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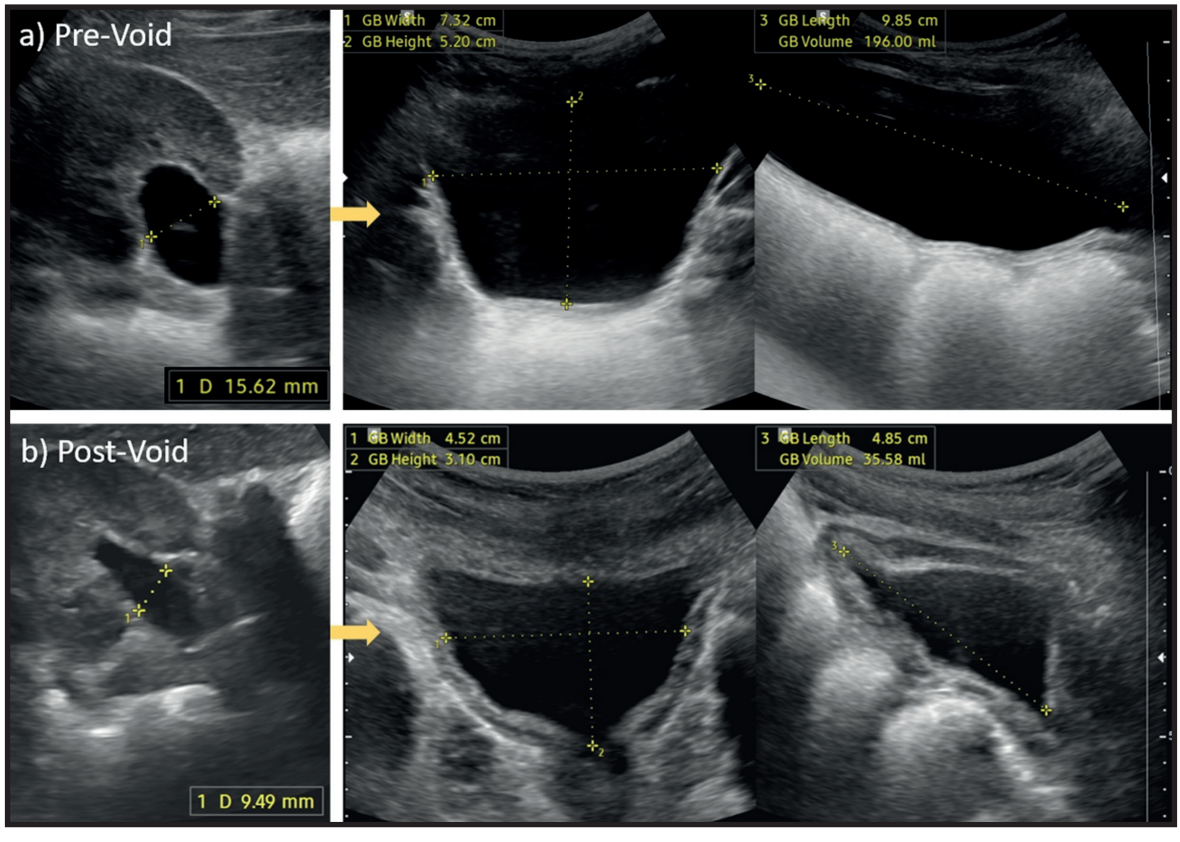

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Review

The importance of preoperative preparation of pediatric patients

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ABSTRACT

Preoperative preparation is a complex series of steps aimed at establishing the conditions for selecting an individualized perioperative plan, bringing the child to the best possible state of health state, stabilizing higher-risk patients and reducing them to a lower-risk stage, informing parents about the type of anesthesia planned and the potential risks and complications, and minimizing parental anxiety. However, anticipation and the route to surgery create preoperative anxiety in children and their parents. Under conditions of increased stress, the child's cooperativeness decreases, the requisite dosages of medications for premedication and induction increase, delirium may occur, and wound healing and recovery as a whole are prolonged. Sensitivity to pain also increases, leading to longer hospital stays and less satisfaction among patients and parents. Premedication is tailored to each patient based on age, body weight, health status, psychological profile, and the extent of the intervention. A thorough discussion with the anesthesiologist, a detailed examination, and an individualized anesthetic plan can minimize these effects. This paper describes pharmacological methods of preoperative preparation, provides recommended dosages, and draws attention to the potential side effects of the medications.

Keywords: preoperative preparation, anxiety, premedication, sedation

INTRODUCTION

Preoperative preparation is a complex series of steps that constitutes the anesthesiologist's daily routine. At the beginning of one's professional engagement, such preparation can seem confusing due to the numerous steps involved, but it gradually becomes routine. The importance of optimal preoperative preparation is only truly appreciated in its absence or during the management of emergencies. The goals of preoperative patient evaluation and preparation in the pediatric setting are to establish the conditions for selecting an individualized perioperative plan, to bring the child to the best possible state of health, to stabilize higher-risk patients and reduce them to a lower-risk stage, to inform parents about the type of anesthesia planned and the potential risks and complications, and to minimize parental anxiety so that all attention is focused on the child.[1] Increased anxiety levels in parents can cause heightened anxiety levels in their children.[2] Preoperative evaluation considers the unique physiological and psychological characteristics of each child, and tailored preoperative assessments are essential to ensure safe surgical outcomes and minimize risks. The key components of the pre-anesthetic visit include a review of the child's personal and family medical history, a clinical examination, laboratory analyses, and diagnostic procedures. Once sufficient data about the patient have been collected, the job of the anesthesiologist is to create an anesthetic plan for preoperative preparation, premedication, anesthetic technique, pain control, and possible treatment in the

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intensive care unit (ICU). Premedication is aimed at ensuring the safest possible conditions for administering anesthesia by using the advantages posed by behavioral preparation and pharmacological procedures. Each physical examination concludes with the signing of an informed consent form by the parents or the child, one which specifically focuses on anesthesia and the specific type of surgery.[3,4] Premedication is tailored to each patient based on age, body weight, health status, psychological profile, and the extent of the intervention. Premedication is essential for every patient, precisely because it acts on the blockade of vagal reflexes, reduces secretion in the respiratory system, ensures an accurate medical history, provides preemptive analgesia, and reduces the likelihood of postoperative delirium. This is especially important for patients with special needs, those undergoing complicated surgical interventions, and children with repeated surgical procedures.[5]

History-taking: The skill and art of the physician

In the context of the patient's personal history, it is important to obtain detailed information about the current surgical treatment since this can guide the anesthetic process. A surgical problem can lead to a range of symptoms in a child that will need to be addressed, such as hyperpyrexia, psychological distress, non-cooperation, dehydration due to excessive vomiting or diarrhea, recent consumption of large meals, or significant bleeding. If the patient is traumatized, information may even be collected from witnesses, parents, guardians, or members of the medical team. It is particularly important to determine the mechanism of injury and the circumstances surrounding it.

The next task is to elicit further information about the patient's previous illnesses, chronic conditions, previous surgeries, allergies, chronic therapies, reasons for previous hospitalizations, and potential complications. It is particularly important to focus on the highest-risk group of patients, namely prematurely born children and term infants who have been treated in neonatal intensive care units (NICUs). These patients represent a challenge for further anesthetic activity due to factors such as respiratory system immaturity, surfactant deficiency, nervous system immaturity, open fetal structures, and underdeveloped liver enzyme systems, as well as many other morphological, biochemical, and functional characteristics.

One significant challenge involves patients receiving chronic therapy. Potential risks in these situations include disease relapse due to therapy exclusion, exacerbation of chronic conditions, allergic reactions, potentiation of adverse effects from the therapy, and interactions between those medications and anesthetics.

Medications that can be safely continued include diuretics (thiazides and furosemide), levothyroxine, immunosuppressants, hyperthyroidism medications, antiepileptics, antipsychotics, corticosteroids, inhalation medications for bronchial obstruction, alpha-blockers, hypnotics, and sedatives. A common scenario in pediatric practice involves patients with microcytic anemia who use iron supplements; the guidelines recommend discontinuing these seven days before surgery. Potassium-sparing diuretics should also be stopped on the day of surgery.

Antidepressants from the monoamine oxidase inhibitor group and anti-tumor necrosis factor (TNF) medications can be safely used up to two weeks before the procedure. In the case of adolescents, contraceptives should be discontinued four weeks in advance. Anticoagulants pose a significant dilemma. Warfarin is becoming increasingly less used in daily practice. However, discontinuation is recommended five days before surgery, with an INR <1.5. In such cases, anticoagulation is performed using bridging with low-molecular-weight heparin (LMWH) at prophylactic or therapeutic doses.

Oral vitamin K can be administered in cases requiring urgent treatment, its effect being expected within 12 hours. A more rapid effect, typically within 6-8 hours, can be expected with the intravenous administration of vitamin K. If the placement or removal of an epidural catheter is planned, LMWH should be paused 12 hours prior to the procedure. In that case, the subsequent dose of LMWH can be safely administered after 4-6 hours. Non-steroidal anti-inflammatory drugs should be discontinued seven days before surgery.

There are various forms of allergies. The most commonly encountered in daily practice include allergies to antibiotics (such as penicillin and cephalosporins), inhaled and nutritional allergens, anesthetics, and latex. It is important to consider mucosal hyperreactivity and the possible development of laryngospasm or bronchospasm during the induction of anesthesia, maintenance, or awakening.

The skilled examiner should also probe for details that parents or children may seek to avoid or dismiss as unimportant. These may include negative habits related to smoking, the use of electronic cigarettes, drug and alcohol consumption, and promiscuous behavior. Social behavior and academic success, as well as cooperation with

peers and the surrounding environment, provide useful insights into the child's intellectual, emotional, and social development.

In terms of hereditary diseases relevant to our assessment, we are interested in the presence of muscle disorders in the family, malignant hyperthermia, confirmed pseudocholinesterase deficiency, predisposition to bleeding or thrombosis, hemolytic anemia, allergies to anesthetics, infectious diseases transmitted through blood (HIV, CMV, hepatitis, etc.), whether either parent has experienced issues with anesthesia, the presence of malignant diseases, and any history of psychiatric problems. It is essential to note the time and type of the patient's last meal, as well as to assess the quantity and type of fluid intake.

Clinical examination and further examinations

The examination begins with observational methods from the first contact with the patient. Consciousness state, skin and mucosal coloration, nutritional status, and signs of dehydration are recorded. The external appearances of patients with some specific syndromes clearly predict the possibility of difficult intubation (such as Pierre-Robin syndrome, Dandy-Walker malformation, and Down syndrome), including visible deformities of the head, thorax, and extremities. It also includes the assessment of loose teeth that may dislocate during laryngoscopy and intubation, which should be noted and communicated to the parents. The remainder of the clinical examination is based on a detailed pediatric assessment tailored to the patient's age.

Further procedures in the investigation are determined by the conclusions reached in the previous two steps. Routine blood work is now a standard method. However, a complete blood count, emphasizing hemoglobin levels, is essential in evaluating children in whom significant intraoperative blood loss may be expected, especially in preterm infants and children with hemoglobinopathies, newborns, and infants up to six months of age. Coagulation status is also mandatory for such types of surgery. Gas analyses should be ordered in cases of suspicion of gas exchange disturbances. Additionally, biochemical analyses of blood and urine should be included depending on the patient's condition. Medication levels do not form part of routine practice. Imaging methods, such as chest X-rays, computed tomography (CT) scans, and magnetic resonance imaging (MRI), are also employed in exceptional cases. Supplementary techniques, including electroencephalography (EEG), electrocardiography (EKG), and evoked potentials (EP), can also be helpful. A rapid drug test, as well as a pregnancy test, may sometimes be required for adolescent patients. Every anesthesiologist is responsible for providing parents with instructions concerning preoperative fasting and explaining the importance of adhering to the dietary regimen before the planned elective procedure. Clear fluids should not be taken one hour before surgery, breast milk four hours before, infant formulas and light meals six hours before, and fatty meals eight hours before surgery.[6,7]

Premedication

Premedication involves a series of pharmacological procedures and behavioral preparation programs aimed at ensuring the safest possible conditions for administering anesthesia. Some 40-60% of children are estimated to exhibit significant stress and anxiety before surgical interventions.[8] This is conditioned by feelings of physical vulnerability, fear of separation from the parents, the hospital environment and staff, anesthesia and surgery, loss of personal integrity, and fear of death. The intensity of fear and anxiety is closely linked to the occurrence of delirium durıng awakening from anesthesia and in the early postoperative period, a time of nightmares, eating disturbances, increased feelings of pain, bedwetting, and separation problems. Significant amounts of stress hormones are released during these times, contributing to delayed wound healing, prolonged feelings of pain, susceptibility to infection, and consequently, slower recovery and longer hospitalization times. The at-risk group consists of children up to three years of age.[9] Preoperative preparation and discussions with the anesthesiologist, psychological support from parents, familiarization with the sequence of events involved, and premedication all contribute to greater patient satisfaction.[5,10] Relative contraindications for the use of premedication are presented in Table 1.[11]

Table 1. Relative contraindications for the use of premedication

Difficult airway	Sepsis	Cyanotic heart defects	Central or obstructive sleep apnea	Desaturation on room air	Neuromuscular diseases
Increased intracranial pressure	Liver or kidney insufficiency	Full stomach	Altered Glasgow Coma Scale score	Proven allergic reaction to premedication drugs	Trauma

These medications can be administered orally, nasally, intravenously (IV), intramuscularly (IM), and rarely rectally. If the medication is given orally, it can be mixed with a sweetened drink, although compounded medications are also available for this purpose. This method of administration should be applied 30 minutes before the planned induction of anesthesia. For nasal administration, special medication formulations with a nebulizer are used, and the doses are determined according to the number of spray puffs. Oral and nasal administration of premedication represents a good option for anxious patients in cases without established venous access. Premedication is administered in specialized rooms designated for that purpose, with essential supervision and monitoring of the premedicated patient and appropriate equipment and medications for resuscitation. Paradoxical reactions to the administered medications are not uncommon, during which an exacerbation of anxiety may be observed.

Medications for preoperative sedation:

1) Benzodiazepines are the most commonly used class of medication (Table 2).

- Midazolam is a short-acting medication with a half-life of approximately two hours. It has the advantage of producing anterograde amnesia. When administered nasally, the medication can irritate the mucous membranes and cause discomfort, and there are also concerns about neurotoxicity due to its direct effect on the olfactory nerve. A paradoxical reaction to midazolam may be expected in some children. In such cases, IV ketamine at a dose of 0.5 mg/kg or flumazenil can be given.
- Lorazepam has a slower onset of action but a longer effect duration. However, it should be avoided in neonates due to neurotoxicity.
- Diazepam is not a popular choice in children. It is mostly used in older children and is administered orally or, more commonly, rectally in the form of a suppository.

The antidote for benzodiazepines is flumazenil, which is used to reverse sedation caused by this class of medications at a dose of 0.01 mg/kg IV over 15 seconds (max 0.05 mg/kg).

2) Barbiturates - these produce their effect by potentiating the inhibitory actions of GABA on the GABA (A) receptor. They are not commonly used for premedication in children since short-acting benzodiazepines have become available. A major disadvantage is hyperalgesia, which can induce agitation in children. Thiopental and methohexital are most commonly employed. Methohexital is the preferred agent for use in electroconvulsive therapy (ECT). However, it is also useful in procedural sedation for cardioversion, as an induction agent for intubation in neonates, and as a sedative in imaging procedures.[12,13] Methohexital is the sedative of choice in ECT since it both reduces the seizure threshold and prolongs seizure duration. The latter is an important consideration during ECT, since the duration of seizures is associated with improved efficacy of ECT[14] (Table 3).

Table 2. Benzodiazepines in premedication of children

Medication	Route of administration	Dose (mg/kg)	Onset of action (min)
Midazolam	Oral	0,5-0,75 (max 20 mg)	20-30
	Nasal	0,2-0,3	10-15
	Rectal	0,5-1	
	IV	0,1-0,2	Few
	IM	0,1-0,15	10-15
	Sublingual	0,2-0,3	10-15
	Nebulizer	0,2	Few
Lorazepam	Oral	0,025-0,05	60
Diazepam	Oral	0,1-0,5	
	Rectal	1	
Flumazenil (antidot)	IV	0,01	

Table 3. Barbiturates as agents for pediatric premedication		
Medication	**Route of administration**	**Dose (mg/kg)**
Thiopental	Rectal	20-40
Methohexital 10%	IV	0.5-2.0
	IM	10

Table 4. Opioids as agents for pediatric premedication		
Medication	**Route of administration**	**Dose (mg/kg)**
Morfin	IM	0,1-0,2 (max 5 mg)
	IV	0,05-0,1
	Oral	0,05-0,1
Fentanyl	Oral (lollipop)	10-15 (250 mcg)
	Nasal (after induction)	1-2
Sufentanil	Nasal	1-3 (max 50 mcg)
Meperidine	IM	1-2 (max 5 mg)
	Oral	1,5
Butorphanol	Nasal	0,025
Tramadol	Oral	1,5
	IV	1,5

3) Non-barbiturate sedatives are not recommended for neonates, since they have an unpleasant taste and can irritate the mucous membranes. These include chlorhydrate 10% (25-75 mg/kg orally at a total maximum dose of 2 g), triclofos sodium (25-100 mg/kg orally), and melatonin (0.25-0.5 mg/kg orally 60 min before the procedure). The pineal hormone melatonin performs several functions, including hypnosis, anxiolysis, sedation, and exhibiting anti-inflammatory activity. It produces a natural sleep and may reduce the incidence of emergence agitation.[15,16]

4) Opioids are rarely used for premedication. Instead, they are primarily employed for preemptive analgesia under strict supervision due to the potential for respiratory depression, nausea, vomiting, and pruritus.[17] Neonates are very sensitive to the respiratory depressant effects of opioids, and these are rarely used to premedicate this age group (Table 4).

5) Ketamine causes the central dissociation of the cortex from the limbic system, thus providing sedation and analgesia without causing respiratory depression while maintaining good cardiorespiratory stability. It also relaxes the smooth musculature of the airway stimulated by histamine and is used in case of a potential risk of bronchoconstriction. One significant advantage is that it can be administered to uncooperative children when an intravenous line has not been established. Expected side effects include hallucinations, sialorrhea, nystagmus, and nausea. Benzodiazepines and anticholinergics (such as atropine and glycopyrrolate) should be given prior to ketamine to mitigate some of these effects. However, even with such preparation, it should still be avoided in children with psychiatric disorders, epilepsy, or eye injuries[17] (Table 5).

Table 5. Ketamine as an agent for pediatric premedication			
Medication	**Route of administration**	**Dose (mg/kg)**	**Onset of action (min)**
Ketamine	Oral	3-6	12
	Nebulizer	2	
	Rectal	5-10	30
	IM	1-10	2-4
	IV	0,25-0,5	<1

Table 6. Alpha-2 agonists as agents for pediatric premedication			
Medication	**Route of administration**	**Dose (mcg/kg)**	**Onset of action (min)**
Clonidine	Oral	3-4	60-90
	Nasal	2	30-60
	IM	2-4	30-60
	Rectal		50
Dexmedetomidine	Oral	2-4	20-30
	Nebulizer	1-3	45

6) Alpha-2 agonists induce dose-dependent sedation through their mechanism of action on the locus cereleus. The use of dexmedetomidine has increased in recent years due to the drug's safety profile since it does not cause respiratory depression or nausea and vomiting. However, it can result in bradycardia and hypotension at higher doses. Clonidine is used in sedation in pediatric intensive care units (PACUs)[18,19] (Table 6).

7) Antihistamines are less frequently used, but exhibit sedative, antiemetic, antihistaminic, and antispasmodic effects. These include hydroxyzine (0.5-1 mg/kg IM) and diphenhydramine hydrochloride (1.5-2 mg/kg orally/IV/IM).

