion criteria. For the long-term naturalistic FU portion of the study, a total of 21 families elected to take part in the study.

All participants had to have: (1) A confirmed diagnosis of ADHD through a standard-of-care health professional prior to study participation; (2) The healthcare professional overseeing their progress and a diagnosis of ADHD; (3) Parent ratings of child's current ADHD behaviour ratings using the Behaviour Assessment System for Children-Second Edition (BASC-2)[26], to indicate the child currently meets DSM-5 ADHD criteria[5]; and (4) A cognitive screener reporting no intellectual disability (scaled score > 4) on both the vocabulary multiple choice and the matrix reasoning subtests from the Wechsler Intelligence Scale for Children-Fourth Edition Integrated (WISC-IV Integrated)[27]. The children were not involved in any behavioural intervention during the medication trial. However, they were allowed to take part in behavioural intervention during the naturalistic FU condition.

Measures

Neuropsychological measures: Children with ADHD completed neuropsychological measures related to working memory and inhibition. Parents of children with ADHD completed two additional standardized behaviour rating scales (questionnaires).

Conners Continuous Performance Test: The Conners Continuous Performance Test (CPT-II) is a computerized task that requires sustained attention to visually presented stimuli[28]. The CPT-II is a 15-min task, with a total of 360 trials where respondents are presented with letters appearing on a computer screen at varying rates (*i.e.*, 1-, 2-, or 4-second inter-stimulus intervals). Participants are required to press the spacebar whenever a "target" letter appears on the screen and refrain from responding (*i.e.*, pressing the spacebar) whenever the non-target stimulus (*i.e.*, letter "X") appears. The CPT-II provides an array of scores following task completion. For the purposes of this study, only the Omission and the Commission errors score was evaluated. Omission errors indicate the number of times the child missed the target item when it was presented. Commission errors represent errors where the child incorrectly pressed the spacebar in response to the non-target stimulus. The reliability coefficient for omission and commission errors were 0.85 and 0.83 respectively. Test-retest reliability for omission and commission errors were 0.48 and 0.65, suggestive of adequate consistency across administrations[29].

WISC-IV Integrated Digit Span Backwards: Digit span tasks are used to evaluate verbal working memory. The Digit Span Backwards task requires children to listen to orally presented numbers with spans increasing in length and repeating in reverse order[27]. The number of digits recalled correctly in the reverse order is used for scoring purposes. Participants were awarded one point if they correctly repeated the sequence in backward order and zero points for an incorrect or incomplete answer or no response. The overall Digit Span Backward reliability coefficient is 0.81 for the normative sample, suggestive of good internal consistency. Test-retest reliability for the Digit Span Backward subtest was 0.74, indicating adequate stability across time [30].

WISC-IV Integrated Spatial Span Backwards: Spatial Span tasks are used to assess visuospatial working memory and require participants to encode and immediately recall a series of presented stimuli mentally. The WISC-IV Integrated Spatial Span board consists of ten cubes attached in a random order to a whiteboard. During the Spatial Span task, examinees observed the examiner tapping a prearranged sequence of blocks on the board at a rate of one block per second. Participants were required to tap the blocks in the reverse order of that demonstrated by the examiner. Participants were awarded one point if they tapped the blocks in the correct backward order or zero points if they provided an incorrect order or no response. The overall Spatial Span Backward task reliability coefficient for the normative sample was found to be 0.81, suggestive of good internal consistency[31].

Parent questionnaires: Parents in the current study completed two behaviour rating scales.

The Behaviour Assessment System for Children (BASC-2) is a widely utilized, norm-referenced rating scale designed to assess emotional, behavioural, and adaptive functioning among children and adolescents[27]. The parent rating scale (PRS) provides T-scores (M = 50; SD = 10) for four broad composite scales [externalizing problems (EP), internalizing problems (IP), behavioural symptoms index (BSI), and adaptive skills (AS)]. For the EP, IP, and BSI composites and associated clinical scales, T-scores of 70 and above are considered clinically significant and suggest a high level of maladjustment. In contrast, lower scores within the adaptive domain denote more problematic behaviours; T-scores of 30 and below are considered clinically significant. Reliability coefficients of the BASC-2 rating scale range between 0.90 and 0.95 for the composite scores, suggestive of strong internal consistency. The BASC-2 PRS composite scales also have high test-retest reliability (0.78 to 0.92)[25].

The Behaviour Rating Inventory of Executive Functioning (BRIEF) was used to assess parental perceptions of EF skills[28,32]. The BRIEF is a questionnaire for parents of school-aged children (ages 5 to 18) that is used to determine a range of EF skills at home and in the community. The BRIEF parent form consists of 86 items within eight theoretically and empirically derived clinical scales and three composite scores that measure different aspects of EF. The BRIEF parent rating scale has high internal consistency (0.80 to 0.98) and test-retest reliability (0.82)[26].

Procedure

The current study was part of a larger-scale project investigating the effect of medications on EF, academic, behavioural, and neuroimaging outcomes in children with ADHD. The larger study used a quasi-experimental, cross-sectional design with simple random sampling. ADHD participants were recruited through referrals from healthcare professionals in a Western Canadian city. The study research assistant conducted the ADHD screening measures to evaluate eligibility for the study before seeking informed consent for participating in the study. Parents completed the rating scales to ensure that their child met the eligibility criteria. If data from the parent behaviour rating scales did not indicate clinical range for attention and hyperactivity problems of at least 1.5 SDs above the norm for the child's age, the child and parent were thanked for their participation, and no further testing took place. Following receiving consent, the study research assistants completed additional screener assessment that included the two subtests from the WISC-IV Integrated intellectual screener. If the child was found to be intellectually deficient on the two WISC-Integrated screener measures (*e.g.*, a scaled score of four or less, M = 10, SD = 3), the physician was notified, and the trial was terminated.

Participants completed assessments at three-time points, BL, post medication trial (BD) and at long-term naturalistic FU. All eligible participants were then scheduled for additional assessments.

BL: On the second testing session, eligible participants were scheduled to complete additional neuropsychological measures, and parents completed further questionnaires. The appointment lasted approximately 90 min. Participants and parents were thanked and compensated for their participation.

Post-treatment trial: Following taking medications for four weeks, participants returned to complete the same neuropsychological assessments completed at BL. Parents also completed rating scales.

FU: Parents of participants with ADHD, who were part of the initial medication trial, were invited to participate in an additional study component that included the completion of parent behaviour rating scales and neuropsychological testing. Families that participated in all components of the current study were evaluated at three separate time points: (1) BL: no medication; (2) BD: following a four-week trial of MPH treatment; and (3) Long-term naturalistic FU: 6 mo to 2 years following BD, see Figure 1.

Data analyses

The Statistical Package for the Social Sciences version 26 was used to conduct all analyses. A preliminary inspection of the data was performed for accuracy and examination of missing values and outliers before running any analyses. Additionally, the assumptions of normality and Mauchly's Test of Sphericity were evaluated in order to conduct parametric data analyses[33].

Descriptive statistics such as mean and standard deviations were calculated. Repeated measures analyses of variance (RmANOVA) were conducted to evaluate changes in EF and behavioural challenges. Specifically, changes were measured between the BL and BD time points. Additionally, changes were measured between the BD and FU time points for participants participating in the long-term FU. Biological sex differences between boys and girls were also conducted across the different EF, behaviour, and adaptive skills ratings.

RESULTS

Participant demographic information

Table 1 presents the sample characteristics regarding their cognitive and behavioural screening measures.

Difference in parent behaviour and EF ratings between BL and BD condition

Table 2 summarizes the BASC-2 behavioural rating results. Analyses revealed a significant difference between BL and BD conditions, EP, F (1, 29) = 44.18, $P \leq 0.001$, partial eta square = 0.60, IP, F (1, 29) = 19.98, $P \leq 0.001$, partial eta square = 0.41, BSI, F (1, 29) = 83.04, $P \leq 0.001$, partial eta square = 0.74, and AS scores, F (1, 29) range = 44.98 , $P \leq 0.001$, partial eta square = 0.61. Specifically, significant improvements across all

Table 1 Participant demographic information at baseline (T1)

Variable	mean ± SD (*n* = 37)
Age	10.11 ± 1.27
Cognitive Tasks	
WISC-IV-I VC SS	98.11 ± 11.69
WISC-IV-I MR SS	97.70 ± 12.89
BASC-2 Attention Problem T-Score	69.59 ± 6.31
BASC-2 Hyperactivity T-Score	71.73 ± 12.77
WJ-III Reading	90.49 ± 13.19
WJ-III Math	80.95 ± 13.86
WJ-III Written Language	87.03 ± 14.75
Biological Sex	*n* (%)
Female	16 (43.2)
Male	21 (56.8)

WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition; VC SS: Vocabulary Subtest Standard Score; MR SS: Matrix Reasoning Standard Score; BASC-2: Behaviour Assessment System for Children-Second Edition; WJ-III: Woodcock Johnson Test of Achievement, Third Edition.

Table 2 Behaviour Assessment System for Children-Second Edition parent symptom reports measured over the three-time points

Variable	BL T-score mean ± SD (*n* = 37)	BD T-score mean ± SD (*n* = 30)	BD-BL (*P* value)	FU T-score mean ± SD (*n* = 18)	FU-BD (*P* value)
Externalizing problems	68.95 ± 13.20	54.83 ± 8.42	$P < 0.001$	63.72 ± 10.26	$P = 0.003$
Internalizing problems	62.86 ± 15.34	52.53 ± 13.0	$P < 0.001$	60.89 ± 13.07	$P = 0.063$
Behaviour symptoms index	72.32 ± 10.20	57.13 ± 7.73	$P < 0.001$	68.06 ± 9.47	$P < 0.001$
Adaptive behaviours	33.95 ± 8.92	40.57 ± 9.22	$P < 0.001$	38.72 ± 8.79	$P = 0.124$

Mean scores on the Behaviour Assessment System for Children-Second Edition subscales; externalizing problems, internalizing problems, behavioural symptom index and adaptive skills, as rated by parents at three-time points: (1) Baseline; (2) Best-dose; and (3) Follow-up. BL: Baseline; BD: Best-dose; FU: Follow-up.

behavioural indices (EP, IP, BSI) were observed in addition to a significant increase in adaptive skills between the BL and BD time points.

Table 3 summarizes the BRIEF rating scale results. Similar to the BASC-2 scores, results from the BRIEF parent rating scale showed significant improvement from BL to BD condition, BRIEF behavioural regulation index [BRI; F (1, 30) = 90.48, $P \leq 0.001$, partial eta square = 0.75) and metacognition index [MI; F (1, 30) = 94.38, $P \leq 0.001$, partial eta square = 0.76).

Difference in EF performance between BL and BD condition

Results indicated significant differences in performance between BL and BD conditions on the CPT omission errors, F (1, 32) = 14.38, $P \leq 0.001$, partial eta square = 0.31. No significant difference was observed in performance on the CPT commission errors, F (1, 32) = 2.93, $P \geq 0.05$, partial eta square = 0.08, Digit Span Backwards, F (1, 30) = 1.89, $P \geq 0.05$, partial eta square = 0.06 and Spatial Span Backwards, F (1, 30) = 0.97, $P \geq 0.05$, partial eta square = 0.03 tasks, see Table 4.

Difference in parent behaviour and EF ratings between BD condition and long-term FU

Analyses revealed a significant effect of time on the EP, F (1, 16) = 12.73, $P \leq 0.01$, partial eta square = 0.44, and BSI, F (1, 16) = 19.38, $P \leq 0.001$, partial eta square = 0.55. Specifically, significant decrease in behaviour was observed by parents at FU time

Table 3 Behaviour Rating Inventory of Executive Functioning-Second Edition parent symptom reports measured over the three-time points

Variable	BL T-score mean ± SD (*n* = 37)	BD T-score mean ± SD (*n* = 31)	BD-BL (*P* value)	FU T-score mean ± SD (*n* = 18)	FU-BD (*P* value)
Behavioural regulation index	72.43 ± 11.94	53.42 ± 8.78	$P < 0.001$	68.28 ± 13.23	$P = 0.001$
Metacognition index	74.76 ± 7.72	57.94 ± 8.48	$P < 0.001$	72.06 ± 9.51	$P < 0.001$

Mean scores on the BRIEF subscales; Behavioural Regulation Index and Metacognition Index as rated by parents at three-time points: (1) Baseline; (2) Best-dose; and (3) Follow-up. BL: Baseline; BD: Best-dose; FU: Follow-up.

Table 4 Neuropsychological Test Performance Scores measured over the three-time points

Variable	BL T-score mean ± SD (*n* = 37)	BD T-score mean ± SD (*n* = 33)	BD-BL (*P* value)	FU T-score mean ± SD (*n* = 18)	FU-BD (*P* value)
CPT omission errors (T-Score)	61.11 ± 15.76	52.88 ± 8.09	$P = 0.001$	49.34 ± 5.90	$P = 0.10$
CPT commission errors (T-Score)	53.59 ± 6.74	49.70 ± 11.75	$P = 0.097$	49.69 ± 10.17	$P = 0.04$
Digit Span Backwards	95.54 ± 11.04	99.19 ± 11.48	$P = 0.059$	96.94 ± 15.54	$P = 0.055$
Spatial Span Backwards	105.68 ± 12.42	108.23 ± 13.0	$P = 0.332$	108.06 ± 12.96	$P = 0.782$

Mean scores on the Continuous performance test commission errors (T-scores) and Wechsler Intelligence Scale for Children, Fourth Edition (standard score) at three-time points: (1) Baseline; (2) Best-dose; and (3) Follow-up. CPT: Continuous performance test; BL: Baseline; BD: Best-dose; FU: Follow-up.

