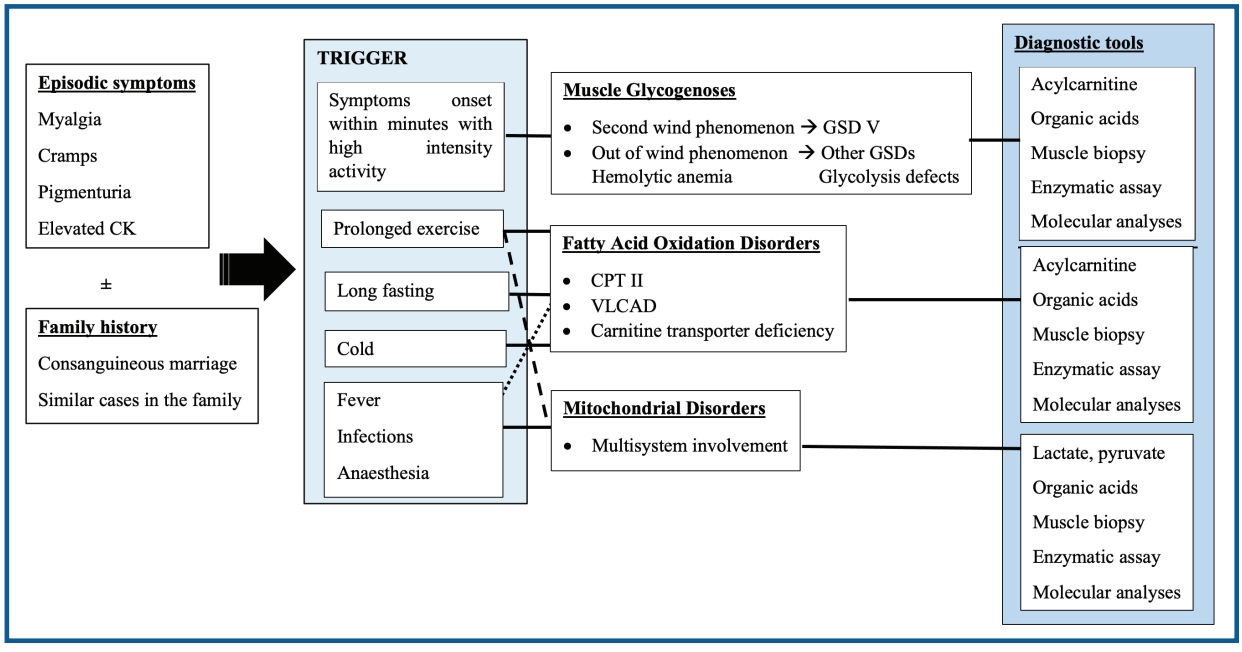
ISSN: 2718-0085

Trends in Pediatrics

Volume: **2** Issue: **4** December **2021**



www.trendspediatrics.com

ISSN: 2718-0085

Trends in Pediatrics

December 2021
Volume: 2
Issue: 4

Administrative Office
Kuyulu Mah. Kavak Sok. No: 264, İç Kapı No: 9
Efeler-Aydın

Publication Type: Periodical

Language Editor
Gürkan Kazancı

Publisher
GALENOS YAYINEVİ
Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publication Date:
December 2021

International scientific journal published quarterly.

Trends in Pediatrics (TP) is an official scientific journal of Aydın Pediatric Society.

It is publiched quarterly as 4 issues every year (March, June, September, December)

Trends in Pediatrics is an open access, free and peer-reviewed journal.

You can reach publication policies and writing guide from
www.trendspediatrics.com

Trends in Pediatrics

www.trendspediatrics.com

Assoc. Prof. Balahan Makay, MD
E-mail: balahan.bora@deu.edu.tr
Department of Pediatrics, Division of Pediatric Rheumatology, Dokuz Eylul University, Medical Faculty, İzmir, Turkey
ORCID ID: orcid.org/0000-0001-6193-0402

Assoc. Prof. Nagehan Emiralioğlu, MD
E-mail: nagehan.emiralioglu@hacettepe.edu.tr
Department of Pediatrics, Division of Pediatric Pulmonology, Hacettepe University, Medical Faculty, Ankara, Turkey
ORCID ID: orcid.org/0000-0002-1405-8401

Asst Prof. Yusuf Ziya Aral, MD
E-mail: yuziar_12@yahoo.com
Department of Pediatrics, Division of Pediatric Hematology and Oncology, Aydın Adnan Menderes University, Medical Faculty, Aydın, Turkey
ORCID ID: orcid.org/0000-0001-7964-6266

Asst. Prof. Ayşe Anık, MD
E-mail: drayseank@yahoo.com
Department of Pediatrics, Division of Neonatology, Aydın Adnan Menderes University, Medical Faculty, Aydın, Turkey
ORCID ID: orcid.org/0000-0002-0673-3403

Asst. Prof. Serkan Fazlı Çelik, MD
E-mail: docser2003@yahoo.com
Department of Pediatrics, Division of Pediatric Cardiology, Aydın Adnan Menderes University, Medical Faculty, Aydın, Turkey
ORCID ID: orcid.org/0000-0003-1595-802X

Asst. Prof. Elif Çelik, MD
E-mail: gencelif80@yahoo.com
Department of Pediatrics, Aydın Adnan Menderes University, Medical Faculty, Aydın, Turkey
ORCID ID: orcid.org/0000-0002-0298-4088