Other medications are used to optimize various cholinergic functions, control pain, manage postoperative nausea and vomiting (PONV), control bacterial infections, and prevent thromboembolic events:

1) Anticholinergic medications include atropine, scopolamine, and glycopyrrolate. These drugs are used

to prevent or treat bradycardia caused by manipulations such as intubation or surgical vagal stimulation. They are often administered in combination with ketamine for their anxiolytic effect, although this can lead to tachycardia and skin flushing. Other significant side effects include dry mucous membranes, hyperthermia, and central nervous system excitation. One representative of this group is atropine (0.01-0.02 mg/kg IV), while glycopyrrolate (0.01 mg/kg), which does not cross the blood-brain barrier, is used in cases of atropine allergy and when a targeted reduction of salivation is desired.[13]

2) Topical anesthetics include EMLA cream, Lidocaine iontophoresis, Ametop, S-Kain patch, and Ela Max.

3) Antiemetics are used when assessment indicates risk factors for PONV, such as a history of PONV, significant blood loss, prolonged surgical interventions, inhalation anesthesia, and specific types of surgeries (e.g., tonsillectomy, strabismus, inner ear surgery, and abdominal or urological operations). If a child has one or two risk factors, a single dose of a 5-HT agonist is administered, while both a 5-HT agonist and dexamethasone are given in the presence of more than three risk factors.

4) Antacids and H_2 receptor antagonists are given to patients with an increased risk of aspiration of gastric contents. This includes patients with trauma, ileus, gastroesophageal reflux, hiatal hernia, or esophageal diseases, obese patients, and children with altered airways.

5) Analgesics: The most commonly used medication for preemptive analgesia is acetaminophen (paracetamol). Dosing varies based on the child's age: neonates: 7.5 mg/kg every 6-8 hours IV; max 30 mg/kg/24 hours, infants up to two years: 10 mg/kg every four hours IV; max 60 mg/kg/24 hours, children up to 15 years: 10-15 mg/kg every six hours IV/orally; max 100 mg/kg/24 hours.

6) Antibiotic prophylaxis: The first dose of antibiotics should be administered 30-60 minutes before incision. A second dose should be repeated during surgeries in which the duration exceeds twice the half-life of the chosen antibiotic or if intraoperative blood loss is estimated to exceed 15% of the patient's blood volume.

7) Prevention of thromboembolic events (TBEs): It is important to assess the risk percentage for each individual patient, including both pharmacological and physical prophylaxis for TBE.[11,20]

CONCLUSION

Preoperative preparation reduces preoperative anxiety, which is frequently observed in pediatric patients and can adversely impact their overall experience. By alleviating anxiety, premedication can lead to smoother inductions and improved outcomes. Additionally, it enhances pain management and minimizes the physiological stress response associated with surgery or invasive procedures. It also contributes to faster recovery times and a lower incidence of postoperative complications. Moreover, premedication can facilitate better communication and cooperation between healthcare providers and young patients, creating a more positive environment for both the child and the family.

Author contribution

Review conception and design: DS; literature review: DK, KS; draft manuscript preparation: IB, IP. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Review

The relationship between autism and autism spectrum disorders and vaccination: review of the current literature

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ABSTRACT

This study evaluates the alleged relationship between childhood vaccination—specifically the MMR (measles, mumps, rubella) and DPT (diphtheria, pertussis, tetanus) vaccines—and the development of autism spectrum disorders (ASD). It addresses public concerns by reviewing existing literature and highlighting the essential role of vaccines in public health. A comprehensive analysis of scientific studies, including systematic reviews, meta-analyses, and population-based investigations, was conducted, with particular attention to research on temporal associations, thimerosal content, and proposed immunological mechanisms. The findings consistently show no causal link between childhood vaccinations and ASD. Neither the MMR vaccine nor thimerosal-containing vaccines were associated with an increased risk of ASD, as confirmed by large-scale cohort studies and international meta-analyses. Additionally, no evidence supports claims that temporal patterns or atypical forms of ASD are related to vaccination. Overall, the current scientific consensus strongly refutes the notion that vaccines cause autism. The findings support the continuation of current immunization programs, stressing the importance of combating misinformation, reinforcing public trust, and safeguarding community health through sustained vaccination efforts. No changes to existing vaccine protocols are warranted.

Keywords: childhood, vaccines, autism, autism spectrum disorder

INTRODUCTION

In the past few years, the concerns regarding the potential relationship between autism and autism spectrum disorders and vaccination have significantly increased. Especially, vaccines such as MMR (measles, mumps, and rubella) and DPT (diphtheria, pertussis, and tetanus) are the ones that are most blamed.[1] The societal worry that childhood vaccination possibly causes autism, increased the distrust in vaccination, thus leading to the resurgence of illnesses (e.g., rubeola, mumps, measles, etc.) that could be prevented by vaccines.[1]

The importance of vaccines on community health is undeniable. Decisions on withdrawing vaccination because of concerns about autism should be attentively evaluated following current evidence. In the last ten years, there have been several pieces of work examining the connection between autism, ASD, and childhood vaccination, and the discussions around it are still proceeding. The search with the keywords “vaccine” and “autism” gives 67,700 article results on Google Scholar; the majority are about MMR and DPT vaccines. This review aims to address the allegations about the link between autism and vaccines from a scientific point of view and to draw attention to this issue, which is highly crucial for community health.

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Background and significance

Autism and Autism Spectrum Disorder (ASD) are lifelong and severe developmental disorders that are characterized by repetitive, limiting, and inflexible behaviors that cause social, communicational (speaking, language), and behavioral (defined and repetitive) difficulties.[2,3] Autism is at the very severe end of the ASD.[3] Symptoms such as mental retardation, epilepsy, and chronic gastrointestinal disorders are common, along with hyperactivity in some cases.[4] Asperger syndrome, the pervasive developmental disorder not otherwise specified (PDD), and autistic disorders are within the ASD categories.[4]

The frequency of ASD is progressively increasing; while the prevalence of autism in the USA was 1 in 2500 children in the mid-80s, it rose to 1 in 300 in the mid-90s.[5] Another study reported that the prevalence of ASD among children aged 6-11 years increased from 3 per 10,000 in 1991-1992 to 52 per 10,000 in 2001-2002.[6] However, it's still unclear whether this increment is real or due to a rise in awareness.[2] Moreover, it is reported that the impact of some environmental risk factors that have not yet been identified should not be ignored.

Parents of children with ASD often notice developmental difficulties in their children in the first year of life.[4] Many parents blame themselves, thinking that the problem may be caused by risky behavior during pregnancy, advanced gestational age, vaccines administered, or a genetic factor.[4,6] The underlying causes of ASD are multifactorial and have a strong genetic component. In very few cases, a specific cause has been identified. Neurological findings associated with autism probably emerge in the early stages of embryonic development.[2] Communication delays and characteristic findings usually become apparent later in life, often after age three. However, since the neuropathological condition underlying autism is present at birth in the majority of cases, it has been suggested that vaccines administered after birth are unlikely to cause autism.[2] In most cases, no abnormal findings may be observed initially during the child's developmental stages; however, developmental stages may regress during follow-up. Such cases of regressive autism raise the theory of a biological link to vaccination. Despite extensive research on the etiology and pathophysiology of autism, few results have been obtained regarding a basic causal mechanism.[4]

Review of the literature

Many parents are concerned about the safety of vaccines given to their infants and children, especially because of the suggestion that the MMR vaccine may be linked to the development of autism.[2,4] One of the most important findings supporting the hypothesis of a link between MMR and autism is the detection of measles virus nucleic acid sequences in the blood cells and intestines of affected children.[3,4] Other researchers have not been able to detect measles virus genome sequences in the leukocytes of autistic children vaccinated with MMR.[5] Independent researchers have found no evidence of a unique syndrome of gastrointestinal disorders or neurodevelopmental regression in children with autism who received the MMR vaccine. Furthermore, no correlation was found between the timing of vaccination and the onset of neurodevelopmental regression.

In February 1998, British gastroenterologist Dr. Andrew Wakefield published an article in *The Lancet* suggesting a link between the MMR vaccine and the development of autism. This article sparked controversy about the safety of vaccines.[7] Wakefield and colleagues[7] claimed that the MMR vaccine caused intestinal dysfunction (inflammatory bowel disease) and impaired absorption of essential nutrients, leading to neurodevelopmental delay and behavioral disorders in 12 cases. Behavioral disorders included autism (nine cases), disintegrative psychosis (one case), and possible postviral or vaccine-associated encephalitis (two cases).[7] This situation has led to a generally negative attitude of parents towards vaccines in both Europe and the United States.[4] The fact that no details were provided about the source population and no "unaffected" control group in the relevant article has caused the hypothesis to receive much criticism as one of its weakest points. It has been emphasized that the association between vaccines and autism is coincidental and that the vaccine is not a cause.[2] It has been underlined that the most frequently detected intestinal abnormality in these patients was ileocolonic lymphonodular hyperplasia and that this condition may not necessarily represent a pathological condition.[2] Wakefield's group[8-11] reported laboratory evidence of the measles virus genome in peripheral white blood cells and intestinal biopsy samples of several patients with mild intestinal inflammation associated with ileocolonic lymphonodular hyperplasia and behavioral regression.[7,8] However, it is not clear whether these laboratory findings have clinical significance. Later studies by Wakefield et al.[7,12] and other investigators have also not supported this hypothesis.[2,13] There was no evidence of measles virus persistence in the peripheral blood mononuclear cells of children with ASD.[14] Because the supposed link between bowel disease and autism was weak and because bowel disease did not

precede the onset of autism in any of the reported cases, the British Medical Research Council took strong action against Wakefield, and his article, published in *The Lancet*, was retracted 12 years later.[4,7] However, as a result of the anti-vaccine movement that began during this period, measles was declared endemic in England and Wales for the first time after 14 years in 2008. These years were a period when hundreds of thousands of children in England were left unprotected due to anti-vaccine sentiment, and public health units made intensive efforts to increase parental confidence in vaccination.[15]

After Wakefield's article, several epidemiologic studies investigated the possible link between autism and the MMR vaccine, and this hypothesis was rejected.[2,3,13] Regardless of the scientific data, it has been assumed that if the mumps virus is not responsible for autism, another MMR component must be responsible.[4]

Following Wakefield et al.[7], in a systematic meta-analysis[16] which evaluated data from 12 studies and five different countries, various hypotheses regarding the relationship between autism and vaccination were suggested.[2,16] The first hypothesis states that ASD frequency increases in people who received the MMR vaccine compared to those who did not receive the vaccine. In a retrospective cohort study conducted by Madsen et al.[17], no statistically significant difference was found in the rates of autism or ASD between MMR-vaccinated and unvaccinated subjects during the same period. The second hypothesis is that ASD occurs at an increased rate because of MMR vaccination. Regarding this hypothesis, six studies have examined whether there is a relationship between MMR vaccination and changes in ASD rates.[13,18-22] These analyses were conducted in the United Kingdom, Sweden, and the United States. Four of the studies found no significant relationship between MMR vaccination and an increase in ASD or ASD variants.[20-23] One of the other two studies evaluated the increase in ASD cases before and after the MMR vaccination programs were initiated and found no increase in ASD rates during the vaccination period.[18] In a study by Fombonne et al.[13], no significant difference was found in the rates of neurodevelopmental regression in the sample before and after MMR vaccination was introduced (15.6% and 18.4%, respectively), and no evidence was found to support MMR-induced autism or "autistic enterocolitis" syndrome. Based on these findings, the researchers recommended that no changes be made to current vaccination programs or to vaccination recommendations.[13] The third hypothesis is that there is a temporal relationship between the development of ASD and MMR vaccination. Eight studies were evaluated for this purpose.[13,17,22-27] Three of these studies compared the age at which ASD was diagnosed, or parental concern arose, in vaccinated and unvaccinated individuals.[13,17,23] The hypothesis in these studies is that if MMR vaccination causes ASD, the populations exposed to the vaccine should develop ASD at a different age than the unexposed populations. However, these three studies found no difference in the mean age at which ASD was diagnosed. Six other studies examined whether there was an increase in the frequency of ASD diagnosis or evidence of features suggestive of ASD after children were vaccinated with MMR. One of these studies did not show that children diagnosed with autism had more frequent physician visits after MMR vaccination when compared to a non-autistic control group.[26] Another study, and an extended analysis of this study, examined a cohort of children with ASD and found that these children were not more likely to be diagnosed with ASD or to have developmental delays at certain points after receiving MMR vaccination.[23,25] Increased parental concern was observed in the 6-month period following vaccination, but this was not significant at other points after MMR vaccination.[23,25] Another study compared rates of parental concerns about bowel symptoms or neurodevelopmental regression among children with autism who received the MMR vaccine, children who were autistic before the MMR vaccine, and children with autism who were not vaccinated, and found no significant differences.[22] A separate study found no cases of ASD among 1.8 million people who received the MMR vaccine.[24] A study in Finland found no evidence of increased hospitalizations for autism after children were vaccinated with the MMR vaccine.[27] A study in Denmark of a population cohort of MMR vaccinated (400,000 cases) and unvaccinated children (100,000 cases) found no increased risk of developing autism or ASD with MMR vaccination. The relative risk associated with MMR was 0.92 (95% confidence interval (CI): 0.68–1.24) for autistic disorder and 0.83 (95% CI: 0.65–1.07) for other autism spectrum disorders.[17] A large, population-based case-control study conducted by the Centers for Disease Control and Prevention (CDC) also found no evidence to support an association between MMR and autism.[28] The fourth hypothesis is that the MMR vaccine may be associated with a new variant form of ASD. Four studies have examined a specific association of the variant form of ASD with MMR vaccine.[13,22,27,29] Variant ASD was defined by the presence of developmental delay or gastrointestinal symptoms. None of the 31 children who developed Gastrointestinal (GI) symptoms after MMR vaccination (three studies and one case report) developed ASD during clinical follow-up.[29] In another study, when comparing the historical

period after the introduction of the MMR vaccine with the historical sample before the vaccine became routine, no difference was found in the rates of developmental delays in children diagnosed with ASD.[13] Another study found no increase in the percentage of children with autism who had GI symptoms or developmental delay after MMR vaccination.[22] Another study found that none of the 309 children who received MMR vaccination and were subsequently hospitalized for autism were also hospitalized for inflammatory bowel disease.[27]

Taylor et al.[1] evaluated 498 known ASD cases born in a London district in 1979 and later found that although the number of cases had increased since 1979, there was no sharp increase after the introduction of the MMR vaccine in 1988. The study found no temporal relationship between vaccination and the onset of regression. They also found that all children with ASD who were vaccinated with MMR before 18 months of age, after 18 months of age, or not vaccinated with MMR at all had similar ages of diagnosis, and that MMR vaccination did not cause autism to appear at an earlier age.[1]

Studies in Japan and Canada have found no relationship between the MMR vaccine and the prevalence of autism.[30,31] A study conducted in Japan found that the prevalence of autism increased in children born between 1988 and 1996, despite MMR vaccination being completely stopped in 1993, and that there was no difference in terms of the decline in autism rates.[30,31] Similarly, a study conducted in Montreal found that the prevalence of autism and pervasive developmental disorders increased from 1987 to 1998, despite the decline in MMR vaccination.[30]

Although observational studies have not found an increased risk of autism after MMR vaccination, concerns about the putative link between the MMR vaccine and autism persist almost two decades after the controversial and later retracted 1998 Lancet article,[1] making it difficult to accept the vaccine. A 2012 Cochrane review (5 randomized controlled trials, one controlled clinical trial, 27 cohort studies, 17 case-control studies, five time-series studies, one crossover study, two ecological studies, and six self-controlled case series studies) found no qualitative evidence of an association between the MMR vaccine and autism.[32] A 2014 meta-analysis identified 10 observational studies on childhood vaccines, including five cohort and five case-control studies: two cohort studies and four case-control studies specifically cited no association between MMR and autism.[1] Similarly, a recent epidemiological study conducted in the USA in 2001 did not show any association between the MMR vaccine and the risk of inflammatory bowel disease.[19] In another meta-analysis study, Mohammed et al.[4] evaluated the results of 21 systematic studies published between 1998 and 2018 and found no causal relationship between childhood vaccination and the development of autism.

Possible mechanism for developing autism following vaccination

Various mechanisms have been put forward regarding the relationship between vaccination and the development of autism (immune system dysfunction, gliadorphin side effects, mercury toxicity, etc.). According to this mechanism, frequent stimulation of the immune system through vaccination causes changes in immunological function in the developing central nervous system, resulting in a strong microglial reaction and consequently dendritic and synaptic losses. When the microglial system is activated, the immune cells of the brain secrete inflammatory cytokines, free radicals, lipid peroxidation products, and excitotoxins such as glutamate and quinolinic acid. As a result, the clinical and pathological features of autism emerge.[4]

Thimerosal is an organic chemical that contains ethylmercury and has been used as a preservative in vaccines since the 1930s. Thimerosal is 49.6% mercury by weight and is metabolized to ethylmercury and thiosalicylate. Ethylmercuric hydroxide rapidly penetrates the brain and is converted to inorganic mercury.[4] In the late 1990s, partly due to increased awareness of the risks of exposure to low doses of organic mercury, the Food and Drug Administration conducted a risk assessment of the use of thimerosal in vaccines.[2] Between 1989 and 1998, as more vaccines (Hepatitis B, Haemophilus influenzae type B, etc.) were added to the recommended infant vaccination schedule, there was an increased exposure to mercury from vaccines. It has been shown that infants vaccinated according to the recommended schedule may have received mercury doses that exceed the Environmental Protection Agency's methylmercury exposure limit.[33] Biological and epidemiological evidence has shown a direct relationship between increasing mercury doses in thimerosal-containing vaccines and neurodevelopmental disorders. A close correlation between thimerosal and autism has been suggested because of the increasing prevalence of autism observed from the late 1980s to the mid-1990s in association with increasing mercury doses in childhood vaccines containing thimerosal.[34] Geier et al.[34] evaluated the CDC Biological Surveillance Summaries, US Department of Education data sets, and CDC annual live birth estimates,

concluding that the contribution of thimerosal (>50% effect) from childhood vaccines to the observed prevalence of autism was higher than that of the MMR vaccine. As a result of this study, it was recommended that thimerosal be removed from all vaccines and that additional research be conducted to produce an MMR vaccine with a better safety profile.[34] Geier et al.[5] examined the Vaccine Adverse Events Reporting System (VAERS) database and the 2001 US Department of Education Report to determine dose-response curves between increasing thimerosal doses in childhood vaccines and neurodevelopmental disorders. It was shown that the increases in neurodevelopmental disorders observed were closely and linearly related to increasing mercury doses from thimerosal-containing childhood vaccines. The authors suggested that the emergence of neurodevelopmental disorders following thimerosal-containing childhood vaccines was not coincidental based on the evidence presented here.[5]

In a population-based cohort study, Hviid et al.[35] found no significant difference in autism and other ASD symptoms and findings when comparing children vaccinated with the same pertussis vaccine with and without thimerosal (relative risk (RR) = 0.85 [95% confidence interval (CI) = 0.60–1.20] for autism; RR = 1.12 [95% CI = 0.88–1.43] for other ASD). Moreover, the lack of evidence of a dose-response correlation was emphasized in the same study (increase in RR per 25 µg ethylmercury = 0.98 [95% CI = 0.90–1.06] for autism and 1.03 [95% CI = 0.98–1.09 for ASD). Consequently, no adverse effects were found in terms of cumulative mercury dose and thimerosal exposure when comparing ASD and ASD developmental disorders.[1] Despite all these positive and negative data, the Public Health Service and the American Academy of Pediatrics called for the removal of thimerosal from infant vaccines as a precautionary measure, despite the lack of any evidence of harm.[2]

CONCLUSION

This review evaluates the relationship between the MMR vaccine and autism and ASD. When epidemiological studies conducted on this subject in the literature are evaluated, no evidence has been found for a link between the MMR vaccine and autism. Although the risk of autism from MMR remains theoretical according to current literature, there are many studies showing the negative effects of not being vaccinated on health. Public health authorities should make efforts to alleviate public concerns about vaccination based on literature data and emphasize the importance of vaccines for public health. When literature data is evaluated, there is no scientific evidence for a vaccine-autism relationship, and therefore no changes are required in current vaccination programs.