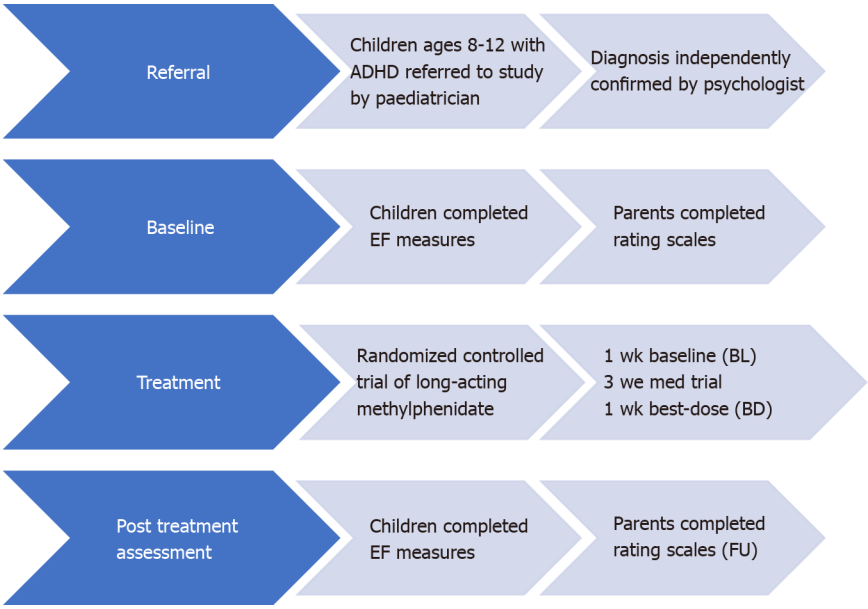

Figure 1 Study flowchart demonstrating the different assessments completed by parents and children with attention-deficit/hyperactivity disorder at the three-time points: Baseline, best-dose and follow-up as part of the study. ADHD: Attention-deficit/hyperactivity disorder; EF: Executive function; BL: Baseline; BD: Best-dose; FU: Follow-up.

point (6 mo to 2 years after the MPH trial).

No significant difference was observed between BL and FU for the IP, F (1, 16) = 4.00, $P \geq 0.05$, partial eta square = 0.20, and AS, F (1, 16) = 2.63, $P \geq 0.05$, partial eta square = 0.14, suggesting no change in internalizing problems and adaptive skills were observed at the FU time.

No significant group differences were observed for any of the BASC-2 scales (EP, IP, BSI, AS) during the FU condition for individuals who were still taking medications compared to those who discontinued taking medications, F (4, 13) = 0.30, $P \geq 0.05$.

Lastly, no significant overall group differences emerged for any of the BASC-2 scales (EP, IP, BSI, AS) at the FU condition for biological sex, F (4, 13) = 2.35, $P \geq 0.05$. However, when analyzing univariately, parents reported higher scores on the Internalizing Problems scale for females compared to males, F (1, 16) = 9.83, $P \leq 0.05$).

The BRIEF parent ratings are presented in Table 3. The EF ratings completed by parents on the BRIEF revealed a significant effect over time: BRIEF BRI [F (1, 16) = 16.16, $P \leq 0.001$, partial eta square = 0.50] and MI [F (1, 16) = 31/64, $P \leq 0.001$, partial eta square = 0.66]. Specifically, results show an increase in symptom ratings between time points BD (BRI M = 54.47; MI M = 59.12) and FU time points (BRI M = 67.12; MI M = 71.71).

MANOVA was used to investigate the impact of medications on EF at the FU time point. Results indicated no significant differences between BRIEF ratings (BRI and MI) at FU condition between participants still taking medications compared to participants who had discontinued, F (2, 15) = 0.40, $P \geq 0.05$. No significant overall biological sex differences between BRIEF ratings (BRI and MI) at FU condition were observed, F (2, 15) = 3.10, $P \geq 0.05$. However, the univariate analyses indicated parents reporting higher BRIEF-MI ratings for males than for females, F (1, 16) = 6.10, $P \leq 0.05$.

Difference in neuropsychological performance between BD condition and long-term FU

RmANOVA analyses were conducted to investigate the difference in neuropsychological test performance across the BD and FU. Results indicated significant differences over time on the CPT omission errors, F (1, 19) = 5.58, $P \leq 0.05$, partial eta square = 0.28). No significant difference over time on the CPT commission errors, F (1, 19) = 3.80 , $P \geq 0.05$, partial eta square = 0.17, Digit Span Backwards, F (1, 15) = 4.31, $P \geq 0.05$, partial eta square = 0.22 and spatial span backwards, F (1, 17) = 0.12, $P \geq 0.05$, partial eta square = 0.007) tasks. Furthermore, MANOVA was used to investigate the impact of medications on EF performance measures at the FU time point. Results indicated no significant difference at FU condition between participants still taking medications compared to participants who had discontinued, F (4, 13) = 1.24, $P \geq 0.05$. No biological sex differences on neuropsychological test performances were observed at the FU condition, F (4, 13) = 1.08, $P \geq 0.05$.

DISCUSSION

The purpose of this study was to evaluate the short- and long-term impact of psychostimulant medications on EF and behaviour across three-time points in children with ADHD who were involved in a medication treatment trial.

In terms of parent behaviour ratings, parents observed improved behaviour in children with ADHD following the medication trial across various internalizing, externalizing, and adaptive domains. This is consistent with previous studies investigating the efficacy of stimulants for children with ADHD[14]. However, this improvement in parent behaviour ratings did not sustain at the naturalistic long-term FU condition, thus indicating that children with ADHD continue to struggle with behaviour challenges in the adolescent years. These results are in contrast to two of the previous naturalistic long-term FU studies where the authors did not find any significant difference between post-test and FU time points, except for inattention[24, 25]. The observed differences in results could be due to different FU timelines between the studies, with the current study's FU condition ranging from 6 mo to 2 years after initial MPH treatment compared to a range of 4.5-8.0 years after treatment in the other studies. Previous studies also included combined treatment modalities, whereas the current study only implemented pharmacotherapy intervention. It is also important to mention that the current findings are consistent with Molina *et al*[22] findings from the MTA study, the largest medication study to date with children with ADHD. This shows that the long-term impact of stimulant medication is variable across individuals and is dependent on other mediating and moderating factors[34].

A number of additional factors could have contributed to the lack of sustained behavioural improvement as measured by parent behaviour ratings. It is conceivable that children become tolerant to medication over time, and thus the effectiveness of the medication declines. Moreover, it is also plausible that adherence to medication was better in the BD medication condition compared to the FU condition when the children were no longer part of the treatment trial. Additionally, other external variables could have impacted the perceived effect of medications as reported by parents; for example, parents could have noticed heightened sleep and/or appetite issues as well as

increased emotional lability, which may lead to increased perceived behavioural challenges. As well, it is possible that as children develop and reach the early adolescent years, they require more support to manage increasing educational and social demands. Thus, effective curricula and targeted interventions would be beneficial to complement medication treatment. Consequently, it is important for clinicians and other healthcare professionals to be aware of continued challenges in behaviour in children with ADHD during adolescent years.

Similar to the behaviour ratings described above, parents also reported significant improvements in EF skills as measured by the BRIEF parent rating scale. These results are consistent with previous studies where increases in EF skills were witnessed by parents following medication treatment[35]. However, the reported improvements in EF skills did not sustain at the long-term FU condition.

While some of the study participants did not continue with their medication treatment, there were no significant differences in EF ratings between the medicated and non-medicated groups, suggesting that other potential variables may have impacted the perceived efficacy of the medication during the FU condition. It is possible that as children with ADHD develop during their adolescent years, their EF challenges increase. Therefore, adolescents with ADHD would likely benefit from additional interventions to supplement medications to support this increasing need.

Given the discrepancies reported in the literature between parent rating scale and performance-based measures[1], the impact of stimulant medication on neuropsychological test performance was also evaluated. Results showed improved performance following the medication trial on the CPT omission errors score. However, CPT commission errors did not change following the four-week medication trial. Similarly, performance on the two working memory tasks (Digit Span Backwards and Spatial Span Backwards) did not change following the medication trial.

At the long-term FU condition, performance on the CPT omission decreased, and the improvement shown after the medication trial did not sustain. There were no significant changes in performance on the CPT commission error and the two working memory tasks. It is possible that these differences in performance could be task specific as the CPT-II task requires sustained attention and concentration. By way of comparison, the digit span backwards and the spatial span backwards is a much shorter task. It is also possible that children with ADHD need additional interventions on top of medications as they enter their early adolescent years.

While this study adds valuable information to the existing literature on ADHD, the observed results should still be evaluated in the context of some limitations. We included a naturalistic FU where it is possible for participants to follow other psychosocial treatments or stop treatment after the post-test, possibly causing differences between initial treatment conditions at FU. Another notable limitation of the current study was the sample size as not all participants enrolled in the medication trial returned for the naturalistic FU portion of the study. While this research included an appropriate sample size to obtain statistically significant findings, the sample size is still considered small. As such, future studies need to be conducted to replicate the results. The small sample size also did not allow investigation of differences between the different presentations of ADHD; as such, the varying presentation subtypes (*i.e.*, inattentive and combined) were collapsed into one heterogeneous group. Another limitation that was not considered in this study is the changes in lifestyle habits of the children with ADHD. It is possible that changes in sleep, diet and appetite could have impacted the effect of the stimulant medication. Lastly, this study only included data from parents. It would have been beneficial to obtain teacher ratings as well, in order to understand the impact of medications at school.

CONCLUSION

The current study provided valuable information about the impact of stimulant medication on behaviour and EF in children with ADHD. Results showed improvement in EF skills and behaviour in children with ADHD following medication treatment. These improvements were reported by parents through standardized behaviour rating scales. Neuropsychological tests of response inhibition also showed improved performance following medication treatment. However, these improvements did not sustain when reassessed at the FU time point based on parent behaviour rating scales. Additionally, neuropsychological assessment results were inconclusive, with no significant differences emerging on the CPT-II commission errors, the Digit Span Backwards and the Spatial Span Backwards tasks. In spite of this, performance

on the CPT-II omission errors declined at the FU condition. Based on these observed findings, these results suggest that healthcare professionals working with individuals with ADHD should consider some form of medication FU to understand the efficacy of continued medication usage. Furthermore, it is possible that as children enter the adolescent years, they may require supplementary psychosocial support combined with pharmacotherapy to ensure more sustained treatment out-comes. Future research investigating the long-term impact of stimulant medication will be helpful to better understand the efficacy of stimulant medications and replicate findings obtained from the current study.

ARTICLE HIGHLIGHTS

Research background

Children with attention-deficit/hyperactivity disorder (ADHD) often exhibit behaviour challenges and deficits in executive function (EF) skills. Typically, psychostimulant medications [*e.g.*, methylphenidate (MPH)] are commonly prescribed for children with ADHD. However, psychostimulants are considered effective in 70% of the cases and often have undesirable side effects, including changes in appetite, weight, and sleep. Furthermore, only a handful of studies have investigated the naturalistic long-term impact of MPH medication on EF and behaviour.

Research motivation

The main topics investigated in the current study were to measure EF and behaviour challenges in children with ADHD using both parent rating scale and neuropsychological assessment measures.

Research objectives

The main objectives of the current study were to evaluate behaviour and EF challenges in children with ADHD who were involved in a MPH treatment trial. The participants were assessed across three-time points using both parent rating scale and neuropsychological assessment measures to understand the short-term and long-term naturalistic impact of stimulant medications.

Research methods

Thirty-seven children with ADHD completed a stimulant medication trial (MPH). Children with ADHD completed neuropsychological assessments assessing working memory (Digit Span Backwards and Spatial Span Backwards) and response inhibition (Continuous Performance Test-2). Parents of children with ADHD completed behaviour rating scales related to executive function [Behaviour Rating Inventory of Executive Function (BRIEF)] and behaviour [Behaviour Assessment System for Children, second edition (BASC-2)]. Participants were evaluated at: (1) Baseline (no medication); and (2) Best-dose (BD; following four-week MPH treatment). Additionally, 18 participants returned for a long-term naturalistic follow up (FU; up to two years following BD).

Research results

The results of the current study found significant effects over time on two subscales of BRIEF and four subscales of BASC-2 measures indicating impact on behaviour and EF according to parents. Neuropsychological assessments showed some improvement, but not on all tasks following the medication trial. These improvements did not sustain at FU, with increases in EF and behaviour challenges and a decline in performance on the CPT-II task being observed.

Research conclusions

Parents of children with ADHD reported improvements in EF and behaviours during the MPH trial but were not sustained at FU. Neuropsychological assessment findings were not consistent with participants showing improvement on some response inhibition tasks but not on the working memory tasks. As a result, it is important to combine screening tools and neuropsychological assessments for monitoring medication responses.

Research perspectives

The current study provided information about the impact of stimulant medication on behaviour and EF in children with ADHD. Results showed improvement in EF skills and behaviour in children with ADHD following medication treatment. These improvements were reported by parents through standardized behaviour rating scales. Neuropsychological tests of response inhibition also showed improved performance following medication treatment. However, these improvements did not sustain when reassessed at the FU time point based on parent behaviour rating scales. It is important for healthcare professionals working with individuals with ADHD to consider medication FU to understand the efficacy of continued medication usage. Furthermore, it is possible that as children enter the adolescent years, they may require supplementary psychosocial support combined with pharmacotherapy to ensure more sustained treatment outcomes. Future research investigating the long-term impact of stimulant medication will be helpful to better understand the efficacy of stimulant medications and replicate findings obtained from the current study.

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ORIGINAL ARTICLE

Case Control Study

Vestibular function for children with insulin dependent diabetes using cervical vestibular evoked myogenic potentials testing

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Abstract

BACKGROUND

Healthy vestibular system adjusts balance during static and dynamic conditions. This is important for normal development (standing up and walking). Vestipulopathies (central and peripheral) are common complications of diabetes in adult population. Related studies are scare in children with type 1 diabetes (T1D).

AIM

To assess saccular function of otolith organ in children with T1D and predictors for its dysfunction.

METHODS

Cervical vestibular evoked myogenic potential (cVEMP) was used for objective evaluation.

RESULTS

The study included 40 patients (boys = 15; girls = 25). Patients had mean age of 13.63 ± 1.50 years, duration of diabetes of 5.62 ± 2.80 years, frequent attacks of diabetic ketoacidosis (55%) and hypoglycemia (30%), hyperlipidemia (20%), hypertension (12.5%) and peripheral neuropathy (40%). Dizziness was found in 10%. Compared to healthy children (n = 25), patients had prolonged cVEMP P1 and N1 latencies and reduced P1-N1 amplitude. Bilateral cVEMP abnormalities were found in 60% (*vs* 25% for unilateral abnormalities). Higher frequencies and severe vestibulopathies were found with chronic diabetes of > 5 years, hemoglobin A1c values > 7%, frequent diabetic ketoacidosis and hypoglycemic

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attacks and presence of dizziness. Regression analyses showed that predictors for prolonged P1 latencies and reduced P1-N1 amplitudes were only chronic diabetes (> 5 years) {odds ratio (OR) = 2.80 [95% confidence interval (CI): 1.80–5.33], P = 0.01; OR = 3.42 (95%CI: 2.82–6.81)} and its severity (hemoglobin A1c > 7%) [OR = 3.05 (95%CI: 2.55–6.82), P = 0.01; OR = 4.20 (95%CI: 3.55–8.50), P = 0.001].

CONCLUSION
Dysfunction or injury of the saccular macula and its pathways is prevalent in children with T1D. Optimum glycemic control is important to prevent diabetes related vestipulopathies.

Key Words: Children; Type 1 diabetes; Otolith organ; Cervical vestibular evoked myogenic potential

Core Tip: Vestipulopathies are common complications of diabetes. The vestibular system is crucial for early normal motor and mental developments. Vestibular evoked myogenic potential testing is objective, noninvasive, inexpensive, rapid and reliable. It is used to assess the function of otolith organs (saccule and utricle) of the inner ear. The otolith organs register forces related to linear acceleration and static tilt to the gravitational axis. Cervical vestibular evoked myogenic potential is vestibulo-collic reflex record from neck muscles in response to acoustic stimulation. It provides information about type 1 hair cells in saccular macula, inferior vestibular nerve, vestibular nuclei, lateral and medial vestibulospinal tracts and accessory nerve nuclei. This study aimed to evaluate saccular function in children with type 1 diabetes and predictors of its abnormalities.

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INTRODUCTION

Large epidemiological studies in the United States have shown an increase in the prevalence of type 1 diabetes (T1D) from 1.48/1000 to 1.93/1000 between years of 2001 and 2009. They also have shown an increase in the annual incidence of T1D in children and adolescents by 1.4% during the years 2002 to 2012[1]. In Egypt, the annual incidence of T1D in younger children (age: Below 15 years) has been estimated to be 8/100000[2]. Previous studies reported that diabetes mellitus (DM) is the cause of peripheral and central auditory and vestibular systems' dysfunctions (*i.e.* vestibulopathies)[3-9]. Vestibular system is important for healthy motor (standing up and walking) development. It adjusts balance during static condition and motion. The vestibular end organs and their connections maintain gaze and postural stabilities through the vestibulo-ocular and vestibulo-spinal reflexes[10,11]. Studies found significant associations between diabetes and manifestations of vestibular dysfunction (*e.g.*, imbalance, unsteadiness, vertigo, *etc.*) independent to other diabetic complications that cause balance disturbance, including proprioception impairment with diabetic neuropathy and defective vision with diabetic retinopathy[10,12]. Functional testing of vestibular system are (1) Caloric irrigation, rotatory chair testing, head-impulse test (HIT) and electronystagmography (ENG) or videonystagmography (VNG), tests for semicircular canals or horizontal angular head acceleration (vestibulo-ocular) and superior vestibular nerve functions; and (2) Vestibular evoked myogenic potentials (VEMPs), tests for otolith organs' (saccule and utricle) functions[13]. The otolith organs register forces related to linear acceleration and static tilt with gravity [11,13]. VEMP testing is objective, noninvasive, inexpensive, rapid and reliable. It causes no discomfort to subjects compared to ENG or VNG. There are two common

types of VEMP recording: (1) Ocular or oVEMP: It is used to assess the integrity of the utricle or a superior vestibular nerve function; and (2) Cervical or cervical VEMP (cVEMP): It is used to assess the integrity of saccular macula or an inferior vestibular nerve function. cVEMP is a short-latency vestibulo-collic reflex (VCR) recorded from neck muscles in response to acoustic stimulation. The otolith organs sense intense acoustic stimulation due to its anatomical proximity to the cochlea[13]. The VCR arc is composed of: (1) Receptors, which are type 1 vestibular hair cells of saccular macula; (2) Afferent pathway, which is the inferior vestibular nerve that relays in the vestibular nuclei; and (3) Efferent fibers of vestibular nuclei, which run along the lateral and medial vestibulo-spinal tracts to the accessory nerve nucleus to supply the sternocleidomastoid muscle (SCM)[14].

Objectives

Studies of vestibular function in children with T1D are lacking. We aimed to assess saccule and its connections' functions using cVEMP testing. The predictors (demographic, clinical and laboratory variables) of vestibular dysfunctions were also determined.

MATERIALS AND METHODS

Study design, period, region

This is a cross sectional case-control study. It included 40 children with T1D (boys = 10, 25%; girls = 30, 75%) and 25 healthy children (boys = 9, 36%; girls = 16, 64%; age range: 9-18 years; mean: 15.44 ± 1.22 years). Children with diabetes were recruited over a year (December 2019–November 2020) from the Endocrinology Clinic of Children's Hospital, Assiut University, Assiut, Egypt. Healthy children were patients' friends and schoolmates. Excluded were children with: (1) External or middle ear diseases; (2) History of head or neck injuries or limitation of neck movements; (3) History of otologic surgery; (4) Regular or recent intake of ototoxic drugs; and (5) History of primary neurologic, psychiatric or other medical disease.

The protocol of work was approved by the research ethics committee of Faculty of Medicine, Assiut University, Assiut, Egypt, No. AUFM_PED_232/2019. Informed written consent to participate in the study was obtained from children's parents or guardians.

Methods

Clinical evaluation: Detailed ear, nose and throat, physical and neurological data were gathered. Data included age at onset and duration of diabetes, family history of diabetes and insulin dose. They also included history of diabetic complications [whether due to the disease or its medications: *e.g.*, diabetic ketoacidosis (DKA), retinopathy, nephropathy, peripheral neuropathy, hypoglycemia, *etc.*], comorbid medical conditions (*e.g.*, other endocrinal disease, hypertension, hyperlipidemia, *etc.*) and hearing or vestibular symptoms. All underwent medical, neurological and ear, nose and throat examinations. The presence of peripheral neuropathy was diagnosed by clinical manifestations and abnormal nerve conduction velocity study in at least two nerves; one must have been the sural nerve.

Audiologic assessment: It included otoscopic ear examination; screening audiograms (250–4000 Hz), tympanometry (200 top–400 dapa) and acoustic (stapedius) reflex (Middle Ear Analyzer Interacoustics, Az26, Assens, Denmark). Speech discrimination thresholds were assessed by identifying the hearing level for understanding and repeating a set of 10 monosyllables. Typically, normal Speech Discrimination Score ranges from 90% to 100%.

Vestibular assessment: It was done by recording cVEMP response from each ear (GN Otometrics, Schaumburg, IL, United States). The stimulus was air-conducted tone burst at frequency of 500 Hz, intensity of 100 dBnHL and rate of 5.1/s. Responses to 200 stimuli were averaged and band-pass filtered between 30-300 Hz for each repetition. The child lay supine and was instructed to turn the head to contralateral side and look at a fixed target on the examination room's wall and right after towards a fixed point located above this target, to induce a vertical viewing angle of approximately 30° above the horizontal plane. The impedance values for the device were checked before each recording to be < 5 KOhms. Four surface electrodes were applied: (1) An active electrode, placed on the middle of ipsilateral SCM; (2) A reference

electrode, placed on ipsilateral mastoid; (3) A ground electrode, placed on the forehead; and (4) A forth electrode, placed on the contralateral mastoid. Data acquisition was accepted by the device if SCM electromyography (EMG) activity was 50-100 μV. Rectified EMGs from 20 milliseconds (ms) before to 80 ms afterwards were collected. To control for the individual differences of SCM contractions during recording, the raw amplitude of each recording was divided over the mean rectified EMG activities, which were recorded for 10 ms before the stimulus onset. VEMP parameters were: (1) Latencies of P1 (P13) and N1 (N23) waves; (2) P1-N1 peak-to-peak amplitude; and (3) Amplitude asymmetry ratio (AR), an inter-aural amplitude difference. AR suggests the side of pathology in unilateral lesions or the severely injured side in bilateral lesions. AR is calculated as follows: AR% = (AL - AR)/(AL + AR) × 100, where AL and AR are the amplitudes due to stimulation of the left and right ears. A clinically significant AR% is > 35%[15]. The absence of defined P1 and N1 waves indicate absent cVEMP response.

Statistical analysis

SPSS, version 22.0 (SPSS Inc., Armonk, NY, United States) was used for statistical analyses. Normality of data was checked by Kolmogorov–Smirnov test. Descriptive statistics were expressed as means ± SD or medians (25^{th}, 50^{th}, 75^{th} percentiles). Differences between groups were calculated by inference statistics (Chi-square with Fisher's exact tests or Mann-Whitney *U* test). Abnormal P1 or N1 latencies were considered if exceeded at least two standard deviations of the mean value for controls. Abnormal P1-N1 amplitude was considered if was less than the 5^{th} percentile of the mean value for controls. Correlations between cVEMP and subjects' variables were done using Spearman's correlation coefficient. The independent associations between vestibular and subjects' variables were determined using multiple logistic regression analysis by calculating the odds ratio (OR) and 95% confidence interval (95%CI). For 2-sided statistics, significant values were considered with probability value less than 0.05.

RESULTS

In this study, 130 ears were examined (patients = 80; controls = 50). Children with T1D had mean age of 13.63 ± 1.50 years and duration of illness of 5.62 ± 2.80 years. Frequent DKA and hypoglycemic attacks were found in 55% and 30%, respectively. The reported comorbid medical conditions and diabetic complications were hyperlipidemia (20%), hypertension (12.5%) and sensory peripheral neuropathy (40%). Manifestations of peripheral neuropathy were lower limbs' numbness, stoking hypoesthesia and reduced sensory unit potential's amplitudes of sural nerves without (axonal neuropathy) or with prolonged distal latencies or reduced nerve conduction velocities (demyelinating neuropathy) (Table 1). Both children with diabetes and healthy children had normal otoscopic ear examination, acoustic reflexes, pure tone audiogram and Speech Discrimination Scores (right ear: 96.32 ± 2.50; left ear = 93.44 ± 2.28) and type A tympanometry. Dizziness, not related to hypoglycemia, was reported in 10% (*n* = 6).

Compared to healthy children, patients had significant prolongation in cVEMP P1 and N1 latencies and reduction in P1-N1 amplitudes (Table 2). Bilateral cVEMP abnormalities were found in 25% (for latencies) and 60% (for amplitude), respectively. AR was found in 25%. No sex difference was found in cVEMP changes. Children with chronic diabetes with duration > 5 years had prolonged P1 and N1 ($P = 0.006$; $P = 0.01$) latencies and reduced P1-N1 amplitudes ($P = 0.001$) compared to those with short diabetes duration (≤ 5 years). Children with dizziness had prolonged P1 and N1 ($P = 0.02$; $P = 0.02$) latencies and reduced P1-N1 amplitudes ($P = 0.01$) compared to those without dizziness. Children with high hemoglobin A1c (HbA1c)% values (> 7%) had prolonged P1 and N1 ($P = 0.01$; $P = 0.01$) latencies and reduced P1-N1 amplitudes ($P = 0.001$) compared to those with HbA1c% values ≤ 7%. Children with history of DKA attacks had prolonged P1 and N1 ($P = 0.003$; $P = 0.001$) latencies and reduced P1-N1 amplitudes ($P = 0.01$) compared to those without. Children with hypoglycemic attacks had prolonged P1 and N1 ($P = 0.02$; $P = 0.03$) latencies and reduced P1-N1 amplitudes ($P = 0.03$) compared to those without. Children with peripheral neuropathy had prolonged P1 and N1 ($P = 0.001$; $P = 0.03$) latencies and reduced P1-N1 amplitudes ($P = 0.02$) compared to those without (Table 3). Significant correlations were identified between P1 with N1 latencies ($r = 0.335$, $P = 0.01$) but not between P1 with P1-N1

Table 1 The demographic, clinical and laboratory characteristics of the studied children

Demographic, clinical and laboratory characteristics	Patients (*n* = 40)	Controls (*n* = 25)	*P* value
Age, yr	10-18 (13.63 ± 1.50)	9-18 (15.44 ± 1.22)	0.438
Sex, *n* (%)			
Male	10 (25)	9 (36)	0.185
Female	30 (75)	16 (64)	0.223
BMI	15.70-25.30 (20.53 ± 2.52)	15.20-27.50 (18.86 ± 2.63)	0.278
Systolic blood pressure, mmHg	100-130 (110.80 ± 10.50)	100-120 (105.00 ± 8.50)	0.365
Diastolic blood pressure, mmHg	60-80 (70.55 ± 2.34)	60-70 (68.33 ± 5.20)	0.544
Age at onset of diabetes, yr	4–15 (8.54 ± 2.33)	-	-
Duration of diabetes, yr	3–10 (5.62 ± 2.80)	-	-
≤ 5	9 (22.5)		
> 5	31 (77.5)		
DKA, *n* (%)	22 (55)	-	-
Number of attacks	0–6 (3.44 ± 0.43)		
Hypoglycemia, *n* (%)	12 (30)	-	-
Number of attacks	0–6 (2.50 ± 0.32)		
Family history of diabetes, *n* (%)	18 (45)	3 (12)	0.01
Hb1Ac, *n* (%)	5.00–15.65 (8.68 ± 1.50)	3.00–6.00 (3.90 ± 0.25)	0.001
≤ 7%	4 (10)		
> 7%	36 (90)		
Insulin dose, IU/kg/d	0.80–2.10 (1.70 ± 0.32)	-	-
Lipid profile, mg/dL			
Total cholesterol	100-250 (180.20 ± 20.50)	90–200 (140.21 ± 15.65)	0.06
Triglycerides	60-280 (168.52 ± 22.50)	50–120 (80.50 ± 20.58)	0.001
LDL	50-160 (100.65 ± 10.62)	65–110 (85.43 ± 6.46)	0.08
HDL	45-65 (55.52 ± 5.33)	35–70 (48.33± 5.62)	0.364
Comorbid medical conditions, *n* (%)			
Hypertension	5 (12.5)	-	-
Hypercholesterolemia/dyslipidemia	8 (20)	-	-
Serum creatinine, mg/dL	0.54–1.20 (0.80 ± 0.15)	0.40–0.90 (0.62 ± 0.05)	0.450
Diabetic complications, *n* (%)			
Nephropathy	6 (15)	-	-
Peripheral neuropathy	16 (40)	-	-
Dizziness, *n* (%)	6 (10)	-	-

BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; Hb1Ac: Hemoglobin A1c; DKA: Diabetic ketoacidosis.

amplitudes (r = 0.230, P = 0.185). Multiple regression analysis showed that presence of prolonged P1 latencies and reduced P1-N1 amplitudes were significantly correlated with longer diabetes duration (> 5 years) [OR = 2.80 (95%CI: 1.80–5.33), P = 0.01; OR = 3.42 (95%CI: 2.82–6.81)] and higher HbA1c levels (> 7%) [OR = 3.05 (95%CI: 2.55–6.82), P = 0.01; OR = 4.20 (95%CI: 3.55–8.50), P = 0.001] but not with the presence of complications or comorbid medical conditions or dizziness.