Author contribution

Review conception and design: GÖ, EÇ; literature review: EÇ; draft manuscript preparation: EÇ, GÖ. All authors reviewed the results and approved the final version of the article.

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Original Article

Effect of large neutral amino acids treatment on blood phenylalanine, tyrosine, and tryptophan levels in adolescent and young adult PKU patients

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ABSTRACT

Objective: We aimed to evaluate the change in phenylalanine (Phe), Tyrosine (Tyr), and Tryptophan (Trp) blood levels in classical PKU patients treated with large neutral amino acids (LNAA) supplementation.

Methods: Twenty-nine PKU patients treated with LNAA between 2013-2022 were enrolled in the retrospective observational study. Four cases were excluded from the statistical analysis due to missing data.

Results: The median age (min-max) onset of LNAA was 11.6 (8-38.1) years, and the median duration (min-max) of LNAA use was a median of 42.7 (5-105) months. The mean current age of the patients was 19.70±9.96 years. The final blood levels of Phe, Tyr, and Trp did not change significantly ($p>0.05$) from the baseline. At the last measurement, the Hb value increased significantly ($p<0.05$) compared to the baseline, while the vitamin B12, total protein, albumin, and ferritin values did not change from the baseline ($p>0.05$). It was seen that there was an increase in the employees' productivity at work, the success of the students in the course, and the focus on maintaining attention.

Conclusions: We want to highlight that LNAA could be a treatment option for adolescents or adults who are not adhering to a Phe-restricted diet.

Keywords: large neutral amino acid, phenylalanine, phenylketonuria, tyrosine, tryptophan

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive amino acid metabolism disorder. It is caused by phenylalanine hydroxylase (PAH) enzyme deficiency due to mutations in the *PAH* gene. Although there are different classification approaches in the literature, the approach accepted in Turkey is phenylalanine (Phe) level between 2 and 6 mg/dl is defined as hyperphenylalaninemia, 6-10 mg/dl as mild; 10-20 mg/dl as moderate, and >20 mg/dl as severe PKU.[1-4]

Central nervous system damage (CNS) may occur due to increased Phe. The brain dysfunction exhibited in PKU patients is caused by several different factors, not just Phe concentration. Large amino acid transporter-1 (LAT-1) protein enables the competitive passage of large

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neutral amino acids, including phenylalanine, across the blood-brain barrier in the CNS and intestine. After Phe crosses the blood-brain barrier, it serves as a precursor for dopamine, norepinephrine, and epinephrine. Hence, elevated plasma and brain Phe concentrations affect brain functions, and the patients present neurocognitive and behavioral problems. Patients diagnosed with PKU will likely exhibit behavioral issues such as hyperactivity, stereotypic movements, aggression, anxiety, and social disengagement if they remain undiagnosed or untreated.[5] Although disagreements and debates continue regarding the cut-off Phe level for preventing neuropsychological issues, guidelines and expert opinion reports exist in the literature.[2,6-10] The goal of PKU treatment is to keep blood Phe levels strictly regulated. American guidelines recommend a target range of 2–6 mg/dL for patients of all ages.[11] However, European guidelines suggest a target range of 2–6 mg/dL for patients younger than 12 years and during pregnancy while recommending a target range of 2–10 mg/dL for patients older than 12 years to prevent neurodevelopmental issues and potential impairment of neurocognitive function.[8]

Diagnosis and starting a Phe-restricted diet in the first days of life [2], the main treatment option, are vital for classic PKU patients. For this reason, it has been screened in newborn screening programs for years in many countries, including Turkey.[6] In case of untreated or late and inadequate treatment, behavioral and psychiatric problems and motor skills deterioration could be observed.[3,6]

Large neutral amino acids (LNAA) are histidine (His), isoleucine (Ile), leucine (Leu), methionine (Met), threonine (Thr), Trp, Tyr, valine (Val), and Phe. LNAA supplements containing these amino acids are an option for treating PKU. It is known that LNAA protects from CNS damage by acting on the transfer of Phe to the brain; this is thought to do so using the same transporter system as Phe (LAT-1). Thus, neurophysiological and neuropsychiatric improvement is observed in patients. It is believed that LNAA supplementation reduces the amount of Phe in the brain, gives patients a supplementation rich in Tyr and Thr, and contributes to the production of dopamine and serotonin. Another hypothesis suggests that being rich in essential amino acids contributes to well-being. In contrast, another opinion indicates that since it is a Phe-free supplement, it reduces the level of phenylalanine in the blood, contributing to decreased Phe in the brain. The LNAA treatment also provides dietary liberalization, which is described as increased dietary Phe or natural protein intake. Therefore, LNAA treatment could be an option in adolescents or adults with low adherence to Phe restricted diet.[7-9,12-17]

We aimed to evaluate the change in phenylalanine (Phe), Tyrosine (Tyr), and Tryptophan (Trp) blood levels in classical PKU patients treated with LNAA supplementation.

MATERIALS AND METHODS

We collected retrospective data from the patients' medical records, ensuring that all procedures were carried out with respect to ethical standards and following approval from the ethical committee by the Medical Research Ethics Committee of Ege University Faculty of Medicine (Document Number: 22-11.1T/9). The study used the principles outlined in the Helsinki Declaration (1964). Data were gathered between January 2013 and December 2022. Twenty-nine patients diagnosed with PKU and under LNAA supplements treatment for longer than six months between 2013 and 2022 were included in the study cohort.

Four cases were excluded from the statistical analysis due to missing data. All of the patients were diagnosed with classic PKU and unresponsive to sapropterin. Demographic and laboratory data were obtained from patients' medical records. The specified total protein subscription of 1 g/kg and total LNAA account for approximately 60% of daily protein intake, divided into four doses. Before the LNAA supplement period, the recommended Phe content of the diet was based on age and gender according to national and international consensuses (4, 18). The Phe-free protein substitutes were also added to the protein content of the three-day food diaries. The Phe content in the Phe-restricted diet was adjusted according to the blood Phe levels at each outpatient clinic visit. Individuals with PKU who started LNAA supplementation were those who were not compliant with the phenylalanine-restricted diet treatment. The recommended daily LNAA supplement dose, about 60% of total daily protein, was divided into three doses with meals. Dietary content, Phe, Tyr, Thr, vitamin B12, ferritin, hemoglobin, total protein, and albumin levels were compared to the LNAA supplement before and after.

Observations, including academic performance or attention span from the patients or their caregivers, were based solely on subjective reports from parents, teachers, and social interactions; however, no objective tests were conducted.

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency, and ratio values were used. The distribution of variables was measured using the Kolmogorov-Simirnov and Shapiro-Wilk test. Wilcoxon test was used to analyze dependent quantitative data. Spearman correlation analysis was used in the correlation analysis. SPSS 28.0 program was used in the analysis.

RESULTS

Ten (40%) patients were female, and 15 (60%) were male. The median age at diagnosis was 15 months (0.04-32.75 years), the follow-up period was 13.1±3.5 years (7.8-24.5), the median current age was 15.79 years (7.8-41.17), the median age of initiation of LNAA supplement was 11.6 years (8-38.1), and the duration of under LNAA treatment median 42.7 months (min:5-max:105 months). There was

Table 1. Patients' demographic, molecular, daily protein intake, daily LNAA supplement, intellectual state, educational and occupational status.

Patient Number	Gender	Age of diagnosis	Age of LNAA treatment initiation	Current age	PAH gene		Total protein intake (g/d)	Natural protein intake (g/d)	LNAA Supplement (g/d)	Follow-up duration	ID	Educational/ Occupational status
					Allele 1	Allele 2						
1	F	4y	28y	29y	c.842C>T	c.842C>T	98	39.2	58.8	24y	Severe	
2	F	20d	11y	17y	c.441+5G>T	c.1066-11G>A	46	18.4	27.6	16y	N	High School
3	M	3y	11y	19y	c.1066-11G>A	c.1066-11G>A	99	39.6	59.4	16y	N	University
4	M	25y	34y	41y	c.165delT	c.1049C>A	83	33.2	49.8	15y	Severe	
5	M	16y	25y	32y	c.842C>T	c.1066-11G>A	54	21.6	32.4	16y	Severe	
6	M	35d	11y	15y	c.116_118delTCT	c.116_118delTCT	58	23.2	34.8	15y	N	High School
7	F	1y	8y	16y	c.194T>C	c.1066-11G>A	96	38.4	57.6	15y	Severe	
8	F	8y	18y	22y	c.441+5G>T	c.441+5G>T	50	20	30	14y	N	Employed
9	F	24d	12y	14y	c.970-1G>T	c.1066-11G>A	41	16.4	24.6	14y	N	High School
10	F	18d	9y	14y	c.638T>C	c.638T>C	30	12	18	14y	N	High School
11	M	40d	12y	14y	c.168+5G>C	c.168+19T>C	75	30	45	14y	Mild	High School
12	M	50d	8y	13y	c.1199+1G>C	c.1199+1G>C	45	18	27	13y	Mild	High School
13	F	42d	12y	14y	c.143T>C	c.473G>A	49	19.6	29.4	14y	N	High School
14	M	2y	13y	16y	c.638T>C	c.638T>C	42.5	17	25.5	14y	N	High School
15#	M	44d	10y	13y	c.1089delG	c.1238G>C	38	15.2	22.8	12y	Severe	Middle School
16	M	25y	28y	12y	c.1066-11G>A	c.1222C>T	36	14.4	21.6	12y	N	Middle School
17	M	3y	12y	37y	c.1066-11G>A	c.728G>A	82	32.8	49.2	12y	Mild	Employed
18	M	25y	27y	16y	c.143T>C	c.331C>T	83	33.2	49.8	13y	N	High School
19#	F	52d	8y	36y	c.1066-11G>A	c.1066-11G>A	88	35.2	52.8	11y	Severe	
20	M	32d	9y	10y	c.1162G>A	c.1162G>A	28	11.2	16.8	10y	N	Middle School
21	M	9y	15y	10y	c.1066-11G>A	c.842C>G	36.5	14.6	21.9	10y	Mild	Middle School
22	F	40d	11y	14y	c.441+1G>A	c.441+1G>A	78	31.2	46.8	13y	N	High School
23	F	9y	38y	17y	c.473G>A	c.1222C>T	39	15.6	23.4	8y	Severe	High School
24#	F	11y	12y	18y	c.473G>A	c.1222C>T	45	18	27	8y	Mild	High School
25	M	33y	8y	41y	c.1066-11G>A	c.143T>C	72	28.8	43.2	8y	N	Employed
26	M	15y	28y	20y	c.1066-11G>A	c.1066-11G>A	66	26.4	39.6	5y	N	University
27	M	32y	11y	35y	c.168+5G>C	c.1066-11G>A	85	34	51	3y	Severe	
28	M	28d	11y	12y	c.1066-11G>A	c.1066-11G>A	34	13.6	20.4	12y	Mild	Middle School
29#	M	32d	34y	8y	c.441+5G>T	c.1066-11G>A	23	9.2	13.80	8y	Severe	

F: female, M: male, d: day, y: year, g: gram, ID: intellectual disability, LNAA: large neutral amino acid. # Excluded due to missing data.

no additional disease or supplement replacement that would affect the nutritional status of the cases (Table 1).

Before starting the LNAA supplement, the mean levels were Phe 16.74±8.86 mg/dL, Tyr 1.13±0.69 mg/dL, and Trp 1.24±0.54 mg/dL. Under LNAA treatment and diet liberalization, the Phe and Tyr levels in the first, second, and third months and at the last visit did not change from baseline (p>0.05) (Table 2).

Before the LNAA supplement, the mean levels were Hb 13.04±1.34 g/dL, vitamin B12 668.8±244.0 pg/mL, total protein 7.29±0.49 g/dL, albumin 4.71±0.36 g/dL, ferritin 40.64±23.83 ng/mL. At the last measurement, only the Hb value increased significantly (p<0.05) (Table 3).

There was a negative correlation between the difference in dietary protein intake of the cases (rho= -0.452, p<0.05) and the difference in the Phe change between the basal

Table 2. Phenylalanine, tyrosine, and tryptophan differences before and after LNAA supplementation. (n=25)

Plasma amino acid levels		Min-Max	Median	Mean±SD	p†	p‡
Phe (mg/dl)	Basal	1.20-33.40	14.60	16.74±8.86	-	
	1st month	1.70-27.20	15.20	15.74±6.95	0.501 ^{w}	
	2nd month	1.80-26.10	18.00	16.85±6.52	0.481 ^{w}	0.977 ^{w}
	3rd month	1.40-27.60	17.55	16.30±7.02	0.659 ^{w}	0.836 ^{w}
	Last visit	5.30-29.60	17.10	17.25±6.56	0.192 ^{w}	0.224 ^{w}
Tyr (mg/dl)	Basal	0.50-3.10	0.90	1.13±0.69		
	1st month	0.50-2.80	0.85	1.28±0.79	0.598 ^{w}	
	2nd month	0.50-4.40	1.20	1.62±1.22	0.232 ^{w}	0.409 ^{w}
	3rd month	0.40-3.00	1.00	1.16±0.58	0.940 ^{w}	0.887 ^{w}
	Last visit	0.60-3.40	1.10	1.42±0.81	0.036* ^{w}	0.055 ^{w}
Trp (mg/dl)	Basal	0.60-2.80	1.20	1.24±0.54		
	Last visit	0.70-2.90	1.10	1.31±0.54	0.435 ^{w}	
Phe/Tyr	Basal	1.50-56.00	17.10	18.05±12.78		
	1st month	2.80-48.00	14.90	16.77±12.08	0.426 ^{w}	
	2nd month	1.80-43.80	14.90	16.65±13.25	0.355 ^{w}	0.975 ^{w}
	3rd month	1.80-53.80	13.90	16.98±11.64	0.932 ^{w}	0.492 ^{w}
	Last visit	4.80-37.30	12.10	15.16±9.73	0.563 ^{w}	0.773 ^{w}

Max: maximum, Min: minimum, Phe: phenylalanine, Trp: tryptophan, Tyr: tyrosine. ^{w} Wilcoxon test. † The difference between basal and last visit values. ‡ The difference with the previous measurement. * Indicates significance at p <0.05.

Table 3. Hematological and nutritional results baseline and last visit (n=25)

		Min-Max	Median	Mean±SD	P
Hb (g/dL)	Baseline	10.70 - 15.60	13.10	13.04 ± 1.34	0.033* ^{w}
	Last	11.20 - 15.30	13.40	13.50 ± 1.14	
Vitamin B12 (pg/mL)	Baseline	206.0 - 1169.0	705.0	668.8 ± 244.0	0.149 ^{w}
	Last	150.0 - 1072.0	616.5	560.2 ± 246.4	
Total protein (g/dL)	Baseline	5.90 - 8.10	7.30	7.29 ± 0.49	0.676 ^{w}
	Last	6.50 - 8.10	7.41	7.35 ± 0.42	
Albumin (g/dL)	Baseline	3.70 - 5.40	4.70	4.71 ± 0.36	0.562 ^{w}
	Last	4.19 - 5.40	4.70	4.78 ± 0.31	
Ferritin (ng/mL)	Baseline	11.00 - 101.00	40.10	40.64 ± 23.82	0.964 ^{w}
	Last	9.06 - 114.00	33.40	42.91 ± 28.87	

Hb: Hemoglobin, ^{w} Wilcoxon test, * Indicates significance at p <0.05.

Table 4. Spearman correlation analysis results between the difference in dietary protein intake of the cases and the difference between baseline and last levels (n=25)

	Difference in daily dietary protein intake	
	Correlation coefficient (rho)	p
Phe	-0.452	0.023*
Tyr	0.420	0.037*
Trp	0.435	0.030*
Phe/Tyr	-0.561	0.004
Hb	0.229	0.281
Vitamin B12	0.116	0.590
Total protein	-0.170	0.449
Albumin	0.295	0.183
Ferritin	-0.104	0.637

Phe: phenylalanine, Trp: tryptophan, Tyr: tyrosine, Hb: Hemoglobin.
* Indicates significance at p <0.05.

and final measurement, a positive correlation between the Tyr change cases (rho= 0.420, p<0.05), and a positive correlation between the Trp change (rho=0.435, p<0.05) (Table 4).

There was not a significant correlation between dietary protein content and Hb, serum total protein, albumin, and ferritin levels change (p> 0.05) (Table 4).

Among the patients, 17 (68%) were students, and three (12%) were employed. At the beginning of the LNAA supplement, 24% of the participants had a moderate-severe intellectual disability, and 28% had mild intellectual disability. Under the LNAA supplement, improvements were observed in employee productivity, student academic performance, and attention span. We provided the changes patients experienced after using LNAA treatment in Table 5.

DISCUSSION

Our research had a large cohort compared to previous studies, and our initial finding in this study was that the LNAA starting age was younger than that of the previous studies.[1,18]

Our results show that the final measurement Phe, Tyr, and Trp values did not change significantly, similar to the previous reports.[14,17] In another study, nine out of ten patients had considerably higher plasma Tyr levels[19], while five had significantly lower Phe/Tyr ratios. Scala et al. reported that Tyr levels considerably increased with LNAA supplementation in PKU patients.[1] Along with providing patients with supplements Tyr and Trp and helping to produce dopamine and serotonin, it is believed that LNAA lowers the quantity of Phe in the brain.[7-9, 12-17]

Our cohort's B12, Hb, and ferritin values did not change between the baseline and last visit, and we hypothesized this was due to the patients being supplemented with a Phe-free medical formula rich in these micronutrients before LNAA treatment. No large study in the literature compared data on these parameters before LNAA treatment, under a Phe-restricted diet, and after initiating LNAA treatment with diet liberalization.

Burlina et al. reported a significant decrease in the Phe/Tyr ratio, even though there was no notable change in blood

Table 5. Changes in patients' emotions after LNAA supplements as reported by themselves or their caregivers.

Patient Number	Describing Person	Answer
2	Father	"She concentrates on her studies better; her sleep periods are more regular."
8	Sister	"She works as a worker in the factory; she works much more harmoniously and efficiently at work."
9	Parents	"School success is better."
10	Mother	"Her attention is much better than before."
11	Father	"His attention is much better than before."
12	Teacher	"An increase in fine skills and musical talent was observed."
17	Himself	"My nights of sleep periods were regular; I had had severe insomnia problems before. My fatigue has decreased."
18	Himself	"No change"
24	Himself	"I am feeling more active and social individual than before."
25	Himself	"I used to be forgetful before."
26	Father	"He is much more attentive compared to before."

Phe levels.[20] All subjects receiving the LNAA supplement indicated that they felt better. While the quality of life scale showed a significant decrease in aggression, no significant changes were noted in mood assessments.[21] No specific tests were performed to assess the participants' moods in the presented study. Nevertheless, it was noted that two individuals experienced more regular sleep patterns, two became more social and harmonious, and one developed an increased interest in music and began playing instruments. All participants reported a significant improvement in the regularity of their sleep patterns.

Research on mice with PKU revealed that supplementing with Tyr and Trp produced effects comparable to a high-protein diet in those given specific Ile, Leu, and Thr. The group receiving Tyr and Trp supplements exhibited significantly elevated serotonin levels.[21] Another experiment on animals demonstrated that LNAA supplementation increased brain serotonin and norepinephrine levels in mice while dopamine levels remained unchanged.[22] A separate study group showed that LNAA supplementation had beneficial effects on various cognitive and physical functions, including executive functioning, sustained attention, vigilance, distress, well-being, exercise training, motor skills, and mental performance.[1] These findings suggest a potential hypothesis regarding the impact of LNAA treatment on mood and cognition.