Table 2 Cervical vestibular evoked myogenic potential results of the studied groups (mean ± SD)

Variables	Children with T1D (*n* = 40)	Controls (*n* = 25)	*P* value (P1)	*P* value (P2)
P1 latency, *n*[1] (%)				
Unilateral	6 (15)	-	-	-
Bilateral	10 (25)	-	-	-
Range, ms				
Right ear	18.00–22.00 (20.16 ± 1.34)	10.40–16.40 (12.03 ± 1.01)	0.03	0.542
Left ear	13.00–29.00 (20.40 ± 1.10)	10.40–17.60 (14.25 ± 1.68)	0.02	
N1 latency, *n*[1] (%)				
Unilateral	6 (15)	-	-	-
Bilateral	10 (25)	-	-	-
Range, ms				
Right ear	22.00–33.00 (28.30 ± 2.66)	18.65–26.70 (22.43 ± 1.82)	0.04	0.364
Left ear	24.00–36.80 (32.35 ± 2.84)	16.82–30.82 (26.45 ± 1.02)	0.03	
P1-N1 amplitude, *n*[1] (%)				
Unilateral	10 (25)	-	-	-
Bilateral	24 (60)	-	-	-
Range, μV				
Right ear				
Range	20.00–90.00	48.60–92.80	0.001	0.458
Median	44.20	72.43		
25th	36.00	60.35		
50th	40.45	76.44		
75th	48.55	86.62		
Left ear				
Range	26.68–86.00	46.03–98.00	0.001	
Median	46.20	74.68		
25th	33.25	54.36		
50th	45.00	80.00		
75th	56.25	88.56		
AR				
Range	1.12–66.20	0.0-15.8	0.001	
Median	18.30	4.88		
25th	6.58	1.88		
50th	13.36	2.90		
75th	32.44	6.30		
n[1] (%)	10 (25)	0		

[1]Number of subjects with vestibular evoked myogenic potential abnormalities results.

P1: Significance for patients *vs* controls; P2: Significance for patients' right *vs* left ear; AR: Asymmetry ratio; T1D: Type 1 diabetes.

DISCUSSION

Developments in research have shown that vestipulopathies are common complications of DM[7-9]. The results of this study showed that: (1) The majority (75%) of children with T1D had asymptomatic vestibular dysfunctions. Few had dizziness

Table 3 Cervical vestibular evoked myogenic potential's results for children with type 1 diabetes in relation to their demographic, clinical and laboratory variables

Variables	P1	N1	P1-N1 amplitude	AR
Sex				
Male (*n* = 10)	22.35 ± 1.12	26.32 ± 2.30	44.82	10.33
P1	0.02	0.320	0.01	0.01
Female (*n* = 30)	18.22 ± 1.63	32.55 ± 1.22	38.36	16.85
P1	0.04	0.01	0.001	0.001
P2	0.125	0.01	0.06	0.126
Duration of diabetes, yr				
≤ 5 yr (*n* = 9)	16.68 ± 1.23	22.65 ± 2.22	38.30	6.50
P1	0.02	0.244	0.03	0.05
> 5 yr (*n* = 31)	28.33 ± 1.11	35.07 ± 2.31	56.26	18.68
P1	0.01	0.01	0.001	0.0001
P2	0.006	0.01	0.001	0.452
Dizziness				
Yes (*n* = 6)	26.03 ± 1.33	34.68 ± 2.57	38.64	10.64
P1	0.002	0.01	0.001	0.01
No (*n* = 32)	16.23 ± 1.28	28.05 ± 2.28	56.00	16.28
P1	0.138	0.302	0.001	0.001
P2	0.02	0.03	0.01	0.06
Hb1Ac, %				
≤ 7 (*n* = 4)	16.83 ± 1.30	22.01 ± 1.20	60.00	8.64
P1	0.306	0.358	0.08	0.023
> 7 (*n* = 36)	25.633 ± 1.28	34.55 ± 1.33	32.50	18.28
P1	0.04	0.01	0.001	0.804
P2	0.01	0.01	0.001	0.246
DKA				
Yes (*n* = 22)	27.23 ± 1.20	34.25 ± 1.88	38.50	16.35
P1	0.01	0.01	0.001	0.001
No (*n* = 18)	14.84 ± 1.11	21.15 ± 1.23	55.84	8.00
P1	0.358	0.682	0.01	0.04
P2	0.003	0.001	0.01	0.323
Hypoglycemia	26.86 ± 1.80	34.22 ± 2.02	30.40	12.86
Yes (*n* = 12)				
P1	0.01	0.01	0.001	0.01
No (*n* = 28)	16.50 ± 1.44	25.24 ± 2.562	54.68	10.35
P1	0.05	0.05	0.01	0.01
P2	0.02	0.03	0.03	0.286
Peripheral neuropathy				
Yes (*n* = 16)	23.28 ± 1.30	32.26 ± 1.45	35.06	16.60
P1	0.001	0.01	0.001	0.01
No (*n* = 24)	16.44 ± 1.03	24.24 ± 1.40	52.66	13.44

P1	0.458	0.542	0.01	0.01
P2	0.02	0.03	0.02	0.322
Control subjects	13.22 ± 1.30	23.82 ± 1.37	74.68	4.88

DKA: Diabetic ketoacidosis; P1: Significance *vs* controls; P2: Significance for a *vs* b for each variable.

(10%); (2) Bilateral vestibular dysfunction was more frequent than unilateral (25%-60% *vs* 10%-25%); and (3) Chronicity and severity of diabetes are the predictors for its related vestipulopathies.

The authors in this study found reduced P1-N1 amplitudes in 85% of children with T1D, and 40% had prolonged P1 and N1 latencies. Previous studies reported similar findings. Kamali *et al*[7] found prolonged P13 and N23 latencies ($P < 0.05$) but normal absolute and relative P1-N1 amplitudes of cVEMP in patients with T1D ($n = 10$) with an age range from 15 to 40 years compared to matched healthy subjects ($n = 24$). Their patients did not have diabetic neuropathy. Konukseven *et al*[8] found prolonged oVEMP and cVEMP latencies in patients with diabetes ($n = 30$) compared to prediabetes ($n = 30$) and healthy controls ($n = 31$). They did not find differences in VEMP amplitudes among the three groups. Kalkan *et al*[9] found reduced cVEMP and oVEMP amplitudes in patients with diabetes whether they had ($n = 33$) or did not ($n = 33$) have polyneuropathy compared to healthy controls ($n = 35$). The authors found no differences in vHIT values among the three groups.

Research studies have suggested the localization of injury within the vestibular organs and their pathways based on cVEMP abnormal findings. They suggested that reduced P1-N1 amplitude is due to labyrinthine pathology, while prolonged P1 and N1 latencies are due to retrolabyrinthine pathology[16]. Murofushi *et al*[16] observed prolonged P13 of cVEMP (*i.e.* slow conduction) with multiple sclerosis and large acoustic neuroma, suggesting brainstem pathology secondary to demyelination in the vestibulo-spinal tract.

We reported dizziness in few patients (10%, $n = 6$). They had unilateral prolonged P1 and N1 latencies and reduced P1-N1 amplitudes. In accordance, Biurrun *et al*[3] did not report dizziness or imbalance with diabetes. Gawron *et al*[4] reported dizziness and imbalance in only 6.3%. It has been observed that vestibular manifestations occur with unilateral lesion or asymmetrical bilateral lesions[3-9]. Diabetes is a metabolic systemic disease. The symmetrical bilateral inner ear dysfunction is the most acceptable explanation for the lack of vestibular symptoms with bilateral compared to unilateral lesions[3,4].

We observed differences in VEMP changes in relation to diabetes duration (*i.e.* > 5 years *vs* ≤ 5 years), severity of diabetes (*i.e.* HbA1c > 7% *vs* ≤ 7%), presence of absence of complications (*i.e.* DKA, hypoglycemia, peripheral neuropathy, *etc.*) and clinical symptoms (*i.e.* dizziness). However, the results of regression analysis showed that the only predictors for vestibular dysfunctions were chronic and severe diabetes. In accordance, Bektas *et al*[6] found no significant difference in cVEMP results between patients with T2D [with ($n = 25$) or without ($n = 25$) peripheral neuropathy] and healthy controls ($n = 21$). Kamali *et al*[7] found prolonged cVEMP latency with T1D and had polyneuropathy, an indication of disease severity.

DM is chronic metabolic disease and a common vascular risk factor. Chronic hyperglycemia causes (1) Tissue injury by advanced glycation end products and oxidative stress factors. Also, the toxic injury to connective tissue results in thickening of the vascular walls and macro- and micro-angiopathies[17,18] and demyelination of the nerves[17]. Kocdor *et al*[18] found selective reduction in type I vestibular hair cells (sensory epithelia) with diabetes. Myers *et al*[17] found large disrupted portions of myelin sheath lamellae of the vestibular and auditory nerves in induced diabetic rats. They also found thinning of the myelin sheath and smaller axonal fibers' diameters, indicating oxidative stress injury; and (2) Alterations of inner ear fluid metabolism. Some suggested that the homeostasis of vestibular structures is very sensitive and rapidly injured by diabetic metabolic disturbance[19].

The strength of the study is the direct evaluation of the function of the saccule and its connections in children with T1D. However, this study has limitations: (1) Small sample size, however, this is an exploratory study done on nationally understudied population; and (2) The cross-sectional study design. Further longitudinal large sample size studies from children with T1D are required to determine the temporal relationship between the development of clinical and objective vestibular and/or auditory manifestations.

CONCLUSION

The results of the study provide evidence for the frequent injury of the saccula of the inner ear and its central pathway with T1D. Predictors for vestibular dysfunction are chronic and severe diabetes. As vestibulopathy is a common comorbid cause of impaired gaze and postural stabilities with diabetes, glycemic control is important to prevent vestibular diabetic complications.

ARTICLE HIGHLIGHTS

Research background

Integrity of vestibular organs and their reflexes is critical for maintaining balance in static condition and during motion and gaze stabilization. In healthy individuals, the brain organizes and integrates information from vision, proprioception and vestibular system. Diabetes is a common chronic metabolic/systemic disease. It causes complications in every organ of the body, especially the eyes, kidney, nerves, heart and blood vessels. Experimental and clinical studies provide evidence that peripheral and/or central auditory and/or vestibular systems' dysfunctions are common complications of diabetes. The mechanism of diabetic vestipulopathy is complex and still has to be explored. It may be related to diabetic complications or its comorbid conditions. It may also be due to alteration of inner ears homeostasis due to diabetic metabolic alterations associated with poor glycemic control.

Research motivation

Vestibulopathy is a known complication in adults with diabetes. The research hotspots include (1) Identification of the spectrum of vestibular and auditory manifestations due to diabetes mellitus and their predictors; (2) Understanding the temporal relation between the onset of diabetes and the development of auditory or vestibular manifestations; and (3) Determining whether diabetes itself and/or its comorbid medical conditions are causes of auditory and vestibular complications.

Research objectives

In children, this is the first study that systematically estimated the prevalence and predictors of vestibular injury or dysfunction with type 1 diabetes.

Research methods

Cervical vestibular evoked myogenic potential (cVEMP) type of VEMP testing was used for assessment of the saccular function of the otolith organ and its pathways.

Research results

Bilateral changes in cVEMP abnormalities are more frequent than unilateral. They are associated with chronic and severe diabetes.

Research conclusions

Injury of the saccule of the inner ear and its central connection occurs with type 1 diabetes.

Research perspectives

Multidisciplinary team is required to follow up regularly children with diabetes for prevention and early identification and treatment of associated complications. The treating endocrinologists have to optimize management of diabetes and its associated comorbidities and complications.

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ORIGINAL ARTICLE

Case Control Study

Tissue Doppler, speckling tracking and four-dimensional echocardiographic assessment of right ventricular function in children with dilated cardiomyopathy

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Author contributions: Elrazaky O, Srour E, and Shabana AH did the echocardiographic studies and collected the data; Mawlana W and Al-Biltagi M analyzed the data and wrote the manuscript; all the authors revised and agreed to the final version of the manuscript.

Institutional review board statement: We performed the study according to the latest version of Helsinki's Declaration. The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University, approved the study.

Informed consent statement: All parents, guardians, or next of kin signed informed consent for the minors to participate in this study.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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Abstract

BACKGROUND

Right ventricular (RV) function is frequently overlooked during dilated cardiomyopathy (DCM) evaluation.

AIM

To evaluate RV function in children with idiopathic DCM using relatively recent echocardiographic modalities.

METHODS

We prospectively studied the cardiac function in 50 children with idiopathic DCM and 50 healthy children as a control group, using four-dimensional echocardiography (4-DE), Tissue Doppler Imaging (TDI), and two-dimensional-speckles tracking echocardiography (2-D-STE). RV EF was measured by 4-DE.

RESULTS

The auto left (LV) ejection fractions (EF) measured by 2-D-STE were significantly lower in the patients' group than in the control. The sphericity index was also significantly lower in children with DCM than in the control. RV EF measured by 4-DE was significantly lower in the patient's group than the control. RV S wave, e´/a' ratio, myocardial performance index (MPI), and tricuspid annular plane systolic excursion (TAPSE) were significantly impaired in children with DCM than in control. Both LV and RV global longitudinal strains (GLS) were significantly reduced in children with DCM than in control. RVGLS was significantly associated with the duration since diagnosis, tricuspid annulus S wave, RV MPI,

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and TAPSE, but not with the age of the patients, RV EF, or e´/a' ratio.

CONCLUSION
There was impairment of the RV LGS and other systolic and diastolic parameters in children with DCM. STE and TDI can help to detect the early decline of RV function.

Key Words: Tissue Doppler; Speckling tracking Echocardiography; Dilated cardiomyopathy; Children; Right ventricle

Core Tip: Cardiomyopathies are a group of cardiac muscle disorders characterized by mechanical and/or electrical impairment that give rise to dilated, hypertrophic or restrictive pathophysiology. In the current study, we prospectively studied the cardiac function in 50 children with idiopathic dilated cardiomyopathy (DCM) and 50 healthy children as a control group using Tissue Doppler Imaging (TDI) and two-dimensional-speckles tracking echocardiography. Right ventricular (RV) ejection fractions was measured by four-dimensional echocardiography. We found impairment of the RV LGS and other systolic and diastolic parameters in children with DCM. Speckles tracking echocardiography and TDI can help to detect the early decline of RV function.