The limitations of our study were that the age and clinics of the cases were heterogeneous, the assessment of cognition and mood performances was not standardized, our study did not include measurements related to parents or caregivers, and we did not have data about other amino acids.

The mainstay treatment of sapropterin-unresponsive classical PKU is still a Phe-restricted diet. Diet compliance of patients and caregivers decreases after the first years of life, especially during adolescence. Therefore, new treatment alternatives are important to protect patients from long-term complications.[1,7,11] The caregivers of every case in our study reported that their charges struggled with dieting due to their advanced age at each control. It was noted that the diet consumption lists were incompatible, particularly regarding the controls, and that formulas without phenylalanine did not want to be ingested. It is stated in the literature that similar problems are experienced by the patients and their caregivers.[21-24]

CONCLUSION

Our results demonstrated no significant changes in Phe, Tyr, and Trp levels, but increased Hb levels were observed during LNAA treatment. LNAA seems to be a potential treatment option for older patients and may merit further consideration in clinical settings.

Ethical approval

This study has been approved by the Medical Research Ethics Committee of Ege University Faculty of Medicine (approval date 17.11.2022, number 22-11.1T/9). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: FE, HY, SKU; Data collection: FE, EC, HY, SKU, MÇ; Analysis and interpretation of results: FE, EC, HY, SKU, MÇ; Draft manuscript preparation: FE, HY, SKU. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Trends in type 1 diabetes incidence among children and adolescents in Bursa (2015-2022): impact of the COVID-19 pandemic and demographic insights

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ABSTRACT

Objective: Type 1 diabetes (T1D) is a common, chronic, systemic disease in children and adolescents, and its incidence globally increases annually. This study aimed to determine the incidence, diagnostic features, and presentation characteristics of T1D in children and adolescents during the pandemic period in Bursa Province, Turkey.

Method: This study included children under 18 with newly diagnosed T1D who consulted the Pediatric Endocrinology clinics of 3 tertiary hospitals in the city center of Bursa between January 1, 2015, and December 31, 2022. Nine hundred twenty-one pediatric patients were included in the study. The patients were divided into four groups according to age: Group 1, 0-4.9 years; Group 2, 5-9.9 years; Group 3, 10-14.9 years; and Group 4, 15-18 years.

Results: Of the patients, 48.6% were female, and 51.4% were male. The median age at diagnosis was 9.23 years, with a significant age difference between genders. The highest incidence was observed in children aged 10-14.9 years. Moreover, two peaks were detected: 10-14.9 years in males and 5-9.9 years in females. The mean annual incidence was 3.8/100,000, peaking in 2017. During the COVID-19 pandemic, a temporary decline in diagnoses was noted, followed by an increase. Diabetic ketoacidosis (DKA) rates showed a significant rise over time, particularly in severe DKA cases during the pandemic.

Conclusion: This study provides the first comprehensive analysis of the rate of newly diagnosed T1D in children and adolescents in Bursa Province. Additionally, the study evaluated age, gender, and seasonal patterns of initial diagnoses, with global trends constantly. The incidence of T1D and the rate and severity of DKA at presentation were affected during the COVID-19 pandemic, causing lockdowns and healthcare avoidance.

Keywords: Bursa, COVID-19, incidence, ketoacidosis, type 1 diabetes, newly diagnosed type 1 diabetes, pandemic, trends

INTRODUCTION

Type 1 diabetes (T1D) is a common, chronic, systemic disease in children and adolescents. Although studies have reported that the incidence of T1D varies significantly among countries, a rising incidence of T1D has recently been detected in many populations.[1-5] Also, seasonal and gender differences in the incidence of T1D have been reported.[5-8] In contrast, some studies reported no change.[9-12] During the COVID-19 pandemic, several studies

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have reported a significant increase in the initial diagnosis of T1D. As compared to previous years, the rate of diabetic ketoacidosis (DKA) was gradually elevated. Although studies have been conducted in recent years on the incidence and incidence trends of T1D in childhood in Turkey[13-16], evaluating the COVID-19 pandemic or comparing it to before the pandemic is limited.[17,18] In addition, no previous study has been conducted on the incidence of initially diagnosed diabetes and patient characteristics in Bursa Province.

This study aimed to determine the incidence of T1D in children and adolescents (under 18 years of age) in Bursa Province of Turkey between 2015 and 2022, to examine whether there was an increase in the incidence of new diagnoses over the years, to evaluate whether there was a difference in the presentation characteristics during the pandemic period, and to evaluate the age, type of diagnosis, gender, and season of diagnosis in children diagnosed with T1D.

MATERIAL AND METHODS

Patient selection

This study includes children under the age of 18 with newly diagnosed T1D who applied to the Pediatric Endocrinology clinics of 4 large regional hospitals in the city center of Bursa between January 1, 2015, and December 31, 2022, and whose T1D diagnosis was confirmed. However, one center could not be included in the study due to the incomplete number of diagnosed patients per year and its data, and the study was completed with the data of 3 centers. In addition, cases diagnosed at the age of 18 or older, those diagnosed with Type 2, monogenic, or neonatal diabetes despite being under the age of 18, and those diagnosed outside of Bursa were excluded from the study. When evaluating the diagnostic features, the patients were divided into four groups according to age: Group 1, 0-4.9 years; Group 2, 5-9.9 years; Group 3, 10-14.9 years; and Group 4, 15-18 years. Comparisons were made according to age and gender groups.

Laboratory

Serum glucose, blood gas, urine test, and blood/urine ketone values at the time of the first visit were examined from the files of all patients. In venous blood gas, pH values >7.30 and/or HCO_3 >15 were classified as normal; 7.20-7.29 and/or HCO_3 10-14.9 as mild acidosis, 7.10-7.19 and/or HCO_3 5-9.9 as moderate acidosis and pH <7.09 and/or HCO_3 <4.9 as severe acidosis. Normal values in urine density were accepted as 1003-1030, negative for glucose, and negative or trace amounts for ketone. A blood ketone level of less than 0.6 was considered ketone-negative.

Statistical analysis

Statistical analyses were performed using IBM SPSS 29.0.2.0 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp.) statistical package program. Annual population sizes were obtained from the 2015-2022 Turkish census data from the address-based population registration system of the Turkish Statistical Institute. Pearson Chi-square and Fisher-Freeman-Halton tests were used in the analysis of categorical data. $P < 0.05$ was considered statistically significant.

Ethics

The study was approved by the Local Ethical Committee (Approval number: 2011-KAEK-25 2023/04-21) and conducted following the Declaration of Helsinki. The patient's parents had signed informed written consent.

RESULTS

Nine hundred twenty-one patients (48.6% were female, and 51.4% were male) diagnosed with T1D from Pediatric Endocrinology clinics of three regional hospitals in the city center of Bursa were included in the study. The median age at diagnosis was 9.2 years (0.1-17.9 years), and the difference in age at diagnosis between the genders was statistically significant (9.00 years in females (0.1-17.8 years) and 9.80 years in males (0.1-17.9 years), p=0.035). Newly diagnosed T1D cases were the highest in males aged 10-14.9 years (n=161), followed by females aged 5-9.9 aged group in females (n=159), females aged 10-14.9 aged group in females (n=146), and 5-9.9 aged group in males (n=144) (Table 1).

Table 1. Distribution of initially diagnosed T1D patients by age group and gender

	Female	Male	Total
0-4.9 years	103	104	207
5-9.9 years	159	144	303
10-14.9 years	146	161	307
15-18 years	40	64	104
Total	448	473	921

T1D: Type 1 diabetes.

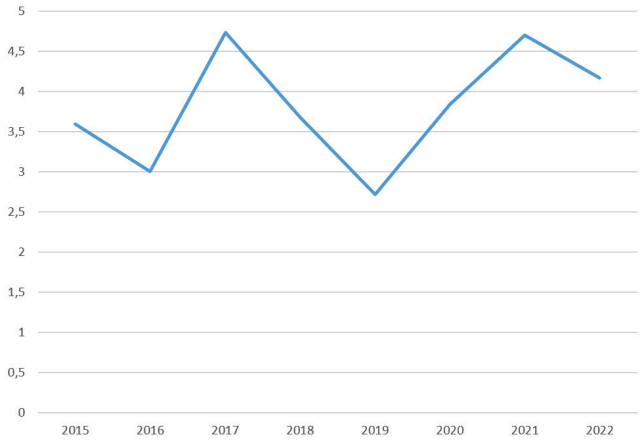

Figure 1. The incidence of newly diagnosed T1D by year

The mean annual incidence in children between 2015 and 2022 was 3.8 per 100.000. When evaluated by year, the highest incidence was found in 2017 (4.73/100.000). Figure 1 shows the incidence of newly diagnosed T1D by year.

The mean annual incidence between males (4.6%) and females (3%) was statistically significant only in 2020 (p=0.022); however, no difference was found for other years. In evaluating age groups, the mean annual incidence was 13.7/100,000 at the 0-4.9 age group, 16.0/100,000 at the 5-9.9 age group, 16.7/100,000 at the 10-14.9 age group, and 9.3/100,000 at the 15-18 age group. The highest incidence was in the 10-14.9 age group; the lowest incidence was in the 15-18 age group (9.3/100,000). As for evaluating seasons and months, winter and December were the most common seasons and months for newly diagnosed T1D through the years (Table 2).

At the beginning of the pandemic period and after the declaration of the pandemic and lockdown in Turkey (March 11, 2020), the rate of new diagnoses showed a significant decrease in April (0.161195), May (0.225673) and June (0.225673) compared to previous years and months [January 2020 (0.29), February (0.16) and March (0.42)], while an increase was detected in the following months, after the end of the lockdown of July (0.451346) and August (0.419107) compared to previous periods.

A statistically significant trend was found regarding DKA rates by year (p<0.001). While the DKA rate progressed similarly in 2016 compared to 2015, an increase was observed in 2017. While there was a decrease in 2019,

Table 2. Distribution of newly diagnosed T1D cases by age group, gender, and season

Incidence		Total (n=921)	2015 (n=102)	2016 (n=87)	2017 (n=139)	2018 (n=110)	2019 (n=83)	2020 (n=119)	2021 (n=148)	2022 (n=133)	p
Gender	Female	46	47	76	56	42	47	65	69	46	0.202
	Male	56	40	63	54	41	72	83	64	56	
Age at diagnosis (years)	0-4.9	21	14	30	27	22	28	37	28	21	0.850
	5-9.9	39	34	43	29	28	35	50	45	39	
	10-14.9	35	26	48	41	26	39	44	48	35	
	15-18	7	13	18	13	7	17	17	12	7	
Female	0-4.9	10	7	15	18	11	10	16	16	10	0.987
	5-9.9	20	20	29	15	14	15	23	23	20	
	10-14.9	12	16	25	19	14	16	20	24	12	
	15-18	4	4	7	4	3	6	6	6	4	
Male	0-4.9	11	7	15	9	11	18	21	12	11	0.692
	5-9.9	19	14	14	14	14	20	27	22	19	
	10-14.9	23	10	23	22	12	23	24	24	23	
	15-18	3	9	11	9	4	11	11	6	3	
Season	Winter	35	31	51	38	23	28	41	35	35	0.093
	Spring	29	23	33	22	18	25	42	33	29	
	Summer	13	10	27	17	23	34	36	29	13	
	Autumn	25	23	28	33	19	32	29	36	25	

T1D: Type 1 diabetes.

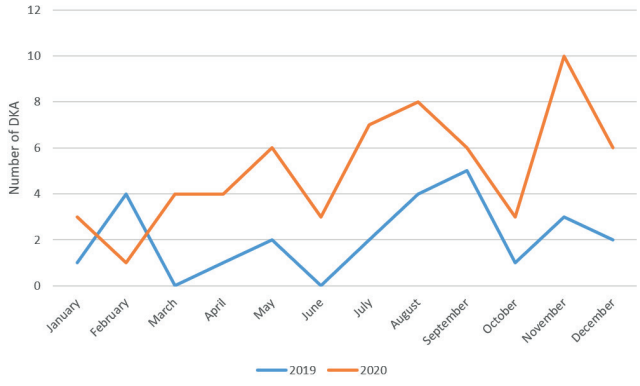

Figure 2. DKA rates by month before and during the pandemic

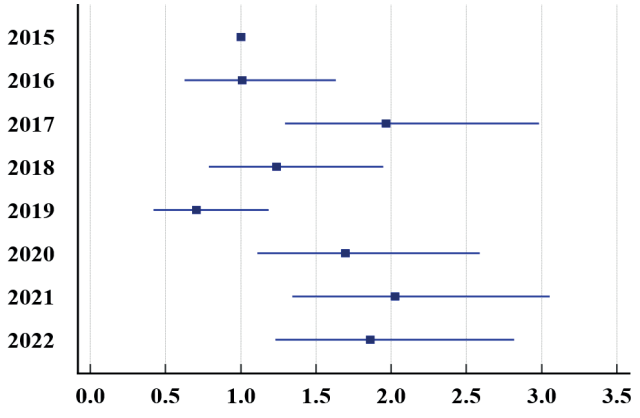

Figure 3. Forest plot of the DKA incidence rate according to trend analysis

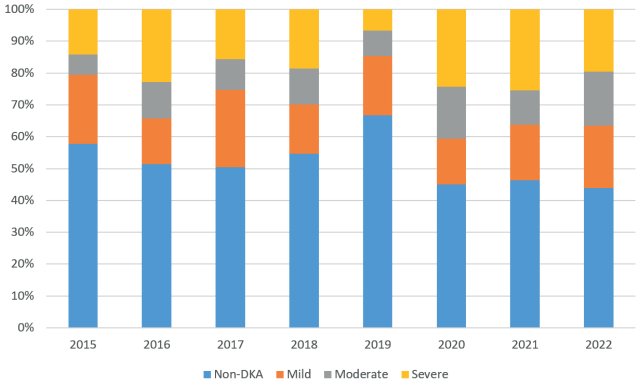

Figure 4. Comparison of DKA severity between 2015 and 2022

there was a significant increase in these rates again with the pandemic (Figure 2 and Figure 3). While there was a statistically significant difference (p=0.038) when the severity level ratios of DKA were examined depending on the years, this difference was found only in the severe DKA. Accordingly, the incidence of severe DKA increased in 2020 and 2021 compared to 2019 (Figure 4).

DISCUSSION

In our study, the mean annual incidence of newly diagnosed T1D in children was found to be 3.8/100.000 between 2015 and 2022 in Bursa Province. Compared to previous studies, the incidence of newly diagnosed type 1 diabetes in Bursa Province was calculated for the first time. Incidence rates of T1D have been shown to be 0.1/100.000 in China and 36.8/100.000 in Sardinia and Finland annually.[3] The worldwide distribution of T1D has been published many times and varies considerably from region to region. It is emphasized that the variability might be due to differential distributions of risk genes for the disease, environmental exposures, or methodological issues.[1-3,7,8,19] In Turkey, a few studies evaluate the incidence of T1D.[4-6,13-15] In 2016, the first study from Turkey showed the incidence and prevalence of Type 1 diabetes in children; the incidence was 10.8/100.000.[14] Moreover, 13.1/100.000 in Malatya Province (2007-2019),[5] 8.03/100.000 in Diyarbakır Province (2020),[6] 16.7/100.000 in Elazığ Province (2009-2019),[15] 7.2/100.000 in Southeastern of Turkey (2010-2011),[13] and 8.99/100.000 in Northwest of Turkey (2013-1015)[4] has been reported. The reason for the lower incidence of T1D compared to other provinces in our study was interpreted as data loss from one of the centers and proximity to Istanbul, the largest city in Turkey. The highest incidence was detected in 2017 and 2021. It was thought that the lower annual incidence values in 2019 compared to the previous and following years may have been due to more applications to the center for which data could not be obtained.

There are no differences between genders (1.06:1), similar to the literature.[4,5,14-16,20,21] The median age at diagnosis was 9.23 years. When the age distribution was evaluated, it was observed that it peaked in two age groups: 10-14.9 years in males and 5-9.9 years in females. Some studies have reported that the 10-15 age group is the most common[6,14,18,22]; otherwise, some studies have found that

the most common age group is 5-10 years old.[4,5,16] Gender dominance in the peaks was only emphasized in Demirbilek et al.'s study, likely our study.[13] This situation is thought to be due to the different ages at which boys and girls enter puberty.

Winter and December were the most common seasons and months for new diagnoses in all years. In many studies, the most common seasons were winter and autumn.[4-6,16,20,21] It is estimated that the increase in the rate of new diagnoses in the winter and autumn seasons may be related to infectious diseases.

The incidence of newly diagnosed T1D showed a significant decrease after the pandemic declaration and lockdown in Turkey in April, May, and June 2020 compared to previous years and months, while an increase was detected after the end of the lockdown in July and August 2020. The systematic review published in 2024 examined 126 studies from 55 countries.[22] The incidence of T1D during the pandemic period was higher than the pre-pandemic incidence. A study from Turkey emphasized that T1D was diagnosed more frequently during the pandemic, particularly in the summer months.[18] This study highlighted that, similar to our research, the number of patients diagnosed with T1D was higher in the summer period when the number of COVID-19 cases decreased, when there were many COVID-19 cases.[18] Although there is no statistical data, it is presumed that a decline in admissions is due to curfew, lockdown, or avoidance of going to hospitals and/or emergency rooms due to fear of COVID-19.

While the DKA rate at diagnosis decreased in 2019, there was a significant increase in these rates again with the pandemic. Moreover, the severe DKA rate in 2020 and 2021 increased compared to 2019. Many studies have shown a rise in DKA or DKA severity during the pandemic, similar to our study.[17,18,23-25] We assume that the reason is lockdown or curfew, or even if there is no lockdown, there may be a delay in going to the hospital due to fear of COVID-19.

CONCLUSION

This study presents the first comprehensive analysis of the incidence of initially diagnosed T1D in children and adolescents in Bursa Province. The findings reveal a lower incidence rate than in other regions of Turkey, possibly due to data loss and geographical factors. The study also highlights patterns in age, gender, and seasonality of diagnoses, aligning with global trends. Notably, the COVID-19 pandemic influenced the incidence and severity of T1D presentations, with delayed diagnoses and increased DKA rates likely resulting from lockdowns and healthcare avoidance. These findings underscore the need for heightened awareness and timely intervention, particularly during global health crises, to prevent complications in pediatric T1D patients. Further research is warranted to explore regional disparities and long-term trends in T1D incidence.

Limitations of the study

The most important limitation of the study is that the data were collected from different centers, and that the data from one center could only be used in part of the study due to insufficient archiving. Additionally, we just speculated this data because there was no statistical data: The COVID-19 pandemic influenced the incidence and severity of T1D presentations, with delayed diagnoses and increased rates of DKA predicted due to lockdown and avoidance of healthcare services.

Ethical approval

This study has been approved by the Bursa Yüksek İhtisas Education and Research Hospital Clinical Research Ethics Board (approval date 19.04.2023, number 2011-KAEK-25 2023/04-21). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: YDÖ, ÖK, EE; data collection: YDÖ, ÖK, EDA, EE; analysis and interpretation of results: YDÖ, GÖ; draft manuscript preparation: YDÖ, GÖ, EE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The phenomenological examination of Turkish mothers who have hemophilic sons

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ABSTRACT

Objective: Hemophilia is a coagulation disorder characterized by bleeding episodes that are genetically transmitted from mothers to sons. The disease affects the family psychologically and socially, especially the mothers, who are closely involved in the care of the affected child. We aimed to question the experiences of Turkish mothers with children diagnosed with hemophilia.