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INTRODUCTION

Cardiomyopathies are a group of cardiac muscle disorders characterized by mechanical and/or electrical impairment that give rise to dilated, hypertrophic or restrictive pathophysiology. Dilated cardiomyopathy (DCM) is a clinical condition associated with left ventricular (LV) or biventricular dilation with an impaired contraction that is not related/caused by abnormal loading conditions (such as hypertension or valvular heart disease) or ischemic changes due to coronary artery disease[1]. It is the most common form of cardiomyopathy and accounts for approximately 55%-60% of all childhood cardiomyopathies, with an average prevalence rate of 1/200000 children. It could be idiopathic or secondary to other causes such as infections (primarily viral), exposure to drugs, toxins, or allergens, metabolic, endocrine, autoimmune, or other systemic diseases. It is commonly diagnosed in younger children with an average age at diagnosis of 2 years[2].

Clinical presentation of DCM mainly relates to the degree of LV or biventricular systolic dysfunction leading to pump failure. Heart failure signs and symptoms may be fulminant, acute, subacute, or chronic[1]. DCM diagnosis is primarily based on echocardiography that can readily identify the dilated chambers and the impaired function of left or both ventricles using M-mode, 2-dimensional echocardiography[3]. Tissue Doppler imaging (TDI) is a relatively new echocardiographic technique, useful to study the myocardial function of children with different pathologies[4]. Two-dimensional speckle tracking imaging is another relatively new echocardiographic modality that can provide non-Doppler, less angle-dependent, and objective quantification of myocardial deformation and left/right ventricular (LV/RV) systolic and diastolic dynamics by analyzing the motion of speckles identified on routine 2-dimensional sonograms. In addition, by tracking the displacement of the speckles during the cardiac cycle, strain and the strain rate can be rapidly measured offline after good image acquisition[5].

Most of the studies concerned with the diagnosis of dilated cardiomyopathies in children focus on LV function. As the disease usually starts in LV then RV, early detection of RV dysfunction could have a prognostic benefit. Unfortunately, few

studies examined RV function[6-9]. So, this work aimed to evaluate the RV function and structure using tissue Doppler and speckling tracking echocardiography in children with primary dilated cardiomyopathy and correlate with other echocardiographic findings.

MATERIALS AND METHODS

The research was a prospective cross-section study between April 2018 to June 2019. It involved 50 children with primary idiopathic dilated cardiomyopathy; aged between six months and eight years, selected in the order in which they were identified, with regular attendance to Pediatric Cardiology Unit in a Tertiary Care University Hospital. It also included o 50 healthy children of matching age and sex, coming for routine health check-up without any systemic disease that could affect the heart (control group). All parents, guardians, or next of kin signed informed consent for the minors to participate in this study. The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University, approved the study.

The diagnosis of DCM based on the detection of dilatation of ventricles (LV) dilatation > 112% corrected to body surface area (BSA), age, and sex, or two standard deviations (SD) from the normal upper limit corrected to age, sex, and BSA plus (5%) and presence of systolic dysfunction [fractional shortening (FS) < 25% and/or left ventricle ejection fraction (LV EF) < 45%] detected in m-mode and 2-D echocardiography following the recommendation of the 2006 American Heart Association and 2017 British Society of Echocardiography[10]. Exclusion criteria included children with congenital or acquired heart diseases and children with dilated cardiomyopathy secondary to systemic diseases such as infections (ruled out by the history and laboratory tests for the previous infection with the common viral and bacterial causes), arrhythmias, endocrine diseases, neuromuscular diseases, rheumatologic and immunological diseases, nutritional deficiencies, conditions leading to ischemia, drug or toxins-induced, and systemic diseases.

All children had complete history taking (including personal, birth, developmental, feeding, and family history) and comprehensive clinical examination (including general, regional, and systemic examination). Cardiac examination aimed to detect cardiomegaly and evidence of the presence of a cardiac murmur. In addition, all children had echocardiographic examinations, including 2-D, M-mode, TDI, and 2D-speckles tracking echocardiography (STE).

Echocardiography

Echocardiography was done using (Vingmed Vivid-7, General Electric Vingmed, and Milwaukee, Wisconsin, United States). The examination was performed using an S7 probe and V3 matrix real-time 3-dimensional probes at a depth of 16 cm in all the standard echocardiographic views following the American Society of Echocardiography recommendation[11]. All children were examined in the right anterior oblique position, when possible, while breathing room air or on oxygen supplement when required. Cardiovascular anomalies were carefully searched for and excluded by all standard views. LV EF, LV FS, end-diastolic and end-systolic volumes, systolic pulmonary artery pressure by using tricuspid regurgitation jet, and LV and RV diastolic function were measured according to the guidelines of the American Society of Echocardiography[12]. Tricuspid annular plane systolic excursion (TAPSE) was measured by 2-D echocardiography-guided M-mode from the apical 4-chamber view, with the cursor was placed at the free wall side of the tricuspid annulus. Care was taken to align the sample volume as vertically as possible concerning the cardiac apex. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the lowest point of descent during ventricular systole. The sphericity index (SI) was measured by calculating the ratio between the length (mitral annulus to apex in the apical view) and diameter (mid-cavity level in the short-axis view) of the LV. The smaller the SI is, the more globular the ventricle will be. It also predicts the functional capacity of patients with LV dysfunction[13]. Simultaneous ECG tracings obtained during M-mode recording were used to measure R-R intervals. Measurements were repeated on three occasions, and the average was obtained[14].

All children had three-dimensional (3-D)-echocardiography immediately after the 2-D-echocardiographic examination, using the same ultrasound machine equipped with a 4V probe. RV 3-D images were obtained in a full-volume dataset from the apical 4-chamber view, optimized for analysis of RV function. All the measurements of RV

volumes and EF were made offline, using dedicated software. The semi-automatic analysis was performed using a manual tracing of the endocardial borders in end-systolic and end-diastolic frames in the sagittal, four-chamber, and coronal views. Besides, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, and EF were calculated using the software (Figure 1).

TDI

We used the same machine and probe to perform TDI at a depth of 16 cm in the parasternal and apical views (standard long axis and two- and four-chamber images). The baseline was adjusted to a low-velocity range (-20-20 cm/s) while using the pulsed-wave angle-corrected colour-coded TDI filters. The Doppler frame rates were varied between 80 and 115 frames/s depending on the sector width of the range of interest. We settled the setting to the minimal gain to reduce the background noise and get the highest quality images. The 2-millimeters sample volume was placed within the myocardium equidistant from the endocardial and epicardial borders.

The pulsed-wave TDI recorded the myocardial velocity curves of the septal mitral valve annulus, lateral mitral valve annulus, and lateral tricuspid valve annulus from the apical four-chamber planes. The timing of cardiac cycle events and their relations to respiratory events were defined by simultaneously tracing the electrocardiogram and respiration curve monitoring. The beginning of the QRS complex was the reference point. At least ten cardiac cycles were recorded at a speed of 100 mm/s. The images were stored electronically.

The systolic and diastolic mitral and tricuspid annulus velocities were determined by placing the PW-TDI sample volume at the level of the septal tricuspid annulus. In the spectral TDI display, the antegrade systolic wave S reflected the systolic function of either RV or LV, e´ retrograde wave reflected the early passive ventricular filling, while the retrograde a´ wave represented the atrial contraction. The early/atrial (e´/a´) ratio of tricuspid or mitral valve annulus reflected the diastolic function of the RV or LV (Figure 2). The isometric contraction time (ICT) (was defined as the time duration between the end of a´ wave to the beginning of S wave by TDI), the isometric relaxation time (IRT) (was defined as the interval between the end of S wave and the beginning of the early wave), and myocardial contraction time (CT) were measured by TDI[15]. Myocardial Performance or Tei index is a Doppler-derived time interval index that combines systolic and diastolic cardiac performance. It was calculated as previously described by Tei and colleagues, using the following formula: ICT + IRT/CT. Both ICT and IRT were corrected for heart rate[16-17]. We used the mean values for three heartbeats during expiration for the analysis, and all the measurements obtained by TDI were indexed for children's body surface area.

Speckle tracking technique (RV longitudinal systolic strain and function analysis)

We used a 3.5-MHz transducer at a depth of 16 cm in the standard apical 4-chamber view (4-chamber image) to acquire an adequate image with novel speckle-tracking software (Figure 3). To prevent foreshortening, we visualized the apex of the left ventricle adequately. Then, 2-D speckle tracking strain imaging was used to study LV and RV deformation on standard grayscale images (frame rate, 55 ± 11 frames/s). It tracked the characteristic pattern of natural acoustic markers in the myocardial wall ("speckles") from frame to frame throughout the cardiac cycle. Two-D longitudinal strain for all RV myocardial segments includes three segments from the lateral (anterior) wall (basal, mid, and apical) and three corresponding segments of the interventricular septum (because of the significant contribution of the interventricular septum to RV ejection). The myocardial strain was then calculated by the change in position of the speckle pattern to the initial position. Peak systolic longitudinal strain was calculated by averaging the peak systolic values of the six segments. Regional lengthening of myocardial strain was expressed as a positive value and thinning or shortening as a negative value[18].

4D RV EF

We obtained RV 4D images in a full-volume dataset from the apical four-chamber view, optimized for analysis of RV function. In addition, we obtained multi-beat (3-6 beats) data on the multislice (short axis) visualization mode to ensure the full inclusion of the right ventricle in the dataset. We obtained all RV volumes and EF measurements offline, using dedicated software (Echo PAC PC, 113; GE, Horten, Norway). We conducted a semi-automated analysis, with a manual tracing of endocardial borders in end-systolic and end-diastolic frames in the sagittal, four-chamber, and coronal views, from the full-volume dataset. In addition, we calculated EDV, ESV, stroke volume, and

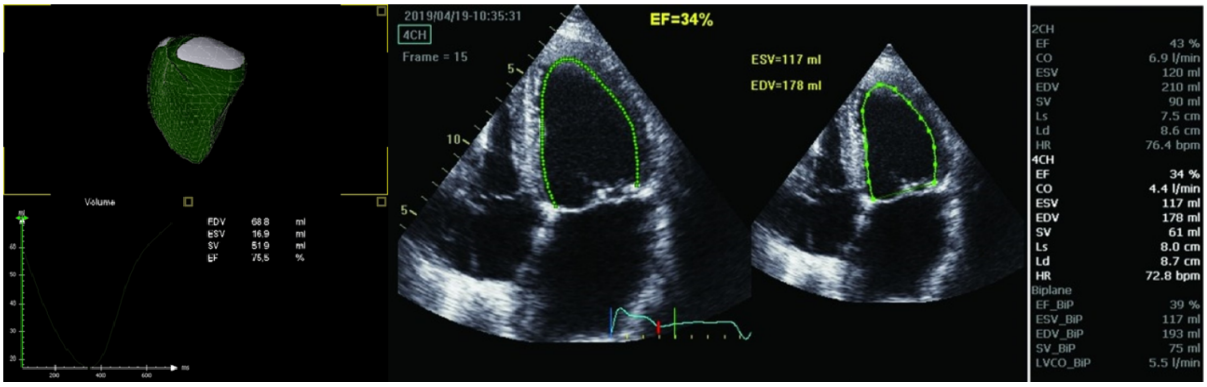

Figure 1 Three-dimensional echocardiographic reconstruction of the delineation of right ventricular ejection fraction. The endocardial border is traced throughout the cardiac cycle using speckle tracking, and the software automatically locates end-systolic and end-diastolic frames. Example of a four-dimensional echocardiographic reconstruction of the delineation of the right ventricle seen from the septal side (end-diastolic volume 68.8 mL, end-systolic volume 16.9 mL, and ejection fraction 75.5%). The mesh is the right ventricle at end-diastole, in green at end-systole. The pulmonary valve is shown in white on the upper left side, the tricuspid valve is shown on the upper right side, and the right ventricular apex toward the bottom.

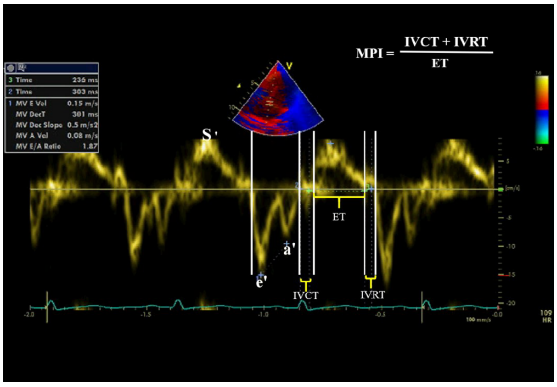

Figure 2 Tissue Doppler echocardiography of septal annulus showed the main tissue waves (S, e´ and a´ waves) and how to calculate Myocardial Performance Index. e´ and a´ Early and late filling waves by tissue Doppler; S wave: Myocardial systolic excursion velocity. IVCT: Isovolumic contraction time; IVRT: Isovolumic relaxation time; MPI: Myocardial Performance Index; ET: Ejection time.

EF using the software (Figure 1)[19].

Reproducibility

Intra-observer variability for echocardiographic data was done for patients and controls, where the same sonographer repeated examinations twice on the same day of diagnosis. Intra-observer agreement in interpreting echocardiographic data was determined using Cohen kappa (κ) statistics.

Statistical analysis

We used Power and Precision V3 program to estimate the power level of the primary endpoint (e´/a´ ratio with a level of 1.2 ± 0.25) (http://www.Power-Analysis.com). It was more than 90% when using 50 patients for each group. We did the statistical analysis using SPSS version 22. We presented the data as mean ± SD and percentages as indicated. We checked the data for normal distribution (about 72% of the results were within one SD from the mean values, and about 96% were within two SD from the mean values). Categorical variables were evaluated using student *t*-test, Chi-square, and *F*-test (ANOVA). The Pearson correlation coefficient examined the correlation of different parameters. P value < 0.05 was considered statistically significant.

RESULTS

Figure 4 shows the flow chart of the study, which enrolled 50 children with idiopathic

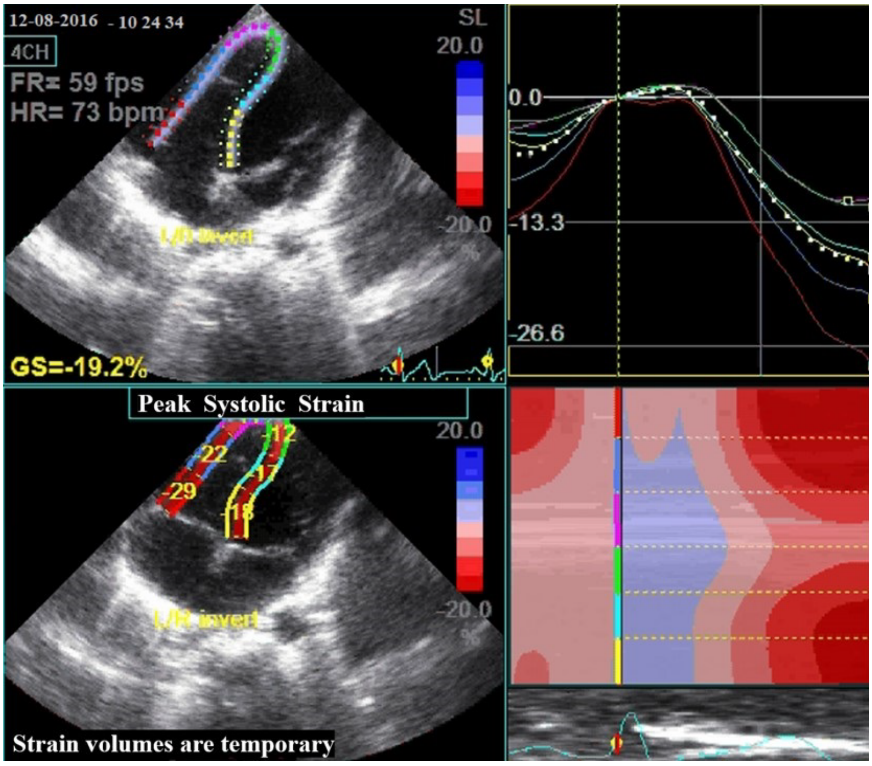

Figure 3 Right ventricular global longitudinal strain measures of a healthy child from the standard four-apical views using two-Dimension speckle tracking method. The upper left quadrant shows tracking. The right half shows color-coded segmental strain curves and average strain curve (dashed line). The lower left quadrant depicts an anatomic M-mode. The dashed yellow line = Time to peak (from R-wave to maximum systolic strain.

Figure 4 The flow chart of the study. DCM: During dilated cardiomyopathy.

DCM and 50 clinically healthy children as a control group in the current study. Table 1 shows the demographics and the clinical data of the studied groups with no significant differences between the two groups regarding age and gender. However, DCM was more prevalent in males than in females (1.8:1). There was also more history of consanguinity and a more positive family history of DCM among children with DCM than in the control group. The table also showed that the patients' group had significantly lower body weight, height, BMI, systolic and diastolic BP, and higher heart rate than the control group. About 58% of the DCM group showed systolic dysfunction when using RV EF measured by 4D echocardiography. The percentage of RV systolic dysfunction increased to 70% when using TAPSE. RV diastolic dysfunction by low RV e´/a´ ratio using tissue Doppler.

Table 2, Figures 5 and 6, show the echocardiographic parameters in both groups. The auto left ventricle ejection fraction measured by STE was significantly lower in the patients' group than in the control. At the same time, the LV SI, which measures the ratio of the LV long axis to the short axis, was significantly lower in the children with

Table 1 Demographic and clinical data of children with during dilated cardiomyopathies and control group

Variables (mean ± SD)	Children with DCM (*n* = 50)	Controls (*n* = 50)	*t*	*P* value
Age	4.9 ± 2.3	5.56 ± 2.4	0.18	> 0.05
Sex				
Male	32 (64.0%)	31 (62%)	ZS: 0.2	> 0.05
Female	18 (36.0%)	19 (38%)	ZS: 0.2	> 0.05
Consanguinity	23 (46%)	5 (10%)	-4	0.0001[1]
Family history of DCM, *n* (%)	4 (8)	0		
Weight	16.92 ± 5.95	20.60 ± 5.97	3	0.002[1]
Length (cm)	98 ± 4.8	105 ± 4.4	7.6	0.0001[1]
BMI	17.6 ± 2.1	18.7 ± 2.5	2.4	0.02[1]
Heart rate	105 ± 12	91 ± 7	7.1	0.0001[1]
Systolic BP	86 ± 8	98 ± 7	8	0/0001[1]
Diastolic BP	63 ± 4	68 ± 5	5.5	0.0001[1]

[1]Significant ($P < 0.05$).

BMI: Body mass index; BP: Blood pressure; ZS: Z-score; DCM: During dilated cardiomyopathy; SD: Standard deviation.

DCM than in control ($P < 0.0001$). The tissue-Doppler derived mitral annulus S wave (which indicates LV systolic function), and e´/a´ ratio (which indicates LV diastolic function) were significantly lower in the patients' group than in control ($P < 0.0001$). It also showed that LV myocardial performance index (MPI) (which reflects the global systolic and diastolic ventricular function) was more prolonged in the patients' group than in the control ($P < 0.0001$). The speckle tracking echocardiography showed that the LV global longitudinal strains (GLS) was more significantly impaired in the patients' group than in the control group ($P < 0.0001$). The table also showed RV echocardiographic parameters in both groups. TAPSE was significantly reduced in children with DCM than in the control. The auto RV EF measured by 4DE and the tissue Doppler-derived S wave and e´/a´ ratio were significantly lower, while RV MPI was more prolonged, and the systolic pulmonary pressure was significantly higher in the children with DCM than in control group. At the same time, the values of RV GLS, RV apical, mid, and basal strains were significantly lower in children with DMC than in the control group.

Table 3 shows the linear regression analysis of RV GLS with some clinical and echocardiographic parameters among the studied children with dilated cardiomyopathy. It was significantly associated with the duration since diagnosis, tricuspid annulus S wave, RV MPI, and TAPSE; while it did not show significant association with age or weight of the patients; RV e´/a´ ratio; or RV EF.

DISCUSSION

Primary DCM is the presence of left or biventricular dilatation with severely impaired systolic function despite the absence of abnormal loading conditions. It is present in approximately 30%-40% of the cases. The pathological involvement is predominantly limited to the myocardium and is associated with a strong genetic inheritance in idiopathic cases[20]. It usually involves LV with some dysfunction of RV with a common clinical presentation of congestive cardiac failure. Recent studies showed the importance of RV dysfunction as a significant prognostic predictor of cardiac mortality [21]. Unfortunately, few studies are concerned with RV function in children with idiopathic DCM.

Assessment of cardiac size and function using various echocardiographic modes is an integral part of evaluating the child's status. Using 4-D echocardiography allows us to have an external view of the heart with multiple internal perspectives[22]. As cardiac dilation precedes dysfunction in many cases of dilated cardiomyopathy, precise assessment of chamber dimensions, indexed according to body surface area, is essential for early diagnosis and the long-term follow-up of DCM[23]. Therefore, a

Table 2 Echocardiographic data of children with dilated cardiomyopathies and control group

Variables (mean ± SD)	Children with DCM (*n* = 50)	Controls (*n* = 50)	*t*	*P* value
LV echocardiographic parameters				
Auto LV EF (speckle tracking)	43.4 ± 11.7	65.2 ± 7.6	11	0.0001[1]
Sphericity index	1.2 ± 0.35	1.6 ± 0.3	6.2	0.0001[1]
Presence of mitral regurgitation, *n* (%)	43 (86)	1 (2)	ZS: 6.6	0.0001[1]
Mitral annulus systolic velocity (cm/sec)	3.7 ± 1.1	6.933 ± 0.785	16.9	0.0001[1]
Mitral annulus e´/a´ ratio	1.15 ± 0.4	1.540 ± 0.246	5.8	0.0001[1]
LV IVRT	75.0 ± 18.3	64.0 ± 7.2	4	0.0001[1]
LV MPI	1.9± 0.3	0.4 ± 0.08	423	0.0001[1]
LV GLS	-12.7 ± 4.9	-24.4 ± 1.6	16	0.0001[1]
RV echocardiographic parameters				
4D RV EF	32.2 ± 10.5	46.2 ± 10.7	8.7	0.0001[1]
Tricuspid annulus S wave (cm/sec)	4.42 ± 0.82	6.9 ± 0.8	15	0.0001[1]
Tricuspid annulus e´/a´ ratio	1.17 ± 0.25	1.52 ± 0.3	6.34	0.0001[1]
RV MPI	0.86 ± 0.16	0.40 ± 0.08	18.2	0.0001[1]
Mean pulmonary pressure (mmHg)	28.5 ± 6	21 ± 4	7.4	0.0001[1]
TAPSE (mm)	12.00 ± 3.56	19.30 ± 2.5	12.5	0.0001[1]
RV GLS	-10.34 ± 4.6	-24.30 ± 2.9	18.5	0.0001[1]
RV apical strain	-13.3 ± 4.3	-26.70 ± 1.3	21	0.0001[1]
RV mid strain	-12.4 ± 3.9	-23.20 ± 1.7	17.9	0.0001[1]
RV basal strain	-13.7 ± 4.8	-25.30 ± 1.5	16.3	0.0001[1]

[1]Significant ($P < 0.05$).

EF: Ejection fraction; LVGLS: Left ventricular global longitudinal systolic strain; IVRT: Isovolumic relaxation time; LV: Left ventricle; MPI: Myocardial Performance Index; RV GLS: Right ventricular global longitudinal systolic strain; TAPSE: Tricuspid annular plane systolic excursion, RV: Right ventricle; ZS: Z-score.

comprehensive echocardiographic examination is indicated in cases with DCM, not only to assess LV size and function, but also to establish the diagnosis, identify the phenotype of DCM and the associated cardiac abnormalities such as valve disease, highlight the features requiring specific therapeutic management, and identify high-risk features associated with an adverse prognosis, including RV dysfunction[11].

Due to the complex three-dimensional geometry of RV wall motion (which affects the evaluation accuracy of the local dynamics derived indices), there is a need to quantify these factors accurately, which becomes possible by using 4-D echocardiography. The relatively newly developed real time 4-D echocardiography has the potential to circumvent the limitations induced by the RV complex anatomy as it does not rely on 2-D views[24]. In the current study, we assessed LV and RV functions using recent echocardiographic modalities (tissue Doppler, speckle tracking, and real-time 4-D echocardiography) in children with dilated cardiomyopathy. We found a marked reduction of LV systolic ejection fraction (EF) measured by real-time 3-Dimensional echocardiography compared to the control. Similar findings were reported by Gentile *et al*[25] which support that EF is an easy and sensitive tool for evaluating LV systolic function.

Tissue Doppler-derived mitral annulus systolic velocity (S wave) was significantly lower in our patients' group than the control, matched with previous studies confirming usefulness for measuring the S as a tool for assessing systolic function. There was also a significant reduction of the mean value of LV (e´/a´ ratio) in our cases with DCM compared to control, clarifying the effect of LV systolic impairment on LV diastolic function[26,27]. These data confirm the presence of diastolic dysfunction in patients with dilated cardiomyopathy and impaired LV filling, which may even precede the presence of systolic dysfunction. These findings agreed with

Table 3 Multiple linear regression showing clinical and echocardiographic parameters that were independently associated with the longitudinal strain of the right ventricle among the studied children with dilated cardiomyopathy (*n* = 50)

Variables	RV LGS (%) among children with dilated cardiomyopathy (*n* = 50)	
	β standardized coefficients	*P* value
Age (yr)	-0.274	0.057
Duration since diagnosis	0.578	0.001[1]
Weight (kg)	0.273	0.058
Tricuspid annulus (S) (cm/sec)	0.384	0.008[1]
RV e´/a´ ratio	0.277	0.059
RV MPI	-0.357	0.01[1]
RV EF (%)	0.119	0.435
TAPSE (mm)	0.670	0.0001[1]

[1]Significant ($P < 0.05$).

RV EF: Right ventricular ejection fraction; LS: Longitudinal strain; MPI: Myocardial performance index; S: systolic velocity by tissue Doppler; TAPSE: Tricuspid annular plane systolic excursion.

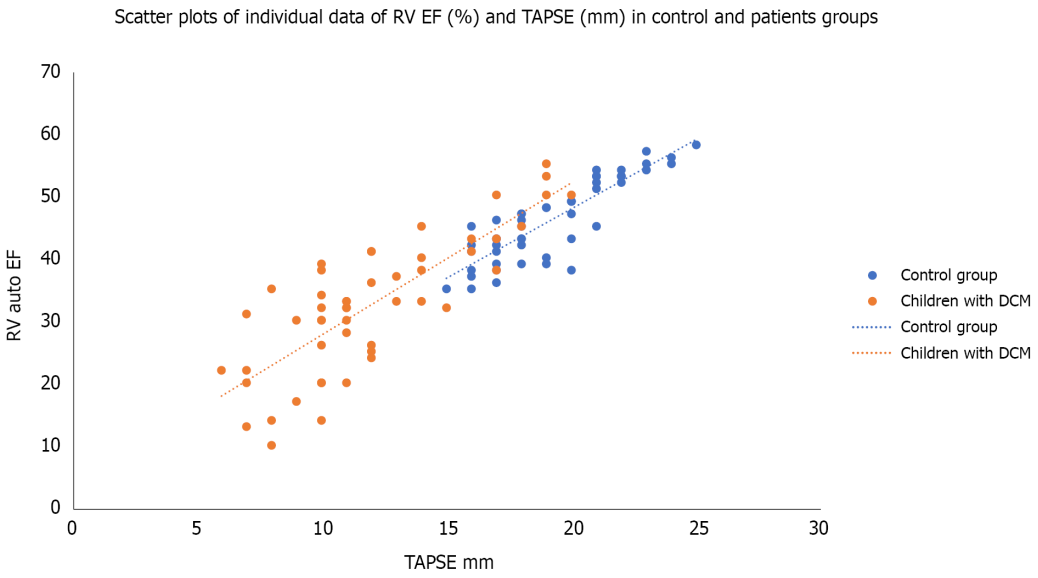

Figure 5 Scatter plots of individual data of Right Ventricular Ejection Fraction (%) and tricuspid annular plane systolic excursion (mm) in control and patients' groups. DCM: During dilated cardiomyopathy; RV EF: Right ventricular ejection fraction; TAPSE: Tricuspid annular plane systolic excursion.

Friedberg *et al*[28] who found that diastolic dysfunction and mechanical desynchrony were more common in children with DCM than in the control. Like other previous reports[26,29], the tissue Doppler-derived MPI of LV in DCM cases was significantly prolonged compared to control, in the current study. This finding could be related to LV systolic and diastolic dysfunction reported in our patients, as the MPI reflects both the systolic and diastolic function of the ventricles.

There is a strong need to assess the SI in patients with DCM due to the presence of a broad spectrum of LV trabeculations, the dynamic interaction between subendocardial and subepicardial fiber helices in LV, and the increase in LV end-diastolic and end-systolic volumes. In addition, the presence of a broad spectrum of LV trabeculations among heart diseases, especially in DCM, could make differentiation of LV non-compaction cardiomyopathy from DCM difficult[30]. Meanwhile, the dynamic interaction between subendocardial and subepicardial fiber helices in LV causing twisting deformation plays a vital role in LV function[31].