Method: The study is based on phenomenology, one of the qualitative research designs. We conducted and recorded face-to-face interviews with nine mothers of patients with severe hemophilia A. Each of the semi-structured interviews, in which the interview form consisting of 23 questions was used, lasted approximately 40 minutes. After the recorded data were deciphered, the interviews were analyzed using qualitative analysis methods and presented under six themes.

Results: There is long-term anxiety in the daily life of mothers. Fatalism in Islam and the presence of a hemophilic individual in the family were the most important factors in accepting the disease. However, the mothers have the potential to live an uneasy and anxious life. It limits the social life of both the hemophilic son and the mother. Children are placed in a "glass bell" like a lonely fish during early childhood. The glass bell suddenly breaks at the beginning of school, and children face various social-emotional risks. In the adolescent period, children's social life expands, and mothers' anxiety about the future of their children begins to increase.

Conclusion: As we know, treatment compliance can improve the quality of life in children with hemophilia. To ensure this compliance, knowing and identifying the psychosocial burden of the disease on the mother and finding solutions will increase her child's compliance with hemophilia treatment and life expectancy.

Keywords: mother, son, hemophilia, phenomenology, psychosocial, life, treatment

INTRODUCTION

Hemophilia is an X-linked recessive coagulation disorder disease caused by coagulation factors (F)VIII (hemophilia A) and FIX (hemophilia B) deficiency.[1] When mothers are carriers, boys get sick, and girls become carriers.[2] The prevalence of hemophilia A and B is reported as 1 in 5,000 and 1 in 30,000, respectively, in males.[3,4] The most effective treatment option all over the world is the intravenous replacement of the missing factor as a prophylaxis. This causes frequent vascular access 2-3 times a week.[5-8]

The fear of bleeding that spreads throughout life, and the limitation in physical activity affect hemophilic individuals

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physically as well as restrict them psychosocially.[9] Parents begin to share all these difficulties experienced by the hemophilic individual.[10] This situation affects the family psychologically and socially, especially the mothers who are closely taking care of the child. Knowing the difficulties experienced by the hemophilic individual and their mothers and identifying their needs are the most important factors that increase compliance with the treatment.[11,12]

Phenomenology is a qualitative research method that allows people to express their understanding, feelings, perspectives, and perceptions about a certain phenomenon or concept. It is used to describe how they experience this phenomenon.[13,14] As in many other chronic diseases, we know that hemophilia does not affect the individual alone but rather affects the whole family, especially the mothers who are primarily responsible for their care and restrict them psychosocially.[15,16] Therefore, in this study, we aimed to phenomenological reveal the experiences of mothers about their son with hemophilia and how these experiences are reflected in their daily lives and psychological states.

METHODS

The aim of this study is to question the experiences of mothers who have children with hemophilia regarding their children's diseases. The study's design is based on phenomenology, one of the qualitative research designs. The experiences of the mothers were questioned in depth. Face-to-face semi-structured interviews were conducted with nine mothers. Interviews were held with the mothers of hemophilic patients who were followed up at the European Hemophilia Comprehensive Care Centre (EHCCC) of KANKA Pediatric Hematology-Oncology and Bone Marrow Transplantation Hospital of Erciyes University. Each interview was recorded on tapes and lasted about 40 to 45 minutes. An "Interview Form" consisting of 23 questions (Appendix 1) prepared by the research team focusing on the experiences of the mothers was used. The interviews ended when the data reached saturation.

Qualitative analysis

The deciphered data was first encoded line by line in the form of open coding. The data whose coding was completed were combined around certain axes. Within the axis codes, divergences and overlaps were determined, and the data were arranged according to these divergences and overlaps. Finally, the data was abstracted and interpreted. Various methods were used to ensure the validity and reliability of the research. The reference adequacy of the study was evaluated by getting the opinions of various professional peers. In addition, the analysis of one of the interviews within the scope of the study was left to the end, and the data belonging to this interview were placed in the categories and themes created. Afterward, it was evaluated whether the data related to these categories and themes also emerged in this interview. To evaluate the predictability of the study, another academician's opinion was taken to evaluate whether "we could reach these results from these answers." Finally, the findings on six themes were presented to the reader. This study was approved by Erciyes University Ethic Committee with the approval code (2022/130).

RESULTS

Nine mothers of children diagnosed with severe hemophilia A were enrolled in the study. The median age of the mothers was 41 (31 to 47 years). Four mothers had a family history of hemophilia. Only one mother had twin hemophilic sons, while the others had one hemophilic son. The median age of the children diagnosed with hemophilia was 12 (7–16) years. The themes were constructed in the context of the child's diagnosis process, the difficulties experienced by the mothers, their coping methods, the risks experienced by the child and the measures taken, the relationship between the mother and the child, school processes, and psychological protection methods of the mother and child.

Theme 1- Standard Sequence in the Diagnostic Process: Shock, Denial, Acceptance:

According to the experiences of mothers of children diagnosed with hemophilia; although individual differences are at the forefront, the diagnostic process usually begins after a trauma or medical intervention. If there is another hemophiliac in the family, diagnosis is easier and takes less time. However, the most important problem experienced in diagnosing and delaying the diagnosis is misleading diagnostic tests.

Participant(P)1- "He was 14 months old. He fell, his mouth and gum bled, and it did not stop for 2–3 days. Interventions were done in the hospital, but they did not stop easily. He was diagnosed with hemophilia at last."

P2-"Small bruises began to appear in certain areas of his body. At first, we thought his brother was pinching him. Then we went to the doctor; he was diagnosed with hemophilia three days later."

P7- "When he was 3 years old, he fell on his knee. A doctor in the private hospital said the fluid was collected in the knee. We couldn't trust the doctor because his uncle had hemophilia. We applied to a university hospital. After the evaluation, we learned that there was bleeding in the knee, and he was diagnosed with hemophilia. I was shocked."

After the diagnosis, a challenging process begins for the diagnosed child and his mother. The post-diagnosis period is described as the "most difficult period in the life" by the mothers. In the first period, shock and denial are observed in mothers; they tend to reject the disease. There are various factors that facilitate and delay the mother's acceptance. The most important factor facilitating acceptance is the presence of a hemophilic individual in the family. While this reduces the age of diagnosis, thanks to the mother's previous knowledge and experiences, it supports the shortening of the shock and denial phases. Belief is another important factor that facilitates the acceptance process. The mother's belief that everything is under Allah's initiative and her devotion to destiny has a positive effect on the acceptance process.

P3- "I'm a bit of a fatalist. Destiny says everything. If Allah has written that I am destined to have 10 children with hemophilia, I have no complaints."

P4- "I spoke to my uncles. They always guided me because they were experienced in this field."

P9- "We were shocked when we learned he was hemophilic. Over time, we said, everything comes from Allah, and we will do everything for the treatment."

Husbands and their relatives generally tend to accept it easily because of their belief that the disease is caused by fate. Sometimes, mothers who are at risk of being criticized for being carriers prefer not to share any information.

P1- "I was very upset, but my husband supported me. Nothing bad happened between us."

P9- "I didn't listen to anyone's criticism. My family is already aware of the hemophilia due to my brother. And I explained to my husband what was going on. They assumed this child would always bleed. Then they saw that this was not so."

Mothers tend to blame themselves or be blamed by their children diagnosed with hemophilia when their children have a problematic event such as bleeding

P7- "Sometimes I wonder if I am to blame for his condition, 'why didn't I get him checked earlier,' but I never expected this."

P8- "Sometimes my son says that the disease was transmitted from me, so I get sad."

Theme 2- What Children Experience: Lonely Fish in a Glass Bell

Although the age at diagnosis of hemophilia varies, the diagnosis is usually made within the first year. The infancy period is dangerous because of the risk of physical trauma. There is uncontrolled mobility, and they may experience many accidents. For this reason, babies are put in a "glass bell" like a "lonely fish" after they are diagnosed. Their playgrounds, play materials, and play opportunities are limited. Both the physical movements and social lives of children are restricted.

P1- "There is a park on our site. We check it through the window. If there are no children, we go there. We prefer to go during the school hours."

P4- "I don't go where there are many children. I can keep him safely when we are alone at home, but it is difficult to keep him away from other children."

There will be no significant changes in restrictions as time progresses. Regardless of the age of a child with hemophilia, there are always limitations in their life. However, as the child's awareness increases in parallel with his cognitive development, problems begin to come along. The more the child's awareness of the process increases, the more their reactions, such as questioning, rebelling, and rejection increase. However, although it is seen as a contradiction, there is also a positive relationship between the child's cognitive development and adaptation to the disease. While some children experience an intense adaptation process and accept routines as of adolescence, some children begin to question and tend to refuse treatment during this period. In this developmental period, the child begins to question and ask why. The answer to this question may have a negative impact on the mental health of the child.

P2- "Mom, why me?" was the one thing I could never really answer."

P7- "First, he forced himself. He was getting tired, and so was I. Now I say 'come on, you'll receive your medicine.' He comes, we're getting it done, and then we're leaving. Everyone has accepted this now. But he

sometimes asks, "Mom, why me? Why can't I play ball like my friends? Why can't I run outside like my friends? Why does my body hurt?"

They may exhibit an introverted and aggressive character during adolescence or may have difficulties belonging to a peer group. Social labelling in this period is also a negative factor for the child's social life.

P8- "He can't express himself and can't speak in a social group. He says, 'I'm ashamed, mom'."

P6- "His relations with friends aren't so great. He's shy. He doesn't have many friends anyway. He pulls himself back since he's ill."

The overprotective attitude of the mother is a risk for the mother-child relationship in every period. However, as the child gets older, this risk becomes larger and spreads over the child's whole life.

P5- I did not let him play ball and ride a bike. I always asked my brother because he had experienced it before. The doctor also said, if necessary, take him with you and make him sit beside you so that nothing happens to him.

P7- "My relationship with him is very close. For instance, he cannot do without me, he always wants to go out with me."

P9- "He gets angry at me, shouts, but never gives up on me. Since he was little, we grew up together. He is all I have, and I am all he has."

Theme 3- What Mothers Experience: A Life on Tenterhooks

After the diagnosis, the mother builds her life on hemophilia and her son. She makes many sacrifices (leaving work, postponing personal needs, reducing social life, organizing the whole day for her diagnosed son, etc.). They are afraid to take risks and try to continue with a "zero error policy" by taking precautions.

P1- "I always keep an eye on my child. We control his steps as if we are constantly taking those steps. Maybe we pay too much attention while walking on the road or something."

P2- "I was so scared that something might happen to him, I started working as a "helper mom" at the kindergarten just to protect him."

The psychological problems that begin with the diagnosis decrease in the future. However, the mother's mental health never becomes "very good". Mothers have the potential to experience mental distress due to their worries about the traumas, future lives, education, and employment opportunities of their sons.

P6- "We look for secluded places and watch over our children. So that they wouldn't do anything to our kids, like throwing a ball to my son."

The mother experiences conflict between her thoughts and practices, and this causes her to fall into various contradictions. The child, who must be restricted in terms of heavy physical activity, has to be directed to different activities. Technological devices and the internet are considered and preferred by mothers.

P6- "I am afraid that my son, who has been diagnosed with hemophilia, will have financial difficulties. How will he be able to support his family when he wants to get married in the future? Will he be able to work? I have a lot of worries."

Although fatalism appears to be a positive factor in acceptance of the reactions against the mother and in the protective mental health of the mother, such fatalism also has a negative effect. Due to the fatalism, mothers refuse to implement protective and preventive measures, and this causes the mother to give birth to a second, third, and even fourth child with hemophilia.

Theme 4- Breaking the Glass Bell: Starting School

The biggest challenge for any hemophilic child is beginning school. By the beginning of elementary school, the glass bell is suddenly broken. The children begin to experience social interactions, get in touch, and spend some time with their peers. Children's awareness about hemophilia also increases. A new friendship brings the possibility of peer bullying.

P3- "His friends were saying to him, "You are sick; don't play with us; you will fall and get us into trouble."

P6- "I went to school and had to administer the factor due to bleeding. The classmates told my child, 'You are sick.'"

Beginning school comes with challenges for all three parties: the hemophilic child, his mother, and the school professionals. The first difficulties experienced by the mother begin in the process of sharing the child's diagnosis

with school staff. Teachers and school staff are often unaware of hemophilia. Therefore, the process starts with anxiety for both them and their mothers.

P1- "He started school in the first year. I went during breaks and waited with him. I take him to class every time. Every break I go, I wait 15 minutes, and then I come back home."

The beginning of school does not mean only negativity for hemophilic children or their mothers. The process begins to "normalize" for both the child and the mother after adaptation. The various requirements of being a hemophiliac have a negative effect on the child's adaptation to education. Especially for the children diagnosed with hemophilia who live in the countryside and have to go to a central hospital for follow-ups and treatments, there are problems with continuing the education.

Theme 5- Practices: How? Where? Why?

Hemophilia treatment consists of vascular access and factor administration. Most parents prefer that the interventions be done in a health institution. Sometimes, interventions can be done by parents or as a self-infusion at home. Mothers are afraid of making mistakes and hurting their children.

P3- "The emergency is so close to us, about 15–20 minutes away. We prefer to go there every three days a week: Monday, Wednesday, and Friday."

P5- "I would try to access an intravenous line for my child 10 times. It was very traumatizing to hurt him as his mother."

P8- "I began infusion at home a few years ago. I tried it on myself first. Then, I did it on him a few times. Then, when I couldn't find one of the veins, I broke off and took a break. I was having a hard time going to the hospital, and this time, I had the courage to establish vascular access."

Treatment in a health institution causes various difficulties, such as transportation. Despite that, the fact that the interventions are carried out by experienced healthcare personnel provides comfort to the mothers. However, encountering healthcare professionals who do not know about hemophilia can make the situation even more difficult.

P3- "Even in the hospital, we tell the nurses how to do the administration. They try to shake the vial of factor; we warn them that they should do it in their palm gently."

Theme 6- Family Dynamics

After the diagnosis of hemophilia, family dynamics never return to their normal state. Over time, the main focus of the family becomes their child, which causes conflicts in relationships. Compared to the hemophiliac, less attention is paid to the other children. This causes the sibling to be negatively affected. In addition, restrictions on the hemophilic child negatively affect relationships.

P6- "I was spending and still spend more time with him. Sometimes, I think I pay less attention to my other child."

DISCUSSION

Having a hemophilic individual in the family and "religious belief" facilitates the diagnosis process.[17-19] The primary caregiver who cares, monitors, and takes responsibility for the preventive measures and treatment process is the mother.[20] The father comes in now and then as a support power for the mother. Although the literature supports that, Limperg et al. did not show any difference in anxiety and depression between mothers and fathers for hemophilia.[17,21,22] Rumours about hemophilia are one of the most important factors complicating the acceptance and adaptation process.[23] The mother may be blamed by her husband and relatives because of carrying the affected gene. We know that this situation was more common in the past since access to treatment was difficult and bleeding was more frequent.[24] We observed that this psychological pressure has decreased with new treatment options and "fatalism" .[17,25]

The glass bell in which the children are placed after the diagnosis suddenly breaks with the beginning of primary school, and children begin to experience social relations; they meet and spend longer time with their peers.[26] The hemophilic child, who begins to understand that he is "different" from others, begins to oppose authority and resist restrictions. The child diagnosed with hemophilia is most exposed to peer bullying during this period.[27]

There are some changes in the daily routines of hemophilic patients, such as treatment interventions, follow-up, and admission to a hospital.[26,28] The focus of a mother's attention is her son with hemophilia.[29] The mother gives up a lot in her life, such as retiring from her job, postponing

her personal needs, and reducing her social life to almost nothing. The mother prefers not to go into crowded places, so she can't socialize and becomes lonely.[28]

Although the facilitating behavior of healthcare professionals and positive developments in the health system (easy application, low frequency of treatment, etc.) are factors that ease life. Mothers have the potential to experience mental distress due to their worries about trauma, bleeding episodes, their son's future lives, education, and employment opportunities.[30,31] This begins with the wrong information about hemophilia and the uncertainty of the treatment process, which spreads through all of life.[22,24,25]

By the beginning of school, the mother has concerns such as the risk of accidents, poor peer relations, and the child's potential to drop out or refuse to go to school.[32] After the adaptation to school, the process begins to "normalize" for both the child and the mother. While the school environment brings many risks for children, it also offers a positive experience in terms of social development. The child begins to spend time with his peers, gets to know new people, and engages in different activities.[26,27,32]

After the son is diagnosed with hemophilia, family dynamics never return to their original state.[12] The unrestricted behavior to the healthy child (absence of restrictions, a more social life, etc.) causes the hemophilic son negatively.[28] Other anxiety states include mothers telling their daughters that they may be carriers, the marriage processes of carrier girls, and possible hemophilia in their sons in the future.[33] However, with a good plan, a well-organized daily life, good precautions, regular prophylactic factor administration, and high motivation, it is possible to establish a near-normal life for people with hemophilia and their families.

CONCLUSION

Hemophilia is a chronic disease that affects patients, their parents, healthy siblings, and carrier sisters psychosocially. The basic condition of leading a healthy life in hemophilic individuals is to reduce bleeding and prevent disability with strong adherence to treatment. To achieve this, the mother, who is primarily responsible for the care, and the hemophilic individual need high motivation for life. We think that the psychological status of hemophilic boys and their mothers, their adaptation to hemophilia, and their social lives are very important in terms of adherence to treatment for hemophilia.

Ethical approval

This study has been approved by the Erciyes University Ethic Committee (approval date 09.02.2022, number 2022/130). The mothers in this study were informed and informed consent in the format was obtained.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: VG, EÜ, MK; data collection: VG, BFK, SA, AÖ; analysis and interpretation of results: SA, VG, EY, BFK; draft manuscript preparation: VG, SA, BFK, EÜ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of cardiac repolarization inhomogeneity in children with type 1 diabetes mellitus

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ABSTRACT

Objective: Type 1 diabetes mellitus is the most common endocrine-metabolic disease in childhood, which progresses with insulin deficiency and can cause serious cardiovascular complications. Atrial and ventricular arrhythmias are important cardiovascular complications of diabetes. In this study, cardiac repolarization inhomogeneity in children with Type 1 diabetes mellitus was evaluated electrocardiographically.

Method: Between February 2021 and April 2021, 48 patients with Type 1 diabetes mellitus and an equal number of healthy control groups were included in the study. Demographic characteristics of all cases were analyzed. P wave dispersion (PWd), QT interval (QT), QT dispersion (QTd), QTc interval (QTc), QTc dispersion (QTcd), Tpeak-Tend interval (Tp-e), Tp-e dispersion (Tp-ed) were evaluated with 12-lead electrocardiography, Tp-e/QT, Tp-Te/QTc ratios were calculated, and parameters were compared between both groups.

Results: The mean age of the patient group was 11.44 ± 4 years, and the mean age of the control group was 9.97 ± 4.5 years. The study group consisted of 18 girls (37.5%) and 30 boys (62.5%). In the control group, there were 21 girls (43.7%) and 27 boys (56.3%). There was no significant difference between the patient and control groups in terms of age and gender. The disease duration of the cases was 35.10±30.7 months, and the HbA1c value was 8.4±1.75%. When heart rates, P wave duration, and PWd, QT, QTd, QTc, QTcd, Tp-e, Tp-ed values were compared between the patient and control groups, there was no statistically significant difference between the PWd, QT and QTc intervals, QTd, QTcd, Tp-e interval, Tp-e dispersion, Tp-e/QT, Tp-e/QTd measurements and ratios of the two groups ($p>0.05$).

Conclusion: In our study, ventricular repolarization parameters of children with Type 1 diabetes and healthy children were found to be similar. Although we think the data we have obtained will contribute to the literature due to the limited number of studies on this subject in children, we believe that long-term and prospective studies involving more patients are needed.