The increase in LV end-diastolic and end-systolic volumes causes an increase in the myocardial mass and a change in the chamber geometry to a more spherical shape

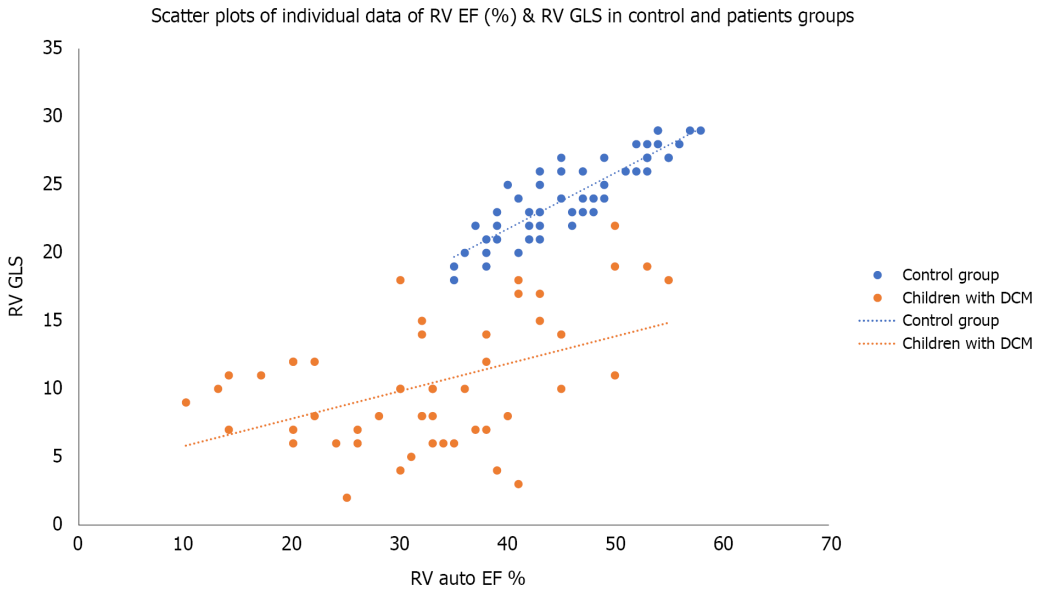

Figure 6 Scatter plots of individual data of right ventricular ejection fraction (%) and right ventricular global longitudinal strain (mm) in control and patients' groups. DCM: During dilated cardiomyopathy; RV EF: Right ventricular ejection fraction; GLS: Global longitudinal strains.

because of heart failure[30]. In the current study, there was a significant reduction in the SI of patients when compared with the controls. Previous studies supported that the LV SI was the strongest independent predictor of basal and apical LV peak systolic rotation and instantaneous LV peak systolic twist. So, LV apical rotation and twist are significantly influenced by LV configuration[13,32].

Ventricular strain can be determined by TDI, 2-D STE (which determines LV GLS %). Unlike the TDI-derived strain, which is angle-dependent, 2-D STE is less angle-dependent and can measure the strain by tracking the speckles, which are acoustic backscatter generated by ultrasound interactions with the myocardium[33]. Due to the complex orientation of the fibers in the intact LV wall, the myocardial deformation occurs in three dimensions and can be characterized not only in the longitudinal direction but also in the circumferential and radial directions. Sub-epicardial fibers play a significant role in radial and longitudinal strains, and sub-endocardial fibers play an essential role in circumferential strain. In the current study, LV GLS was significantly impaired in children with DCM compared to control. This finding agreed with several publications reporting different types of systolic strain impairment in patients with DCM[34].

Assessment of the RV function is paramount, especially in predicting the outcome, as it plays an important role in determining cardiac symptoms and exercise capacity in chronic heart failure. However, it is not easy to study the RV due to its complex anatomy and physiology. The current study showed a significant systolic dysfunction of the RV (as indicated by the reduced RV EF, TAPSE, and S', and increased RV MPI) in children with DCM compared to the controls. RV dysfunction may be due to the close interaction between LV and RV function. The RV has mainly transverse muscle fibers in its free wall and shares oblique fibers in the IVS with the LV. Subsequently, its contraction augments RV contraction; a condition defined as systolic ventricular interaction[21].

The presence of MR further impairs the already compromised LV systolic and diastolic functions observed in children with DCM. The resulting dysfunction consequently led to pulmonary venous congestion, pulmonary hypertension, and increasing the RV afterload. Furthermore, these changes make the RV contraction more dependent on the oblique septal fibers, which are mechanically more efficient than the transverse fibers in the free wall. Besides, the marked impairment of the global LV deformation (including the IVS containing these oblique fibers) further reduces the systolic ventricular interaction and reduces the RV deformation. Moreover, as the LV acquires a more spherical shape, the septal fibers become less oblique, decreasing their mechanical efficiency with more and more deterioration of the RV deformation. This deterioration will further impair the RV GLS, as observed in our study. This finding also agreed with several publications reporting the decrease of the longitudinal systolic strain in cases of dilated cardiomyopathy[26,35].

The current study reported a significant RV GLS with tricuspid annulus S wave, RV MPI, and TABSE. However, the RV GLS was not associated with either the RV EF or RV e´/a´ ratio. Although RV MPI, RV S, and RV TABSE are tissue-dependent factors, reflecting the RV systolic function, they are more reliable than RV EF, which is load-dependent. This finding agreed with the work done by Agha *et al*[6] 2015, who found that TAPSE, S wave, and RV MPI were significantly correlated with the LV GLS. However, they also found a positive correlation of e´ wave and e´/a´ ratio with the LV GLS[6]. The differences between the current study and their study arise because they correlated the RV MPI, RV S wave, RV e´/a´ ratio, and RV TABSE with LV GLS and not RV GLS as observed in our study. Another difference was using the linear regression analysis in the current study to avoid any confounding factor. Seo *et al*[7] also found a significant association of the RV-Free wall LS with the prognosis in patients with DCM. Similarly, Zairi *et al*[8] found that TAPSE, S, Tei index, and strain of the lateral wall of the RV were independent predictors of major cardiovascular events in non-ischemic dilated cardiomyopathy. Tigen *et al*[9] also observed that the RV free wall basal segment longitudinal strain was sensitive to predict RV systolic dysfunction.

Early recognition of the RV dysfunction could help early detection of complications; and give us enough window to interfere with aggressive intervention, including cardiac transplantation, to avoid the increase in mortality rate. However, there are some limitations to the current study. The study was conducted as a cross-sectional study without doing serial echocardiographic examination and relating worsening cardiac function with the possibility of complications. The study also had relatively few numbers of patients.

CONCLUSION

There was impairment of the RV LGS and other systolic and diastolic parameters in children with DCM. Speckle tracking echocardiography and tissue Doppler can help detect the RV function's early decline, which serves as a good prognostic factor.

ARTICLE HIGHLIGHTS

Research background

Dilated cardiomyopathy (DCM) is a clinical condition associated with left ventricular (LV) or biventricular dilation with an impaired contraction. Clinical presentation of DCM mainly relates to the degree of LV or biventricular systolic dysfunction leading to pump failure.

Research motivation

To diagnose early cardiac dysfunction in dilated cardiomyopathy, we need to perform a cardiac examination using a tool with high sensitivity. M-mode, 2-dimensional echocardiography, tissue Doppler imaging (TDI), and Two-dimensional speckle tracking imaging are commonly used echocardiographic modalities to provide accurate and early detection of cardiac dysfunction.

Research objectives

The study aimed to evaluate right ventricular (RV) function in children with idiopathic DCM using relatively recent echocardiographic modalities.

Research methods

The study was a prospective case-control study, including 50 children with idiopathic DCM and 50 healthy children as a control group, to study RV function using four-dimensional echocardiography (4-DE), TDI, and two-dimensional-speckles tracking echocardiography (2-D-STE). RV ejection fractions (EF) was measured by 4-DE.

Research results

The auto left (LV) EF measured by 2-D-STE were significantly lower in the patients' group than in the control. The sphericity index was also significantly lower in children with DCM than in the control. RV EF measured by 4-DE was significantly lower in the patient's group than the control. RV S wave, e´/a´ ratio, myocardial performance index

(MPI), and tricuspid annular plane systolic excursion (TAPSE) were significantly impaired in children with DCM than in control. Both LV and RV global longitudinal strains (GLS) were significantly reduced in children with DCM than in control. RVGLS was significantly associated with the duration since diagnosis, tricuspid annulus S wave, RV MPI, and TAPSE, but not with the age of the patients, RV EF, or e´/a´ ratio.

Research conclusions

Impairment of the RV LGS and other systolic and diastolic parameters in children with DCM using STE and TDI can help detect RV function's early decline.

Research perspectives

We need to do a serial long-term echocardiographic study and relate worsening cardiac function to the possibility of complications.

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ORIGINAL ARTICLE

Observational Study

Correlation of cardiac troponin T levels with inotrope requirement, hypoxic-ischemic encephalopathy, and survival in asphyxiated neonates

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Author contributions: Yellanthoor RB and Rajamanickam D conceptualized the study, analyzed and interpreted the data; Rajamanickam D collected the data; Yellanthoor RB wrote the manuscript and critically revised it; both Yellanthoor RB and Rajamanickam D approved the final manuscript.

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Abstract

BACKGROUND

Cardiac involvement in neonates with perinatal asphyxia not only complicates perinatal management but also contributes to increased mortality.

AIM

To assess cardiac troponin T (cTnT) levels in asphyxiated neonates and their correlation with echocardiography findings, inotrope requirement, hypoxic-ischemic encephalopathy (HIE) stages, and mortality.

METHODS

cTnT levels, echocardiographic findings, the requirement of inotropes, HIE stages, and outcome were studied in neonates of gestational age ≥ 34 wk with perinatal asphyxia.

RESULTS

Among 57 neonates with perinatal asphyxia, male gender, cesarean section, forceps/vacuum-assisted vaginal delivery and late preterm included 33 (57.9%), 23 (40.4%), 3 (5.3%), and 12 (21.1%) respectively. The mean gestational age was 38.4 wk (1.6 wk). HIE stages I, II, and III were observed in 7 (12.3%), 37 (64.9%), and 9 (15.8%) neonates respectively. 26 (45.6%) neonates had echocardiographic changes and 19 (33.3%) required inotropes. cTnT levels were elevated in 41 (71.9%) neonates [median (IQR); 0.285 (0.211-0.422) ng/mL]. The Median cTnT level showed an increasing trend with increasing changes in echocardiography (P = 0.002). Two neonates with mitral regurgitation and global hypokinesia had the

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highest cTnT levels (1.99 and 0.651 ng/mL). Of 31 neonates with normal echocardiography, 18 (58.06%) showed elevated cTnT. cTnT levels were significantly higher in those who required inotropic support than those who did not (P = 0.007). Neonates with HIE stage III had significantly higher cTnT levels compared to those with HIE stage I/II (P = 0.013). Survivors had lower median cTnT levels [0.210 (0.122-0.316) ng/mL] than who succumbed [0.597 (0.356-1.146) ng/mL].

CONCLUSION
cTnT levels suggestive of cardiac involvement were observed in 71.9% of asphyxiated neonates. cTnT levels correlated with echocardiography findings, inotrope requirement, HIE stages, and mortality.

Key Words: Asphyxia; Cardiac dysfunction; Inotropes; Neonates; troponin T; Survival

Core Tip: Cardiac involvement in perinatal asphyxia complicates the management and increases mortality. We assessed cardiac troponin T (cTnT) levels in asphyxiated neonates and their correlation with echocardiography findings, hypoxic-ischemic encephalopathy (HIE) stages, and mortality. Elevated cTnT levels suggestive of cardiac involvement were found in 71.9% of neonates and correlated with increasing grades of ischemic changes in echocardiography. cTnT levels were elevated in 58% of neonates in the absence of echocardiographic findings. Significantly higher cTnT levels in neonates with HIE stage III than those with HIE stage I and II as well as higher cTnT levels in non-survivors than survivors show its predictive role.

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INTRODUCTION

The myocardium is vulnerable to ischemic injury in asphyxiated neonates[1-5]. Perinatal asphyxia causes significant morbidity and mortality, especially in developing countries[6-9]. The cardiac involvement in perinatal asphyxia varies. The reported asphyxial cardiomyopathy in neonates ranges from 24%-78%[3-6].

Ischemic cardiac dysfunction results in decreased cardiovascular reserve. The affected neonates may present with myocardial failure, bradycardia, and hypotension along with morbidities related to other systems. The assessment of the extent of myocardial injury and appropriate management influence treatment and outcome. Clinical assessment alone is considered inadequate to guide management or predict the outcome. Serum creatinine kinase muscle-brain isoenzyme (CK-MB) lacks cardiac specificity in the neonate and the levels are affected by gestational age, mode of delivery, and birth weight. CK-MB levels were reported to be 2 to 5 times higher in neonates born by normal vaginal delivery as compared to those born by cesarean section[2]. Echocardiography helps in identifying the extent of cardiac dysfunction but needs expertise.

Cardiac troponin T (cTnT) has been explored as a more specific biomarker for the diagnosis of myocardial injury in asphyxiated neonates[10,11]. Troponin T can be detected at earlier stages than CK-MB and it also remains high for a longer period[10]. Further, cTnT levels are found to be elevated in 30%-50% of cases having normal CK-MB levels[2]. The levels also may correlate with mortality. In this context, we aimed to evaluate the role of cTnT in perinatally asphyxiated neonates as a marker of myocardial injury and assess its correlation with inotrope use, hypoxic-ischemic encephalopathy (HIE), and mortality.

MATERIALS AND METHODS

Neonates of gestational age ≥ 34 wk with perinatal asphyxia were prospectively studied over two years in a neonatal intensive care unit of a University teaching hospital. The demographic and birth details, clinical examination data were collected. cTnT levels, echocardiographic findings, the requirement of inotropes, evidence of other system involvement, HIE in particular, and outcome were collected.