Keywords: type 1 diabetes mellitus, p wave dispersion, QT dispersion, QTc dispersion, Tp-e interval

INTRODUCTION

Type 1 diabetes mellitus (DM) is the most common endocrinological and metabolic disease of childhood and adolescence, which progresses with abnormalities in carbohydrate, fat, and protein metabolism and causes serious cardiovascular complications. Cardiovascular complications are the main cause of mortality and morbidity in diabetic patients.[1] It is under consideration that conditions such as cardiac conduction abnormalities, myocardial damage, autonomic system dysfunction, and ventricular repolarization changes, which are caused by

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diabetes, may predispose individuals to arrhythmias. The most common heart rhythm disorders that can cause mortality in these patients are atrial fibrillation and ventricular dysrhythmias.[2]

P wave dispersion (PWd), QT interval (QT), QT dispersion (QTd), QTc interval (QTc), QTc dispersion (QTcd), Tpeak-end dispersion (Tp-ed), Tp-e/QT, Tp-e /QTc ratios are parameters that can be calculated non-invasively from superficial electrocardiography and can be used to predict the risk of developing arrhythmia.[3-6] Increased PWD duration indicates impaired interatrial and intraatrial conduction.[7] QT and QTc values corrected for heart rate indicate the duration of ventricular myocardial depolarization and repolarization. QT dispersion indicates ventricular repolarization heterogeneity. This heterogeneity may be the cause of fatal ventricular arrhythmias.[1]

Prolongation of QT and QTc durations and increased QTd were found in patients with diabetes, and it was found to be associated with sudden cardiac death and arrhythmias in these patients.[8] The Tp-e interval indicates transmural dispersion of ventricular repolarization and has been associated with an increased risk of sudden cardiac death by causing ventricular arrhythmias. Tp-e is affected by changes in heart rate and body weight.[9] Tp-e/QT and Tp-e/QTc ratios are newly defined parameters that are recommended as more accurate measurements for the dispersion of ventricular repolarization since they are not affected by heart rate changes compared to other parameters.[10,11]

Studies on cardiac repolarization changes in pediatric patients with Type 1 diabetes are rare in the literature. Our aim in this study was to evaluate cardiac repolarization inhomogeneity in children with type 1 diabetes.

MATERIALS AND METHODS

The study was conducted prospectively in the Pediatric Cardiology and Pediatric Endocrinology outpatient clinic of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital between February 2021 and April 2021. Forty-eight patients followed up with the diagnosis of Type 1 DM in the Pediatric Endocrinology outpatient clinic were included in the study group. Those with congenital and/or acquired heart disease were excluded from the study. The control group was selected from healthy children under the age of 18 who applied to the Pediatric Cardiology outpatient clinic for reasons such as innocent heart murmur or non-specific chest pain, had normal heart examination and tests, and had no other diseases. A detailed history of all cases in the patient and control groups was taken, and via routine physical examinations, anthropometric measurements were recorded. The fasting blood glucose, HbA1c level, blood lipid panel, liver and kidney function tests, thyroid function tests, and hemogram values of the patient group in the last 3 months, age at diagnosis, and duration of being diabetic were obtained from the pediatric endocrine outpatient clinic files.

Heart rate was measured by calculating three consecutive R-R intervals from the derivation of DII. P wave duration was calculated as the time between the separation and junction of the P wave from the isoelectric line. P wave durations were measured in milliseconds, and the difference between the longest and the shortest duration was evaluated as PWd. QT duration was measured as the time between the onset of the QRS complex and the junction of the T wave with the isoelectric line. QT durations were measured in milliseconds, and the difference between the longest and the shortest duration was evaluated as QTd. QT measurements in each lead were corrected for heart rate with Bazett's formula (QTc = QT/√RR), and QTc calculation was made. The difference between the longest QTc and the shortest QTc duration was evaluated as QTcd. Tp-e time was calculated by measuring the time in milliseconds between the peak of the T wave in the chest leads V5 and V6 corresponding to the left ventricle and the junction of the tangential line from the peak to the junction of the isoelectric line. Tp-e time was not calculated in cases where the end of the T wave could not be clearly distinguished and/or the T wave height was less than 1.5 mm. Tp-e/QT and Tp-e/QTc ratios were calculated by measuring QT and QTc from the same lead in which the Tp-e interval was measured.

Statistical analysis

All analyses of the study were performed using the "IBM SPSS Statistics Version 25" package program. Continuous variables were expressed as "mean ± standard deviation". The distributions of all data were analyzed using Kolmogorov-Smirnov tests. In comparing the means of two independent groups, the independent Student T-test was used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. The significance level of all statistical analyses was accepted as p value below 0.05.

RESULTS

The study group consisted of 18 girls (37.5%) and 30 boys (62.5%), and the mean age was 11.44±4 years. In the control group, there were 21 girls (43.7%) and 27 boys (56.3%), and the mean age was 9.97±4.5 years. There was no significant difference between the patient and control groups in terms of age and gender. The disease duration of the cases was 35.10±30.7 months, and the HbA1c value was 8.4±1.75%. Fasting blood glucose was 257.46±116.35 mg/dL, total cholesterol level 165.9±24.7 mg/dL, triglyceride level 96.02±46.3 mg/dL, LDL level 91.4±19,8 mg/dL, and HDL level was determined as 52.8±13.9 mg/dL. When the results of the patients were compared with the laboratory reference values, fasting blood glucose, HbA1c, and lipid panel values were found to be high. When the biochemical parameters were examined, AST was 25.5±15.6 IU/l, ALT was 17±9.4 IU/l, BUN was 13.1±3 mg/dL, and creatinine values were 0.6±0.13 mg/dL. AST and ALT values of 2 patients were higher than laboratory reference values (Table 1).

When heart rates, P wave duration, and PWd, QT, QTd, QTc, QTcd, Tp-e, and Tp-ed values were compared between the patient and control groups, there was no statistically significant difference between the two groups. Tp-e/QT and Tp-e/QTc ratios were also similar between the groups (Table 2).

DISCUSSION

It is under consideration that conditions such as cardiac conduction abnormalities, Myocardial damage, autonomic system dysfunction, and ventricular repolarization changes that, due to diabetes, predispose to arrhythmias.[2] In this study, cardiac repolarization inhomogeneity was examined in children with Type 1 diabetes and evaluated in terms of possible ventricular and atrial arrhythmias, and no difference was found between children with DM diagnosis and healthy children in terms of cardiac repolarization abnormality.

In diabetic patients, HbA1c is a reliable parameter that shows the mean blood glucose value in the last 2-3 months and is used to monitor the success of treatment.[12] According to the 2020 recommendations of the American Diabetes Association (ADA), the target HbA1c level should be <7.5%.[13] According to the 2018 guideline of ISPAD (International Society for Pediatric and Adolescent Diabetes), the target HbA1c level should be < 7% in the treatment of diabetes.[14]

Table 2. Comparison of electrocardiographic measurements of the patient and control groups

	Patient (n: 48)	Control (n: 48)	
	Mean ± SD	Mean ± SD	P
Herat rate (/min)	95.15±17.6	96.6 ±21.9	0.71
P wave duration (ms)	91.46±13.5	95.2 ±15.1	0.20
P dispersion (ms)	41.67±11.5	45.6 ±12.8	0.11
QT interval (ms)	331.88±39.7	346.8± 41.4	0.07
QT dispersion (ms)	50.42±24	58.5 ± 23.6	0.09
QTc interval (ms)	418.31± 32.2	427.4 ± 24	0.12
QTc dispersion (ms)	64.0 ± 31.9	76.2 ±35.4	0.08
Tp-e interval (ms)	83.75± 20.8	91.25±18.05	0.07
Tp-e dispersion (ms)	40.4 ±17.2	36.8±14.6	0.28
Tp-e/QT rate	0.24 ±0.06	0.26 ± 0.04	0.1
Tp-e/QTc rate	0.20±0.08	0.20±0.04	0.61

Table 1. Laboratory findings and reference ranges of the patient group

	Minimum	Maximum	Mean±SD	The reference range
Blood glucose (mg/dL)	89	427	257.46± 116.3	70-100
HbA1c (%)	5.9	10.2	8.40±1.7	<6.5
T. cholesterol (mg/dL)	127	240	165.94±24.7	0-200
LDL cholesterol (mg/dL)	50	155	91.48±19.8	0-100
HDL cholesterol (mg/dL)	8	75	52.89±13.9	>35
Triglyceride (mg/dL)	38	264	96.02±46.3	0-150
AST (IU/l)	11	94	25.56±15.6	0-50
ALT (IU/l)	8	68	17.02±9.4	0-50
BUN (mg/dL)	7	19	13.10±3	7.9-20
Creatinine (mg/dL)	0.4	1.0	0.6±0.1	0.8-1.4

HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein,
T. cholesterol: Total cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen

In Wood et al.'s study, which included 13.316 pediatric patients followed up with a diagnosis of type 1 diabetes, only about one-third of the participants met the age-specific ADA and ISPAD targets for HbA1c.[15] In a multicenter study conducted by Hatun et al. in Turkey, it was found that 29.1% of the patients had an HbA1c value of <7.5%.[16] The mean HbA1c value of the cases in our study was 8.4%, and the target HbA1c value was reached only in one-third of the patients, similar to other studies.

In patients with type 1 diabetes mellitus, hypertriglyceridemia, low HDL cholesterol, and high LDL cholesterol levels can be observed due to hepatic lipase activities related to abnormal lipoprotein lipase and exogenously administered insulin.[17,18] According to the study of Zabeen et al., including 422 Type 1 DM patients with an average age of 15 and a mean diabetes duration of 3 years, the overall dyslipidemia frequency was found to be 65%, and the mean HbA1c level was 9.8.[19] In our study it was determined that the mean age of the patient group was 11.4, the mean duration of being diabetic was 35 months, and the frequency of dyslipidemia was 37.5%. It was found that 6.2% of the patients have high total cholesterol, 10.4% low HDL, 25% high LDL, and 8.3% high triglyceride. Although our study is similar to the study of Zabeen et al. in terms of diabetes duration, the incidence of dyslipidemia is lower. This may be because the patients in our study had better glycemic control and had a lower mean age.

Diabetes can affect the conduction system of the heart due to autonomic dysfunction, atrial and ventricular remodeling, mitochondrial changes, inflammation, and blood glucose irregularities.[20,21] Given the limited number of studies focusing on adolescents and young adults with T1DM, the etiology of sudden cardiac death remains underdiagnosed in childhood despite the heightened risks of mortality and morbidity. Patients with Type 1 Diabetes Mellitus (T1DM) face a significantly elevated risk of ventricular arrhythmias and sudden cardiac death. Potential mechanisms underlying these arrhythmias include reentry circuits, triggered activity, and heightened autonomic tone. However, the exact pathophysiological pathways responsible for arrhythmogenesis in diabetic individuals remain incompletely understood. Chronic hyperglycemia may induce structural cardiac alterations, including myocardial fibrosis and cellular loss within viable myocardial tissue and conduction pathways. These changes are thought to facilitate the development of micro-reentry circuits. Furthermore, disruptions in the heart's electrical homeostasis, combined with increased sympathetic nervous system activity, may further contribute to the initiation of ventricular arrhythmias.[5] It has been shown that cardiac autonomic dysfunction can be diagnosed by ECG even if type 1 DM patients are asymptomatic.[22]

QT, QTc, and QT dispersion (QTd) have been identified as useful predictors of ventricular arrhythmic events and sudden cardiac death across various clinical conditions. The QT interval reflects the duration from the onset of ventricular depolarization to the end of repolarization. Given that the QT interval is influenced by heart rate, the corrected QT interval (QTc) has been introduced to provide a more reliable assessment independent of heart rate variations. QTc prolongation has been documented in numerous cardiovascular and systemic diseases, and it has also been proposed as an independent risk marker for ventricular arrhythmias, sudden cardiac death, and increased mortality in individuals with Type 1 Diabetes Mellitus (T1DM). In T1DM patients, QTc prolongation has been positively associated with advancing age, longer disease duration, and suboptimal glycemic control. A study by Inanır et al. further supports this association, reporting a significant correlation between QTc interval, duration of diabetes, and elevated HbA1c levels.[5]

In a study conducted by Uysal et al. in 150 children with Type 1 DM with a mean age of 11.61 ± 3.72 years, QT and QTc intervals and QTcd duration were found to be significantly higher in diabetic children compared to the healthy control group.[22] In a study conducted by Köken et al. on 33 children with type 1 diabetes with a mean age of 12.3 years, P wave duration and PWd were found to be significantly higher than the healthy control group.[23] In a study conducted by Şahan et al. on 165 children with type 1 diabetes, when compared to the control group, the increased QTc and QTcd values in the patient group indicate a predisposition to arrhythmia in these children.[24] In our study, unlike these studies, no significant difference was found between the PWd, QT, and QTc interval and QTcd durations between the patients and the control group. This may be due to the limited sample size of our study, which is a cross-sectional study.

Studies on Tp-e interval, Tp-e/QT, and Tp-e/QTc values in patients with type 1 DM are limited. The Tp-e interval is a relatively new ECG parameter that indicates ventricular repolarization. Tp-e measurement is an important parameter associated with sudden cardiac death, especially in cases where the QTc duration is normal or cannot be measured due to prolonged QRS duration. The Tp-e/QT ratio has also

recently been used as a novel electrocardiographic marker for ventricular repolarization and has been reported to be associated with malignant ventricular arrhythmias.[25,26] In a study with a large number of people with T1DM (855 patients, 1710 controls), depolarization parameters were observed to be higher in people with T1DM. In this study, depolarization parameters were found to be higher in T1DM patients of any age, but repolarization parameters are only increased in young people with T1DM, and this situation is thought to be related to sudden cardiac death and the dead-in-bed syndrome.[27]

The Tp-e/QT ratio includes the transmural dispersion (Tp-e) and dimensional dispersion (QT) values of ventricular repolarization. In the study of Güney et al., it was observed that Tp-e increased in children with Type 1 DM compared to the control group, but Tp-e/QT and Tp-e/QTc ratios were similar to the healthy control group.[1] In the study conducted by Olmez et al. in 35 patients with Type 1 DM, they found that the Tp-e interval and Tp-e/QT ratio were similar in both groups, while QT and QTc durations were increased in the patient group compared to the control group.[28] In our study, no significant difference was found between the QT durations, QTc durations, and QTcd, Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc measurements of children with type 1 diabetes and healthy children. We think that the reason for this is the low sample size and short follow-up period.

The most important limitation of this study is that it is a cross-sectional, not a long-term study. Pediatric patients with T1DM have a long life expectancy after diagnosis, and given the impaired ventricular depolarization and increased sensitivity to repolarization, meticulous cardiological surveillance for arrhythmias may be necessary. Even in the absence of T1DM and cardiac symptoms, periodic ECG monitoring can be performed during outpatient clinic visits. We think it would be more useful to compare the ECG obtained at the time of diagnosis with the ECG obtained after long-term follow-up. In addition, since our study was a single-center study with a low sample size, multicenter studies with large participation should confirm the data obtained.

In conclusion, this study examined the effect of new repolarization parameters on cardiac arrhythmia in patients with type 1 diabetes and QT durations, QTc durations, and QTcd, Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc measurements were found to be similar between children with type 1 diabetes and healthy children. We think the data we obtained will contribute to the literature since there are very limited articles examining the possible effects on the cardiac conduction system in children with Type 1 DM. However, long-term prospective studies involving larger numbers of patients are needed.

Ethical approval

This study has been approved by the Kütahya Health Sciences University Non-Interventional Clinical Research Ethics Committee (approval date 16.12.2020, number 2020/17-18). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: İE, RÖ; data collection: İE, DG; analysis and interpretation of results: İE, RÖ, VNB; draft manuscript preparation: İE, RÖ, VNB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Bacteria isolated from blood cultures in a neonatal and pediatric intensive care unit and their antibiotic resistance: 5-year results

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ABSTRACT

Objective: Bloodstream infections represent a leading cause of illness and death among children in developing nations. The aim of this study was to determine the bacterial profile and antibiotic resistance status of pathogens isolated from blood cultures taken from children in the neonatal and pediatric intensive care units of a university hospital in Türkiye.

Methods: Isolation, species identification, and antibiotic susceptibility testing of 1,197 blood culture samples from the neonatal and pediatric intensive care units of a university hospital were conducted using classical methods and automated Bact Alert and BD Phoenix systems between January 2018 and December 2022.

Results: Of the 1197 blood cultures included in the study, 776 (64.82%) were isolated from neonatal, and 421 (35.18%) were isolated from the pediatric intensive care unit. Of the 1197 microorganisms identified in blood cultures, 868 (72.51%) were gram-positive, 259 (21.63%) were gram-negative bacteria, and 70 (5.84%) were fungi. Among the identified bacteria, the most common microorganism was coagulase-negative staphylococci (62.40%), followed by *Klebsiella pneumoniae* (6.59%) and *Acinetobacter baumannii* (6.26%). Methicillin resistance was 93.44% in coagulase-negative staphylococci and 54.54% in *Staphylococcus aureus*. Among Gram-negative bacteria, *Acinetobacter baumannii* showed a high resistance to all antibiotics tested, while *Serratia marcescens* had the highest susceptibility rate.

Conclusion: According to the results of our study, the antibacterial resistance rates of microorganisms isolated from blood cultures differ. We believe that regular monitoring of susceptibility patterns of strains will encourage rational antibiotic use and provide more effective treatment by reducing resistance among bacteria.

Keywords: antibiotic resistance, child, intensive care units, neonatal, Türkiye

INTRODUCTION

Bloodstream infections are quite common in the pediatric age group and are a significant cause of morbidity and mortality, particularly in neonates and children. These infections pose a life-threatening risk, especially in immunocompromised patients admitted to intensive care units (ICUs).[1] Globally, bloodstream infections affect approximately 30 million people annually, resulting in 6 million deaths.[2] Every year, 3 million neonates and 1.2 million children suffer from sepsis, leading to serious health issues.[3]

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In ICUs, Gram-positive microorganisms are most frequently isolated from blood cultures. Among them, *coagulase-negative staphylococci* (*CoNS*) are the most common, followed by *Staphylococcus aureus* (*S. aureus*) and *Enterococcus* species.[4,5] Gram-negative bacteria, such as *Acinetobacter* species, *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Klebsiella pneumoniae* (*K. pneumoniae*), and *Haemophilus influenzae* (*H. influenzae*), are also frequently isolated.[1,5]

The identification of bloodborne pathogens and the determination of their antibiotic susceptibility are urgent medical priorities.[6] However, since bacteriological cultures and susceptibility testing take several days, empirical antimicrobial treatment is typically initiated before blood culture results are available in nearly all cases.[7] A major issue associated with empirical therapy is the emergence of antibiotic resistance.[8] The increasing antimicrobial resistance in bloodstream infections, particularly in developing countries, is a growing concern, and studies conducted in these regions have reported a rise in antibiotic resistance.[9-12] Rational and appropriate use of antibiotics requires knowledge of the most commonly isolated bacteria from blood cultures and their antibiotic susceptibility patterns.[13] Early detection of antimicrobial susceptibility patterns has been shown to reduce morbidity and mortality associated with bloodstream infections.[14]

The aim of this study is to determine the bacterial profile and antibiotic resistance status of pathogens isolated from blood cultures of children admitted to neonatal and pediatric intensive care units of a university hospital in Türkiye over a five-year period.

MATERIAL AND METHODS

Study design

This study is a retrospective evaluation of approximately 1,197 blood cultures sent from neonatal and pediatric ICUs to the Medical Microbiology Laboratory of a university-affiliated Health Application and Research Hospital.

Study population and sample

The study includes blood culture results from patients admitted to neonatal and pediatric intensive care units between January 1, 2018, and December 31, 2022. The hospital where the study is conducted has a 39-bed neonatal intensive care unit (5 at level 1, 17 at level 2, and 17 at level 3) and a 15-bed pediatric intensive care unit (5 at level 2 and 10 at level 3). These units serve as a center with a high volume of cases involving anomalies, chronic diseases, and post-surgical patients. Patients without blood culture data were excluded from the study.

Data collection tools

The data regarding blood culture results were obtained through a retrospective review of patient records. Microorganisms were identified using conventional methods and the Phoenix automated system (Becton Dickinson, Sparks, Maryland, USA). Antibiotic susceptibility results were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.[15]

This study was approved by the Kahramanmaraş Sütçü İmam University Medical Research Ethics Committee (approval date 12.09.2023, number 2023/13-03).

Statistical analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Categorical data were presented with n and %.

RESULTS

Over the course of five years, 6,291 blood cultures were collected from neonatal and pediatric intensive care units, with microbial growth detected in 1,197 samples (19.02%). Of the microorganisms isolated, 621 (51.88%) were from male and 576 (48.12%) from female patients. Among the 1,197 cultures with growth, 776 (64.82%) were obtained from neonatal ICUs, while 421 (35.18%) were from pediatric ICUs.

Among the 1,197 microorganisms isolated, 868 (72.51%) were identified as Gram-positive bacteria, 259 (21.63%) as Gram-negative bacteria, and 70 (5.84%) as *Candida* species. The most frequently isolated microorganism was *CoNS (62.40%)*, followed by *K. pneumoniae* (6.59%), *A. baumannii* (6.26%), *Candida parapsilosis (C. parapsilosis)* (3.17%), and *Enterococcus faecalis (E. faecalis)* (2.08%). The distribution of microorganisms isolated from blood cultures is shown in Table 1.

Table 1. Bacteria isolated from blood cultures		
Gram-Positive Bacteria	**868**	**72.51**
***Staphylococcus* spp.**	**770**	**64.32**
Staphylococcus aureus	23	1.92
Coagulase Negative Staphylococci	747	62.40
***Streptococcus* spp.**	**29**	**2.42**
Streptococcus mitis	9	0.75
Streptococcus oralis	8	0.66
Other streptococci		
Streptococcus pneumoniae, Streptococcus acidominimus Streptococcus constellatus, Streptococcus oralis, Streptococcus cristatus, Streptococcus gallolyticus, Streptococcus sanguinis, Streptococcus salivarius, Streptococcus parasanguinis, Streptococcus vestibularis	12	1.00
Other Gram-Positive Bacteria	**6**	**0.50**
Aerococcus viridans Leuconostos lactis, Listeria monocytogenes, Gemella morbillorum, Pediococcus pentosaceus, Rothia dentocari-osa	6	0.50
***Enterococcus* spp.**	**49**	**4.09**
Enterococcus faecalis	25	2.08
Enterococcus faecium	20	1.67
Other enterococci (*Enterococcus avium, hirae, raffinosus, casseliflavus / gallinarum*)	4	0.33
***Corynebacterium* spp.**	**14**	**1.16**
Corynebacterium amycolatum/minutissimum	4	0.33
Corynebacterium jeikeium	4	0.33
Corynebacterium matruchotii	2	0.16
Other Corynebacteria *(bovis, pseudodiphtheriticum, amycolatum, striatum)*	4	0.33
Gram-Negative Bacteria	**259**	**21.63**
***Klebsiella* spp.**	**88**	**7.35**
Klebsiella pneumoniae	79	6.59
Klebsiella oxytoca	6	0.50
Other Klebsiella species *(Klebsiella ozaenae, aerogenes)*	3	0.25
***Serratia* spp.**	**18**	**1.50**
Serratia marcescens	18	1.50
Escherichia coli	**15**	**1.25**
***Enterobacter* spp.**	**9**	**0.75**
Enterobacter cloacae	8	0.66
Enterobacter aerogenes	1	0.08
***Proteus* spp.**	**2**	**0.16**
***Pseudomonas* spp.**	**19**	**1.58**
Pseudomonas aeruginosa	18	1.50
Pseudomonas putida	1	0.08
***Acinetobacter* spp.**	**78**	**6.51**
Acinetobacter baumannii	75	6.26
Acinetobacter lwoffii / haemolyticus	3	0.25
***Bacillus* spp.**	**6**	**0.50**
Bacillus cereus	2	0.16
Bacillus pumilus	4	0.33
Other gram-negative bacteria	**24**	**2.00**
Stenotrophomonas maltophilia	9	0.75
Other bacteria *(Morganella morganii, Pantoea agglomerans, Brevundimonas diminuta, Burkholderia cepacia complex, Rhizobium radiobacter, Chryseobacterium meningosepticum)*	15	1.25
***Candida* spp.**	**70**	**5.84**
Candida albicans	20	1.67
Candida parapsilosis	38	3.17
Other candidas *(candida lusitaniae /tropicalis / kefyr / glabrata*)	12	1.00
Total	1197	100

Table 2. Antibiotic resistance rates of gram-positive bacteria isolated from blood cultures

Antibiotics	*S. aureus*		*CoNS		*Enterococcus* spp.		*Streptococcus* spp.	
	n	R (%)	n	R (%)	n	R (%)	n	R (%)
Ampicillin	-	-	554	552 **(99.63)**	45	18 (40.00)	-	-
Clindamycin	22	9 (40.90)	747	556 (74.43)	-	-	9	3 (50.00)
Daptomycin	22	1 (4.54)	747	16 (2.14)	-	-	1	**0 (0.00)**
Erythromycin	23	10 (43.47)	747	664 (88.88)	-	-	4	3 (75.00)
Fusidic Acid (STAFINE)	23	2 (8.69)	747	452 (60.50)	-	-	-	-
Gentamicin	22	3 (13.63)	747	586 (78.44)	-	-	1	1 **(100)**
Levofloxacin	22	4 (18.18)	747	540 (72.28)	-	-	3	0 **(0.00)**
Linezolid	23	1 (4.34)	747	16 (2.14)	45	0 **(0.00)**	5	0 **(0.00)**
Oxacillin	22	12 **(54.54)**	747	698 (93.44)	-	-	-	-
Ciprofloxacin	22	4 (18.18)	747	548 (73.36)	-	-	-	-
Teicoplanin	23	2 (8.69)	722	89 (12.32)	45	10 (22.22)	11	**0 (0.00)**
Tetracycline	23	6 (26.08)	747	210 (28.11)	-	-	3	2 (66.66)
Trimethoprim/sulfamethoxazole	23	1 (4.34)	676	159 (23.52)	30	30 **(100)**	3	2 (66.66)
Vancomycin	23	**0 (0.00)**	747	6 **(0.80)**	45	11 (24.44)	13	**0 (0.00)**
HLGR **	-	-	-	-	45	20 (44.44)	8	2 (25.00)
HLSR ***	-	-	-	-	45	16 (35.55)	-	-

**CoNS*: coagulase-negative staphylococci, **HLGR: High-Level Gentamicin Resistance, ***HLSR: High-Level Streptomycin Resistance, R: Resistance
- Indicates that antibiotics have not been tested against this organism.

Among *CoNS* isolates, the highest resistance was observed against ampicillin (99.63%), oxacillin (93.44%), and erythromycin (88.88%). The lowest resistance was found against vancomycin (0.80%), linezolid (2.14%), and daptomycin (2.14%). In *S. aureus* isolates, the highest resistance was noted against oxacillin (54.54%), erythromycin (43.47%), and clindamycin (40.90%). No resistance to vancomycin was detected in *S. aureus* isolates, while the lowest resistance was observed against linezolid (4.34%) and daptomycin (4.54%). *Enterococcus* species showed 100% resistance to trimethoprim/sulfamethoxazole, with no resistance detected to linezolid. Among *Streptococcus* species, the highest resistance was observed against erythromycin (75%), while no resistance was detected to vancomycin, teicoplanin, linezolid, levofloxacin, or daptomycin. Antibiotic resistance rates for Gram-positive bacteria are presented in Table 2.

Among Gram-negative bacteria, *Klebsiella* species, *Serratia marcescens* (*S. marcescens*), and *Enterobacter cloacae* (*E. cloacae*) isolates demonstrated the highest resistance to ampicillin, with a 100% resistance rate. The ampicillin resistance rate for *E. coli* was 85.71%. *A. baumannii* was identified as the most resistant bacterium, with resistance rates exceeding 90% for most antibiotics tested, except trimethoprim/sulfamethoxazole. The second-highest resistance rates were found in *Klebsiella* species, while the lowest resistance rates were observed in *S. marcescens* and *E. cloacae* isolates. The highest carbapenem resistance was found in *A. baumannii*, followed by *Klebsiella* species, *Pseudomonas*, and *E. cloacae*. Antibiotic resistance rates for Gram-negative bacteria are shown in Table 3.

In *Candida albicans (C. albicans)* isolates the highest antifungal resistance was observed against voriconazole (85.00%). In contrast, in *C. parapsilosis* isolates, the highest resistance was observed against fluconazole (24.24%). No resistance to caspofungin was detected in either *Candida* species. Antifungal resistance rates for *Candida* species are presented in Table 4.

Table 3. Antibiotic resistance rates of gram-negative bacteria isolated from blood cultures

Antibiotics	*Klebsiella spp.*		*Serratia marcescens*		*E. coli*		*Pseudomonas aeruginosa*		*Acinetobacter spp.*		*Enterobacter cloacae*	
	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)
Amikacin	84	36 (42.85)	18	2 (11.11)	15	1 **(6.66)**	18	2 **(11.11)**	74	69 (93.24)	8	2 **(25.00)**
Gentamicin	85	45 (52.94)	18	1 (5.55)	15	3 (20.00)	8	1 (12.50)	75	72 **(96.00)**	8	3 (37.50)
Ciprofloxacin	80	50 (62.5)	18	0 **(0.00)**	13	1 (7.69)	18	6 (33.33)	73	69 (94.52)	8	2 **(25.00)**
Levofloxacin	58	31 (87.93)	9	0 **(0.00)**	12	1 (8.33)	13	7 (53.84)	53	49 (92.45)	6	2 (33.33)
Ampicillin	84	84 **(100)**	18	18 **(100)**	14	12 **(85.71)**	-	-	-	-	8	8 **(100)**
Ertapenem	85	64 (75.29)	18	6 (33.33)	14	1 (7.14)	-	-	-	-	7	3 (42.85)
Imipenem	84	27 **(32.14)**	18	6 (33.33)	14	1 (7.14)	18	13 **(72.22)**	75	71 (94.66)	8	2 **(25.00)**
Meropenem	84	44 (52.38)	17	2 (11.76)	15	1 (6.66)	18	7 (38.88)	75	71 (94.66)	8	3 (37.50)
Ceftriaxone	85	71 (83.52)	18	2 (11.11)	14	6 (42.85)	-	-	-	-	8	2 **(25.00)**
Cefuroxime	83	71 (85.54)	-	-	14	9 (64.28)	-	-	-	-	-	-
Cefepime	83	70 (84.33)	18	1 (5.55)	15	4 (26.66)	17	7 (41.17)	-	-	7	2 (28.57)
Ceftazidime	84	71 (83.52)	18	0 **(0.00)**	15	7 (46.66)	18	7 (38.88)	-	-	7	2 (28.57)
Piperacillin/ tazobactam	84	66 (78.57)	18	5 (27.77)	15	4 (26.66)	18	5 (27.77)	-	-	8	2 **(25.00)**
Trimethoprim/ sulfamethoxazole	85	58 (68.23)	18	0 **(0.00)**	14	6 (42.85)	-	-	75	40 **(53.33)**	8	2 **(25.00)**

- Indicates that antibiotics have not been tested against this organism.

Table 4. Antifungal resistance rates of Candida isolated from blood cultures

Antifungals	*Candida albicans*		*Candida parapsilosis*	
	n	R (%)	n	R (%)
Voriconazole	20	17 **(85.00)**	33	1 (3.03)
Caspofungin	20	0 **(0.00)**	33	0 **(0.00)**
Fluconazole	20	8 (40.00)	33	8 **(24.24)**
Amphotericin-B	20	3 (15.00)	33	6 (18.18)

DISCUSSION

The 19.02% culture positivity rate observed in this study is consistent with findings from previous research on the subject. For instance, Deku et al.[16] reported a culture positivity rate of 13.1% in Ghana, Gupta et al.[17] found 16.5% in North India, and Oyekale et al.[18] reported 19.2% in Nigeria. However, some studies have reported lower rates, including Khanal et al.,[19] Gohel et al.,[20] and Gülmez et al.[21] who documented culture positivity rates of 10.3%, 9.2%, and 7.7%, respectively, in bloodstream infection cases.

Gram-positive bacteria were the most frequently isolated strains from blood cultures, followed by gram-negative bacteria and candida.[22] In this study, gram-positive bacteria were found to be the predominant strains (72.51%) (Table 1). This finding aligns with prior studies, which have also reported Gram-positive bacteria as the dominant isolates in bloodstream infection cases.[16,23] However, some research has highlighted Gram-negative bacteria as the most frequently isolated pathogens in bloodstream infections.[17,18]

Although the importance and role of *CoNS* as etiological agents of neonatal sepsis have been proven in many studies, determining whether *CoNS* isolates are true pathogens or contaminants remains problematic.[24] In this study, *CoNS* was the most frequently isolated microorganism (62.40%), followed by *Enterococcus* spp. (4.09%). This result is consistent with the findings of Ergül et al.[22] The high isolation rate of *CoNS* may be attributed to the frequent invasive procedures performed on patients.

The prevalence of *S. aureus* in blood cultures varies across different studies. For example, *S. aureus* rates of 42.39% in Pakistan[25], 40.72% in India[26], 11.95% in Afghanistan[27], and 8.87% in Iran[7] have been reported, while lower rates (0.9-12.8%) have been observed in Türkiye.[21,22,28,29] The isolation rate of *S. aureus* in our study (1.92%) is consistent with the rates reported in Türkiye.

In our study, in addition *to CoNS, Klebsiella, Acinetobacter, S. aureus, Enterobacter, E. coli, Pseudomonas, Streptococcus, Serratia*, and *candida* species were isolated (Table 1). These findings are consistent with previous studies[22,27,30] and it has been reported that infections caused by these bacteria pose a significant threat to the lives of children.[27]

In our study, the methicillin resistance rate in *CoNS* was found to be significantly higher compared to *S. aureus* (*CoNS* 93.44%, *S. aureus* 54.54%) (Table 2). Similar findings have also been reported in several studies conducted in Türkiye.[22,28] In this study, which evaluated five years of data, no vancomycin resistance was detected in *S. aureus*. In contrast, vancomycin resistance rates in *CoNS* and *enterococci* were found to be 0.80% and 24.44%, respectively. The resistance rates for teicoplanin were determined to be 8.69%, 12.32%, and 22.22%, while linezolid resistance was 4.34% in *S. aureus* and 2.14% in *CoNS* (Table 2). Previous studies have reported higher susceptibility to vancomycin, teicoplanin, and linezolid.[26,31]

In our study, the most frequently isolated gram-negative bacteria were *Klebsiella* spp. (7.35%), followed by *Acinetobacter* spp. (6.51%) (Table 3). This finding contrasts with reports from a study in Western India, where *Acinetobacter* spp. was the most frequently isolated bacterium, followed by *Klebsiella* spp.[31] Additionally, similar studies have shown variability in bacterial ranking.[6,22,25,27] *Klebsiella* spp isolated in our study showed high levels of resistance to most of the tested antibiotics. Specifically, the antibiotics to which *Klebsiella* spp. showed the highest resistance were ampicillin (100%), cefuroxime (85.54%), cefepime (84.33%), and ceftriaxone (83.52%) (Table 3). These results are consistent with other studies.[6,22] Our study suggests that the high aminoglycoside and cephalosporin resistance observed in *Klebsiella* strains may be due to the inappropriate use of these antibiotics in empirical treatment.

Acinetobacter spp. has shown high levels of resistance to all tested antibiotics (Table 3). Consistent with our findings, Shehab El-Din et al.[24] reported even higher resistance rates. Moradi et al.[11] also found results similar to ours, although they reported still high antibiotic resistance. In contrast, Maham et al.[7] presented lower antibiotic resistance rates for *A. baumannii* than our study. The high resistance observed in *Acinetobacter* species to various antibiotics has led to colistin and tigecycline becoming important treatment options.[22]

In this study, among the bacteria isolated from blood cultures, *S. marcescens*, which was isolated at a rate of 1.50%, was identified as the bacterium with the highest sensitivity rate to the tested antibiotics (excluding ampicillin) (Table 3). However, Shehab El-Din et al.[24] reported higher resistance rates for *S. marcescens* than our findings. This discrepancy may be attributed to Shehab El-Din et al.[24] isolating *S. marcescens* more frequently (7.17%) from blood cultures, which suggests that they may have used antibiotics more often in treating infections caused by this pathogen.

P. aeruginosa was isolated at a rate of 1.50%, and the most resistant antibiotic was imipenem, with a resistance rate of 72.22%, followed by levofloxacin, with a resistance rate of 53.84%. The most sensitive antibiotic was amikacin, with a resistance rate of 11.11%, followed by gentamicin, with a resistance rate of 12.50% (Table 3). Our study is consistent with the study of Akman et al.,[29] in which they found the resistance rates of amikacin (14.8%) and gentamicin (24.1%) to be lower than the resistance rate of imipenem (66.6%). However, Maham et al.[7] reported resistance rates (amikacin 37.1%, gentamicin 69.0%, imipenem 21.6%), contrary to our study. In this study, high carbapenem (66.6%) and quinolone resistance (53.84%) observed in *P. aeruginosa* strains may be related to inappropriate antibiotic use in empirical treatment. According to our results, aminoglycosides and ciprofloxacin may be preferred before carbapenems and quinolones in empirical treatment in patients with suspected *Pseudomonas* infection.

In our study, 1.25% of *E. coli* was isolated from blood cultures (Table 3). Khan et al.[25] isolated *E. coli* strains from blood cultures at a rate similar to our study (1.09%). However, in a study conducted by Fox-Lewis et al.[32], the percentage of *E. coli* was reported to be 47.2%, while a study conducted in Pakistan reported this percentage as 5%.[33] In our study, *E. coli* strains showed resistance rates of 85.71% to ampicillin, 64.28% to cefuroxime, and 20% to gentamicin; resistance rates for other tested antibiotics remained below 10%. The literature reports varying resistance rates for *E. coli*; for instance, Khan et al.[25] indicated that *E. coli* strains were susceptible to amikacin but highly resistant to imipenem and cefepime. Fox-Lewis et al.[32] did not detect carbapenem

resistance, but they found gentamicin resistance to be approximately 45% and ampicillin resistance to be over 90%. Er et al.[34] reported low resistance rates for imipenem, meropenem, and amikacin while noting high resistance to cephalosporins and quinolone antibiotics. These differences may be related to the diversity of microorganisms that are frequently isolated in the hospitals where the studies were conducted and the frequency of treatment practices associated with them.

In this study, *E. cloacae*, which was isolated at a rate of 0.66% and has the highest antibiotic susceptibility after *S. marcescens* (excluding ampicillin), shows antibiotic resistance rates generally around 25% and slightly above (Table 3). However, various resistance rates have been reported in studies conducted in different countries and geographical regions.[24,29]

In recent years, there has been a significant increase in the isolation of *Candida* species in blood cultures due to the rise in occurrences of neutropenia, preterm birth, surgical procedures, and the use of intravascular catheters.[21] In this research, 5.84% of positive blood cultures were identified as Candida (Table 4). Different Candida rates have been reported in studies: Khan et al.[25] 2.17%, Tariq et al.[27] 3.41%, Mokaddas et al.[8] 7%, Gülmez et al.[21] 10.8%, Kumar et al.[35] 21%. In our study, *C. parapsilosis* (3.17%) was the most frequently isolated fungal species (Table 4). These findings contradict reports indicating that *C. albicans* is the most commonly isolated fungal pathogen in neonatal ICUs.[22,28,35]

Limitations of the study

The fact that the broth microdilution method used to determine colistin sensitivity was not tested in our hospital during the periods when the data were collected is among the limitations of our study.