About 0.5 mL of blood collected using standard sampling tubes (BD red vacutainers) was processed for estimation of cTnT levels. Biochemical analysis of cTnT levels in this study was done with an Elecsys 2010 and Cobase 411 analyzer using the Elecsys Troponin Ths (high sensitive) STAT (short turnaround time) Immunoassay (Roche Diagnostics, Germany). This is an electrochemiluminescent sandwich enzyme-linked immunosorbent assay. The total duration of the assay is 9 min. The lower limit of detection is 3 ng/L or 3 pg/mL, if the values are below this level it was reported as < 3 ng/L. The upper limit of detection is 10000 ng/L or 10000 pg/mL, if the values are above this level it was reported as > 10000 ng/L or up to 100000 ng/L for the 10-fold diluted sample. The kit specifications include the sensitivity of 99% and specificity of 98% at 100 ng/L and, the sensitivity of 100% and specificity of 75% at 14 ng/L. Normal values for cTnT: Interquartile Range: 0.01–0.062/mL, 95th centile: 0.153 ng/mL, 99th centile: 0.244 ng/mL. For the study purpose, cTnT levels of more than 0.15 ng/mL were considered elevated.

Neonate was considered to have perinatal asphyxia if he/she met any of the following criteria: Need of bag and mask or bag and tube ventilation at birth with Apgar score of ≤ 6 at 5 min; hypoxic encephalopathy features (lethargy, seizures, hypotonia, coma or irritability); cord blood pH ≤ 7.0, or arterial pH in neonates ≤ 7.2. Neonates with congenital heart defects, major anomalies, and those who expired within the first hour of birth were excluded.

HIE was considered in asphyxiated neonates if they had neurologic manifestations (seizures, coma, hypotonia). HIE was divided into Sarnat stages 1, 2, and 3 based on standard clinical features[3,4,12]. Heart rate < 100/min was considered bradycardia. Systolic and or diastolic blood pressure (BP) equal to or lower than the 5th percentile for age and sex was considered hypotension. Capillary filling time (CFT) > 3 s was considered as increased CFT.

Echocardiograph was obtained with the "Philips CX-50" machine. Following echocardiographic findings were considered as suggestive of myocardial ischemia: Mitral regurgitation (MR) or right ventricular (RV)/left ventricular (LV)/global hypokinesia, tricuspid regurgitation (TR), and pulmonary artery hypertension (PAH) with TR[2]. Renal dysfunction was considered if creatinine level was more than the upper limit of the normal reference range for gestational age with or without urine output < 1 mL/kg/h[2]. Transaminase levels more than twice the normal levels (normal aspartate transaminase (AST) up to 40 U/L and alanine transaminase (ALT) up to 45 U/L) were considered as hepatic dysfunction.

The results are expressed as frequencies and percentages. Data were analyzed using SPSS v16.0 software. Differences in the median of quantitative data among different stages of HIE and echocardiographic changes were compared by Kruskal- Wallis test and proportions by Chi-Square tests. A $P < 0.05$ was considered statistically significant. Ethical approval was obtained from the Institutional Ethical Committee. Informed consent was obtained from the parents.

RESULTS

This study included 57 neonates with perinatal asphyxia (Figure 1). Male gender, lower segment cesarean section (LSCS), forceps or vacuum-assisted vaginal delivery, and late preterm included 33 (57.9%), 23 (40.4%), 3 (5.3%), and 12 (21.1%) respectively. The mean gestational age was 38.4 ± 1.6 wk.

Mode of resuscitation at birth included intubation in 26 (45.6%) and bag and mask ventilation in 15 (26.3%). Organ involvement in perinatal asphyxia included brain in 53 (93%), hepatic in 35 (61.4%), renal in 26 (45.6%), and cardiac in 30 (52.6%). Mechanical ventilation was needed in 20 (35.1%) neonates. HIE stage 1, 2 and 3 were observed in 7 (12.3%), 37 (64.9%) and 9 (15.8%) neonates respectively. Four neonates did not have HIE. Six neonates died.

Of 57 asphyxiated neonates, 26 (45.6%) neonates had echocardiographic changes. MR with global hypokinesia was observed in two (3.5%) neonates. Inotropic support was required in 19 (33.3%) neonates.

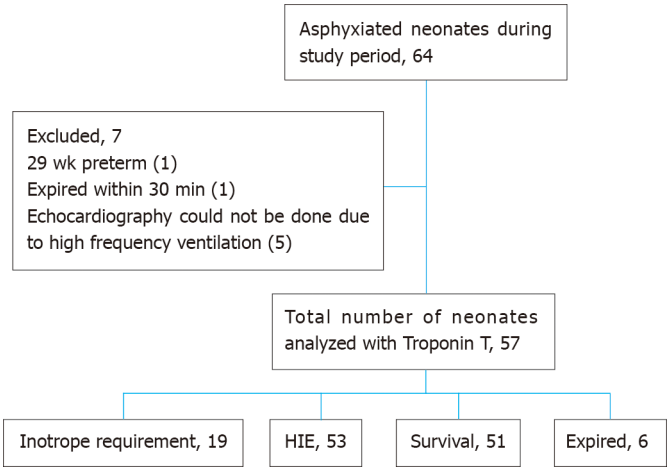

Figure 1 Study flow chart. HIE: Hypoxic-ischemic encephalopathy.

Elevated cTnT levels were observed in 41 (71.9%) neonates studied, with median (IQR) of 0.285 (0.211-0.422) ng/mL. The maximum value observed was 1.99 ng/mL (Table 1).

The median cTnT level showed an increasing trend with the increase in changes in echocardiography (P = 0.002 Kruskal-Wallis Test) (Table 2). MR with global hypokinesia was observed in two neonates with high cTnT levels (1.99, 0.651 ng/mL) who eventually succumbed. Of 31 neonates with normal echocardiography findings, 18 (58.06%) cases had elevated cTnT levels.

cTnT levels in those who required inotropic support were significantly higher when compared to those who did not require inotropic support (P = 0.007, Chi-Square test) (Table 3).

Neonates who had HIE stage III had significantly higher levels of cTnT levels when compared to neonates with HIE stage I and II (P = 0.013 Kruskal-Wallis test) (Table 4). Six out of these 9 neonates with HIE stage III, having much higher cTnT levels succumbed.

Six neonates among 57 enrolled with perinatal asphyxia died. Median cTnT levels in those who survived were 0.210 (0.122-0.316) ng/mL which is comparatively lower than the median cTnT level in those who succumbed [0.597 (0.356-1.146) ng/mL] (Table 5).

DISCUSSION

Cardiac involvement secondary to tissue ischemia in neonates with perinatal asphyxia can occur as a part of a multi-organ involvement or isolated cardiac event[12-16]. Myocardium involvement not only complicates perinatal management but also increases mortality. The present study has identified the significant role of cTnT levels in identifying cardiac involvement, its correlation with echocardiography findings, inotrope requirement, HIE stages, and mortality.

In severely asphyxiated infants, cardiac dysfunction more commonly affects the right ventricle. The various manifestations related to cardiac dysfunction are respiratory distress, congestive cardiac failure, hypotension, delayed capillary refilling time, bradycardia, cardiogenic shock, and systolic murmur due to MR and TR[8,17]. Sinus bradycardia and lowered systemic BP are commonly seen in neonatal hypoxic ischemia. These features are observed in the present study. Costa *et al*[18] looked at BP in asphyxiated newborns. They observed significantly lower systolic and diastolic BPs in asphyxiated neonates compared to control newborns[18]. Hypotension is a late sign of under-perfusion. Hypotension is often due to peripheral vasodilatation or poor cardiac output. González de Dios *et al*[19] studied cardiac involvement (n = 31) in 156 asphyxiated term neonates. They categorized dysrhythmias and mild hypotension as minor cardiac involvement and TR, myocardial ischemia, cardiogenic shock, or hypovolemic shock as major cardiac involvement[19].

Echocardiography certainly could guide the management of these infants about fluid resuscitation and choice of inotropic support. Echocardiography is helpful in the early identification of tricuspid insufficiency, compromised LV output, and stroke volume in infants who suffer from perinatal asphyxia. Echocardiographic findings

Table 1 Cardiac troponin T levels in perinatally asphyxiated neonates

cTnT levels (ng/mL)	*n* (%)	Median	IQR
Normal	16 (28.1)	0.084	0.052-0.114
Elevated	41 (71.9)	0.285	0.211-0.422

cTnT: Cardiac troponin T.

Table 2 Correlation of cardiac troponin T levels with echocardiograph findings (*n* = 57)

Echocardiograph findings	*n* (%)	cTnT levels (ng/mL); median (IQR)
Normal	31 (54.4)	0.193 (0.085-0.282)
TR	8 (14.03)	0.223 (0.199-0.266)
PAH with TR	16 (28.07)	0.405 (0.228-0.557)
MR + Global hypokinesia	2 (3.5)	1.99, 0.651[1]

[1]Exact values mentioned.
TR: Tricuspid regurgitation; PAH: Pulmonary artery hypertension; MR: Mitral regurgitation; cTnT: Cardiac troponin T.

Table 3 Correlation of cardiac troponin T levels with inotrope requirement (*n* = 57)

Inotrope use	*n* (%)	cTnT levels (ng/mL); median (IQR)
Inotrope not required	38 (66.6)	0.192 (0.087-0.272)
Inotrope required	19 (33.4)	0.394 (0.269-0.543)

cTnT: Cardiac troponin T.

Table 4 Correlation of cardiac troponin T levels with stages of hypoxic ischemic encephalopathy (*n* = 53)

HIE stages	*n* (%)	cTnT levels (ng/mL); median (IQR)
Stage 1	7 (13.2)	0.086 (0.047-0.271)
Stage 2	37 (69.8)	0.255 (0.133-0.349)
Stage 3	9 (17.0)	0.394 (0.239-0.758)

cTnT: Cardiac troponin T; HIE: Hypoxic-ischemic encephalopathy.

Table 5 Correlation of cardiac troponin T levels with survival (*n* = 57)

	n (%)	cTnT levels (ng/mL); median (IQR)
Survived	51 (89.5)	0.210 (0.122-0.316)
Succumbed	6 (10.5)	0.597 (0.356-1.146)

cTnT: Cardiac troponin T.

such as regional wall abnormalities, increased echogenicity of papillary muscle, compromised LV function, and tricuspid or mitral valve insufficiency resulting in reduced contractility, low cardiac output, decreased stroke volume, and elevated pressure of pulmonary artery suggest myocardial ischemia[17,19]. The mitral valve insufficiency and patent ductus arteriosus correlate with severe degrees of asphyxia injury. Tricuspid insufficiency was observed significantly at a higher rate in as-

phyxiated neonates than healthy neonates and it was more frequent with increasing severity of asphyxia[18]. Most of these features were observed as the main findings in echocardiography in the present study.

In asphyxiated neonates, despite preferential myocardial perfusion, hypoxia leads to myocardial damage. If ischemia progresses, especially beyond 20 min, over 60% of the cellular adenosine triphosphate will be used up, lactate in myocardial tissue increases about 12 times, glycogen and creatine phosphate reserves decrease resulting in dramatic structural changes[10,20,21]. This also causes damage to the cell membrane and releases CK-MB and cTnT into the bloodstream. CK-MB levels although significantly elevated in asphyxiated infants they do not appear to discriminate well those infants with cardiovascular compromise[10,21]. The highest levels occur at 12 h following birth and the levels decrease by 48 h of life[20].

The structure of troponin T is unique to the myocardium. Troponin concentration in the myocardium is much higher compared to CK-MB. In healthy humans, troponin levels in plasma are negligible. The troponin levels raise within a few hours after the acute ischemic episode and remain high for 10–14 d. This increases the diagnostic time range[2].

The present study has identified elevated cTnT levels in 71.9% of asphyxiated neonates and established a correlation of these levels with echocardiographic findings. Costa *et al*[18] reported significantly higher cTnT in neonates having echocardiograph signs of myocardial damage[18]. They also found that cTnT levels in neonates suffering from asphyxia with echocardiography changes were higher compared with those of normal newborns. TR was observed in all asphyxiated neonates. The cTnT levels ≥ 0.21 ng/mL had a significant association with abnormal echocardiographic findings. This cTnT level had 100% specificity and 39% sensitivity. The authors suggested the cTnT 0.19 ng/mL as the differentiating cut-off level. In the present study, all neonates with echocardiographic findings of asphyxia had cTnT levels beyond this cut of value. The two neonates with global hypokinesia on echocardiograph had the highest cTnT levels and both of them died.

Myocardial dysfunction also impacts cerebral hemodynamics and decreases cerebral perfusion[22-25]. Cerebral hemodynamic disturbances such as a decreased rate of flow of blood including the velocity of highest systolic blood flow and velocity of blood flow at the end of diastole, raised index of pulsatility and resistance observed among neonates suffering from perinatal asphyxia are more frequent in infants who have cardiac dysfunction affecting the left ventricle. In the present study, neonates with HIE stage 3 had the highest cTnT levels. Higher cTnT levels in neonates with HIE and its correlation with mortality was also reported by Bhasin and Kohli[25] The limitation of the present study includes not analyzing the values of cTnT during therapeutic hypothermia and its changes as a prognostic marker of the final outcome.

CONCLUSION

Elevated cTnT levels suggestive of cardiac involvement in 71.9% of asphyxiated neonates establish its importance. The cTnT levels correlate with an increasing grade in echocardiography findings. Elevated cTnT levels in 58% of neonates with normal echocardiography findings suggest its biomarker role even in the absence of echocardiographic findings. Elevated cTnT levels in neonates with HIE stage III being significantly higher than those with HIE stage I and II show its predictive role. cTnT levels in non-survivors are likely to be much higher than those among survivors.

ARTICLE HIGHLIGHTS

Research background

The myocardial ischemic injury in asphyxiated neonates complicates management and may lead to higher mortality. Cardiac troponin T (cTnT) levels are expected to rise early in myocardial ischemia and remain high for about two weeks.

Research motivation

cTnT levels are better markers than Serum creatinine kinase muscle-brain isoenzyme levels and could be predictive of mortality.

Research objectives
The present study determined cTnT levels in asphyxiated neonates and found out its relationship with echocardiography findings, inotrope requirement, hypoxic-ischemic encephalopathy (HIE) stages, and mortality.

Research methods
cTnT levels are estimated in all asphyxiated neonates along with echocardiography evaluation.

Research results
Among asphyxiated neonates, cTnT levels were elevated in 71.9%. Further, the cTnT levels correlated with increasing grades of ischemic changes in echocardiography. Elevated cTnT levels in 58% of neonates with normal echocardiography findings suggested its role as a biomarker. cTnT levels in neonates with HIE stage III were significantly higher than those with HIE stage I and II. cTnT levels were higher in non-survivors than survivors.

Research conclusions
cTnT could be a potential and clinically useful biomarker for asphyxia related myocardial injury in neonates.

Research perspectives
Further studies to determine the exact cut of levels of cTnT predicting mortality are needed.

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