CONCLUSION

In conclusion, this study identified gram-positive bacteria isolated from blood cultures as the dominant strains, with *CoNS* being the most frequently isolated bacteria. Antibiotic resistance was observed at the highest rate in *A. baumannii*, while resistance rates vary according to bacterial species. Studies in the literature reveal that the types of microorganisms isolated from blood cultures and antibacterial resistance rates vary significantly among hospitals in different countries. The main factors contributing to the increase in antimicrobial-resistant bacteria include poor infection control practices and inappropriate antibiotic use. Restriction of unnecessary antibiotic use, promotion of rational use, and specific antibiotic use strategies such as combination antibiotic therapy may help control the development of resistance. In addition, it would be useful to update the bacteriological profile and antibiotic susceptibility pattern in blood cultures at regular intervals to ensure correct empirical treatment.

Ethical approval

This study has been approved by the Kahramanmaraş Sütçü İmam University Medical Research Ethics Committee (approval date 12.09.2023, number 2023/13-03).

Author contribution

Study conception and design: MeA, AK, ZO; data collection: BK, ÖK; analysis and interpretation of results: MuA, ÖK; draft manuscript preparation: ZO, AK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Impact of bladder volume on renal pelvis dimensions in pediatric hydronephrosis

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ABSTRACT

Objective: To evaluate the effect of pre-void and post-void bladder volume on the anteroposterior (AP) diameter of the renal pelvis in asymptomatic pediatric hydronephrosis and to determine its influence on ultrasonographic measurement variability.

Method: A retrospective analysis was conducted on 113 children aged 4–9 years who were referred for renal ultrasonography (US) between 2019 and 2023. Patients were excluded if they had end-stage renal disease, congenital anomalies of the kidney and urinary tract, polycystic kidney disease, bilateral hydronephrosis, prior renal surgery, suboptimal image quality, or pathological findings on additional diagnostic tests such as scintigraphy or voiding cystourethrography. Standardized protocols were used to measure the AP diameter of the renal pelvis and bladder volume in both pre-void and post-void states, utilizing the ellipsoid formula. Paired t-tests and Pearson's correlation coefficient were applied for statistical analysis.

Results: The mean AP diameter of the renal pelvis significantly decreased from 7.43 ± 1.90 mm in the pre-void state to 5.62 ± 1.46 mm in the post-void state ($p < 0.05$). Similarly, bladder volume was markedly reduced from 183.6 ± 88.0 mL to 16.4 ± 14.9 mL ($p < 0.05$). Pearson's correlation analysis revealed a strong positive correlation between pre-void bladder volume and the reduction in AP diameter ($r = 0.65$, $p < 0.05$), demonstrating the considerable effect of bladder volume on renal pelvic measurements.

Conclusion: Incorporating pre- and post-void measurements into routine renal ultrasound protocols may enhance diagnostic accuracy, reduce variability, and improve clinical decision-making in pediatric hydronephrosis evaluation.

Keywords: renal pelvis, hydronephrosis, ultrasonography, urinary bladder, volume, pediatrics, pre-void, post-void

INTRODUCTION

The widespread use of prenatal US has significantly increased the diagnosis of children with asymptomatic renal pelvic dilatation. Renal pelvic dilatation is a prognostic indicator in the initial diagnosis and follow-up of severe urological diseases. A critical measure in assessing hydronephrosis is the AP diameter of the renal pelvis, particularly how it changes over time in follow-up US examinations. For neonates, an AP diameter greater than 6 mm raises concerns about potential obstruction, while values exceeding 15 mm are strongly associated with severe uropathology, with sensitivity and specificity surpassing 90%.[1-5] To address this, the Society for Fetal Urology's grading system has become a widely accepted approach for classifying and managing such cases.[6,7] Despite these advancements, measuring renal pelvis dimensions continues to face challenges, particularly due to factors such as the patient's hydration level and bladder volume.

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One of the most influential yet often overlooked factors in routine US is bladder volume. This variable can significantly alter the AP diameter of the renal pelvis, leading to variability in measurements. While some studies have examined the effects of hydration on renal pelvis dimensions, limited data exist regarding the impact of bladder volume on renal pelvis dimensions.[8-10] Clarifying this relationship is essential to avoid diagnostic errors, which could otherwise result in unnecessary invasive tests or delays in treatment.

In line with our hypothesis that bladder volume has a significant impact on the renal pelvis diameter, we propose that bladder volume should be incorporated into the routine renal US evaluation protocol. We believe that this quantitative parameter could enhance diagnostic accuracy, minimize confounding variables, and reduce misleading results, thereby optimizing patient management. In this context, this study aims to investigate the effect of pre- and post-void bladder volume on the AP diameter of the renal pelvis in children under clinical and radiological follow-up for asymptomatic hydronephrosis.

MATERIAL AND METHOD

Study population

This study was approved by the local ethics committee (approval date: 24.10.2024; approval no: 632227). Pediatric patients aged 4–9 years who were under clinical follow-up for hydronephrosis and referred to the radiology department for ultrasonographic evaluation between January 2019 and January 2023 were retrospectively assessed. Radiological images of the patients were retrieved and reviewed from the picture archiving and communication system, while clinical data were obtained from the hospital information management system.

Only patients with clinically asymptomatic hydronephrosis and those under follow-up for renal pelvis AP diameter were included in the study. Patients with the following conditions were excluded from the study: (1) end-stage renal disease of any etiology, (2) congenital anomalies of the kidney and urinary tract (CAKUT), (3) polycystic kidney disease, and (4) history of prior renal surgery. Additionally, patients with suboptimal ultrasonographic image quality, measurement errors, missing data, or bilateral hydronephrosis were excluded to ensure a homogeneous study population. Patients with pathological findings on scintigraphy and/or voiding cystourethrography, as well as those with a renal pelvis AP diameter greater than 10 mm who had not undergone these diagnostic tests, were excluded. Nonetheless, a small subset of patients with a renal pelvis AP diameter greater than 10 mm but with normal findings on additional diagnostic tests were included. The images and clinical data of the patients were evaluated by two experienced radiologists. As a result, 113 patients met the inclusion criteria and were included in the final analysis.

Measurement technique

All US examinations were performed using RS-80A and HS-50 devices equipped with a convex array probe (CA1-7A, 1-7 MHz) (Samsung Medison Co., Ltd., Hongcheon, Korea). Renal US examinations were performed with the patient in the supine or lateral decubitus position, as deemed appropriate. The renal pelvis AP diameter was measured twice for each patient. The first measurement was taken before voiding, along with the calculation of bladder volume. The second measurement was performed immediately after voiding, and the residual bladder volume was also calculated.

The AP diameter of the renal pelvis was measured in the mid-renal transverse plane, along the longest axis where the renal hilum was visible, and at the level of the hilum.[11] The measurement was taken from the inner edge to the inner edge of the pelvis, and the average of repeated measurements was recorded. The bladder volume was automatically calculated by the US device using the ellipsoid formula (L×W×D×0.523), where L represents the maximum length of the bladder, measured in the longitudinal plane from the bladder fundus to the internal urethral opening; W is the maximum width, measured in the transverse plane perpendicular to the midline at its midpoint; and D is the maximum depth, measured in the transverse plane along the midline from the anterior to posterior mucosal surface (Figure 1).[12]

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation for normally distributed data. Categorical variables were presented as frequencies and percentages. The Shapiro–Wilk test was used to assess the normality of continuous variables. The primary analysis compared the renal pelvis AP diameter before and after voiding using the paired t-test, as the data followed a normal distribution. The association between pre-void bladder volume and the change in renal pelvis AP diameter was analyzed using Pearson's correlation

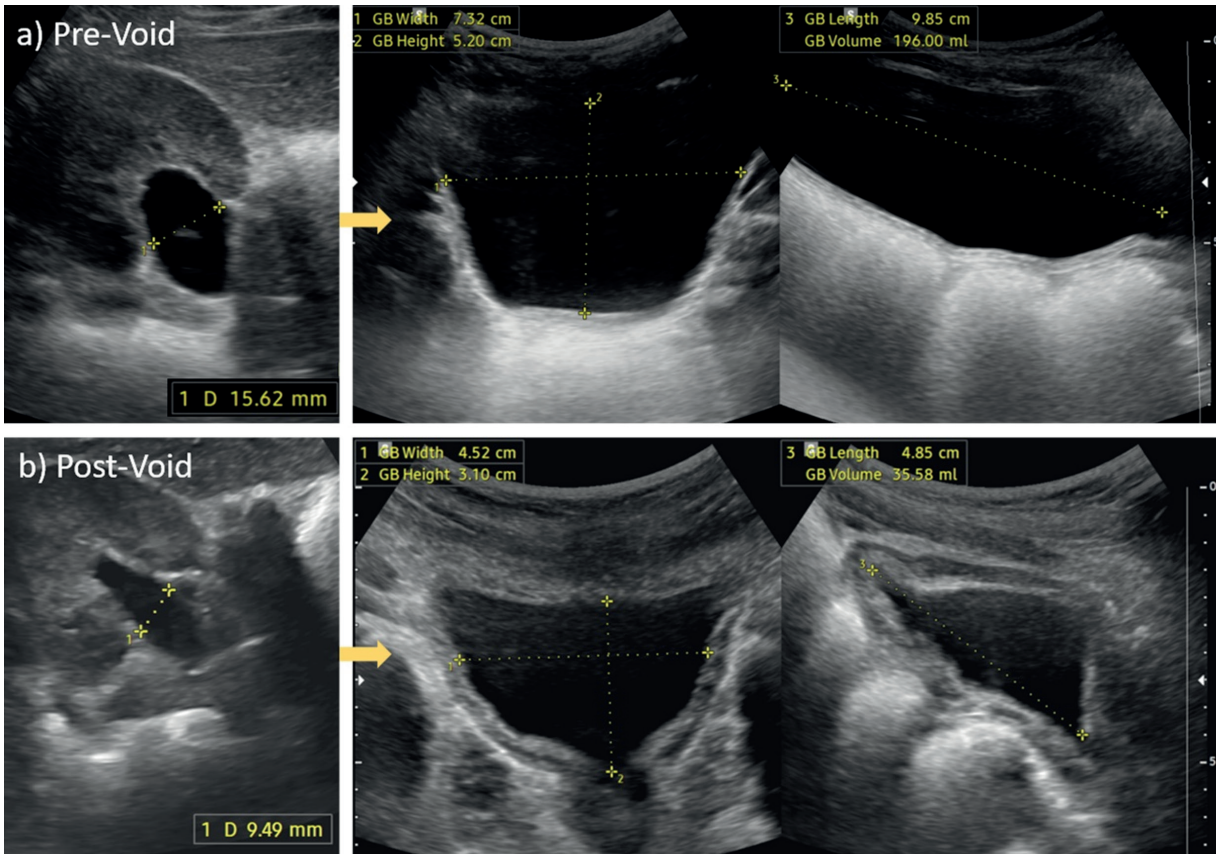

Figure 1. Renal US examination of an 8-year-old male patient being monitored for right renal pelvis dilation. a) Pre-void US: The AP diameter of the renal pelvis was measured 15.6 mm, and the bladder volume was calculated 196 mL. b) Post-void US: The AP diameter of the renal pelvis was measured 9.5 mm, and the bladder volume was calculated 36 mL.

coefficient. A p-value <0.05 was considered statistically significant for all analyses.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 113 patients were included in the study, with an age range of 4 to 9 years. The mean age of the patients was 6.3 ± 1.44 years, and the cohort comprised 59% males (n = 67) and 41% females (n = 46). Unilateral renal pelvis dilation was more common on the left side (n = 71, 63%) compared to the right side (n = 42, 37%).

Renal Pelvis and Bladder Volume Measurements

The mean AP diameter of the renal pelvis in the pre-void state was 7.43 ± 1.90 mm, which significantly decreased to 5.62 ± 1.46 mm in the post-void state ($p < 0.05$).

Table 1. Pre-void and post-void measurements of renal pelvis diameter and bladder volume

Category	Pre-void	Post-void	p-value
Renal pelvis AP* diameter (mm)	7.43 ± 1.90	5.62 ± 1.46	< 0.05
Bladder volume (mL)	183.6 ± 88.0	16.4 ± 14.9	< 0.05

*: Anterior-posterior.

Similarly, the mean bladder volume decreased significantly from 183.6 ± 88.0 mL in the pre-void state to 16.4 ± 14.9 mL post-void ($p < 0.05$) (Table 1, Figure 2)

Correlation Between Bladder Volume and Renal Pelvis AP Diameter

Pearson's correlation analysis revealed a significant positive correlation between pre-void bladder volume and the

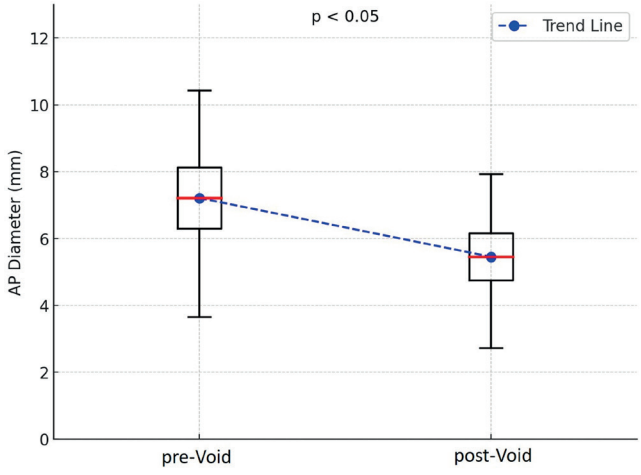

Figure 2. The box plot illustrates the comparison of renal pelvis AP diameters pre- and post-voiding. The red horizontal lines within the boxes indicate the median values. The dashed blue line connects the medians of the two groups, emphasizing the reduction in AP diameter following voiding.

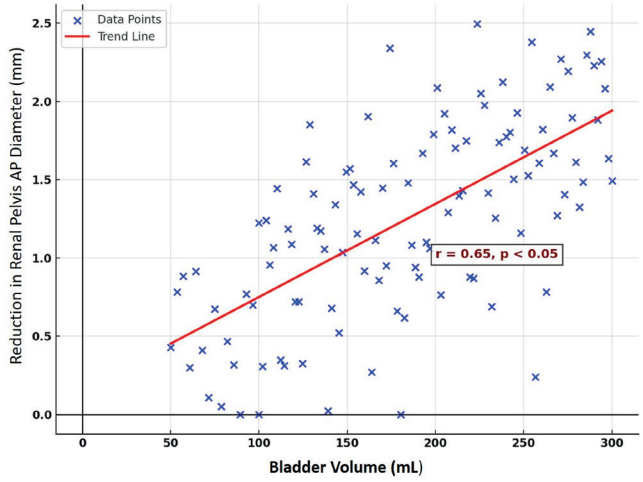

Figure 3. The scatter plot illustrates the correlation between pre-void bladder volume and the reduction in renal pelvis AP diameter. The linear regression line indicates a significant relationship, where larger bladder volumes are associated with greater reductions in post-void renal pelvis AP diameter ($r = 0.65$, $p < 0.05$).

reduction in post-void renal pelvis AP diameter ($r = 0.65$; $p < 0.05$). This finding suggests that higher bladder volumes were associated with greater decreases in renal pelvis AP diameter after voiding (Figure 3).

DISCUSSION

Ultrasonography serves as a fundamental tool in evaluating renal diseases in pediatric patients, owing to its non-invasive nature, safety, and widespread accessibility. This study highlights the significant impact of bladder volume on renal pelvis AP diameter measurements, offering a clearer perspective on the interpretation of such data.

Hydronephrosis is a common finding during prenatal US or those performed for various reasons, such as urinary tract infections. In such cases, invasive procedures are typically avoided if there is no significant dilatation of the collecting system, with follow-up commonly relying on the renal pelvis AP diameter. Several factors indirectly influence the AP diameter of the renal pelvis, one of which is hydration status. Studies have documented the effects of hydration on these measurements.[13] Koff et al. reported that diuresis can cause dilatation of the collecting system, even in the absence of obstructive pathology, with this effect being more pronounced in non-obstructive conditions.[14] In routine practice, renal US is performed under variable hydration conditions, with no clear recommendations regarding fluid intake or the timing of the examination. Consequently, it seems impractical to eliminate the influence of hydration on renal pelvis AP diameter.

Another variable affecting renal pelvis dilatation is bladder volume. Studies have explored the effect of bladder volume on renal pelvis measurements. For instance, Demir et al. demonstrated that bladder volume significantly influenced renal pelvis AP diameter in patients with vesicoureteral reflux, with a marked reduction observed after bladder emptying.[15] Morin et al. emphasized that bladder volume can moderately dilate the ureter and pelvicalyceal system, recommending that renal US be performed with an empty bladder to prevent misinterpretation.[16] Similarly, a comprehensive review of pediatric renal imaging suggested that empty bladder protocols should be implemented to enhance the reliability of US assessments.[17] Leung et al. introduced the "hydronephrosis index," calculated by dividing the renal pelvis AP diameter by the bladder volume to minimize the misleading effects of bladder volume on renal pelvis AP measurements.[18] This correlation was validated in their study involving infant patients.[19] Another study on neurogenic bladder dysfunction highlighted the impact of bladder volume on US measurements, underscoring the need for standardized protocols.[20] Research on renal imaging principles also addressed the influence of bladder volume on renal pelvis AP measurements, advocating for emerging technologies

to address these challenges.[21] Additionally, the integration of urodynamics with the US has reinforced the importance of considering bladder volume in US protocols.[22] Overall, the literature agrees on the significant influence of bladder volume on renal pelvis AP measurements. The quantitative findings of this study further support this consensus, underscoring the need for standardization.

The Society for Fetal Urology (SFU) and the European Society of Pediatric Radiology (ESPR) do not provide specific recommendations regarding the impact of bladder fullness on renal pelvis measurements in their current hydronephrosis assessment guidelines.[2,23] Incorporating standardized pre- and post-void renal pelvis measurements into routine ultrasonographic protocols may reduce measurement inconsistencies and improve patient management strategies. Considering changes in bladder volume could enhance the precision of diagnostic decision-making and prevent the overestimation of hydronephrosis severity. Ultimately, this quantitative, data-driven approach may reduce the need for invasive tests in asymptomatic patients.

This study has several limitations. Its retrospective and single-center design may limit the generalizability of the findings, as patient demographics and sonographic techniques may vary across institutions. Additionally, ultrasonography is inherently operator-dependent, and although all images were reviewed by two experienced radiologists and suboptimal cases were excluded, some degree of interobserver variability may still be present. This study focused on asymptomatic hydronephrosis without a known pathology, but undiagnosed underlying conditions may have influenced the results. The lack of hydration status control constitutes a critical limitation. As hydration can physiologically alter the degree of renal pelvic dilatation, variability in fluid intake prior to imaging may have influenced the measurements. This factor was not standardized in our protocol and may affect the reproducibility and consistency of the results. Future studies should consider implementing controlled hydration protocols before ultrasound examinations to minimize measurement variability and enhance diagnostic reliability.

CONCLUSION

In conclusion, this study demonstrates that bladder volume has a significant and measurable impact on renal pelvis AP diameter, emphasizing its clinical relevance in pediatric renal US. Incorporating pre- and post-void measurements into standard US protocols may enhance diagnostic accuracy, minimize variability, and reduce the need for unnecessary invasive investigations in children with asymptomatic hydronephrosis. This approach may also promote consistency in longitudinal follow-up and support more reliable clinical decision-making.

Ethical approval

The study was approved by Aydın Adnan Menderes University Ethics Committee (date: 24.10.2024, number: 632227).

Author contribution

Study conception and design: AT, MBÇ; data collection: AT, EHN; analysis and interpretation of results: AT, EHN; draft manuscript preparation: AT, EHN, MG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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