Asst. Prof. Şükrü Güngör, MD
E-mail: sukru.gungor@yahoo.com
Department of Pediatrics, Division of Pediatric Gestroenterology, Kahramanmaraş Sütçü İmam University, Medical Faculty, Kahramanmaraş, Turkey
ORCID ID: orcid.org/0000-0002-0433-5970

Research Methods
Prof. Pınar Okyay, MD
E-mail: pinarokyay@hotmail.com
Department of Public Health, Aydın Adnan Menderes University, Medical Faculty, Aydın, Turkey

Sercan Öztürk, MD
E-mail: dr.sercanozturk@gmail.com
Department of Pediatrics, Aydın Adnan Menderes University, Medical Faculty, Aydın, Turkey

Abbott'un koşulsuz katkılarıyla

Trends in Pediatrics
www.trendspediatrics.com

Advisory Board

**prepared alphabetically by last name

Trends in Pediatrics
www.trendspediatrics.com

Advisory Board *(continue)*

Trends in Pediatrics
www.trendspediatrics.com

Contents

DOI: 10.4274/TP.galenos.2021.30502
Trends in Pediatrics 2021;2(4):147-153

Review

A Metabolism Perspective on Pediatric Rhabdomyolysis

Havva Yazıcı, Sema Kalkan Uçar

Ege University Faculty of Medicine, Department of Pediatrics, Division of Metabolism and Nutrition, İzmir, Turkey

Cite this article as: Yazıcı H, Kalkan Uçar S. A Metabolism Perspective on Pediatric Rhabdomyolysis. Trends in Pediatrics 2021;2(4):147-153

ABSTRACT

Rhabdomyolysis is a clinical emergency that can result in life-threatening complications. The etiology for rhabdomyolysis is broad. Infecitons are the most common cause in pediatric patients. Underlying inherited metabolic diseases are also a cause of rhabdomyolysis and can often have a diagnostic challenge, considering their marked heterogeneity and comparative rarity. The purpose of this review is to summarize the essential characteristics and diagnostic clues of inborn errors of metabolism associated with rhabdomyolysis.

Keywords: Rhabdomyolysis, inborn errors of metabolism, diagnosis

INTRODUCTION

Rhabdomyolysis is a clinical condition resulting from skeletal muscle fibers damage due to many reasons. The damaged muscle cell breaks down, and the intracytoplasmic proteins such as creatine kinase (CK) and myoglobin are released into the plasma. Subsequently, it can cause life-threatening complications such as electrolyte disturbance, acute kidney injury (AKI), and disseminated intravascular coagulation. These causes include severe trauma, vigorous exercise, burns, electrical injury, prolonged immobilization, seizure, electrolyte imbalances such as hypokalemia, hyponatremia, hypophosphatemia, and drugs such as levetiracetam, colchicine, lithium, and infectious agents such as Mycoplasma pneumoniae, enteroviruses, Human parainfluenza viruses (Table 1).[1,2]

Although there is a lack of consensus for diagnosis, in the pediatric literature, CK level greater than five times the upper limit of normal, or greater than 1.000 U/L, is commonly used for diagnosis. Myalgia, weakness, and red urine are common complaints with elevated CK. This differs from myositis, in which there is muscle inflammation. However, the cell wall remains intact, so minimal intracellular content leaks into the circulation, and the serum CK level is much lower than 1.000 U/L.[1-3]

If rhabdomyolysis is suspected, the physician can confirm the diagnosis by detecting elevated serum CK levels. Rhabdomyolysis is a cause of red urine (Table 2). In the absence of red blood cells in the sediment, Heme-positive urine should raise the suspicion for hemolysis or rhabdomyolysis. Detecting urine myoglobin can be helpful for the diagnosis of rhabdomyolysis.[4,5] Early recognition of rhabdomyolysis by pediatricians is vital because it can be encountered oftenly in the pediatric routine due to various etiologies and is mortal when there is delay in treatment.[6]

Inborn errors of metabolism (IEM) are also one of the main topics in the etiology of rhabdomyolysis. These conditions are listed in Table 3. IEMs may be overlooked, considering the high frequency of viral infections in pediatrics and the fact that these infections are the most common causes of rhabdomyolysis. Pediatricians should consider IEMs when symptoms are recurrent, progressive, unexplained, unresponsive to standard treatment, or inexplicably associated with the involvement of other organ systems. Consanguinity and patients who have similar clinical features in

S. Kalkan Uçar: 0000-0001-9574-7841

Address for Correspondence: Havva Yazıcı
Ege University Faculty of Medicine, Department of Pediatrics, Division of Metabolism and Nutrition, İzmir, Turkey
E-mail: havvaya@gmail.com **ORCID-ID:** orcid.org/0000-0002-2564-7420
Received: 12.11.2021 **Accepted:** 19.12.2021 **Publication date:** 04.01.2022

family history are other supportive findings.[3,7] This review aims to provide pediatricians with an overview of IEMs that can present with rhabdomyolysis. A summary of these conditions with a focus on diagnostic tools is presented in Figure 1.[8]

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are inherited carbohydrate metabolism errors and are classified into two groups as hepatic and muscle glycogenoses. Hepatomegaly, hypoglycemia, elevated transaminases, and hepatosteatosis are common findings in hepatic glycogenosis. Glycogen is an important energy source for skeletal muscle during exercise. The absence of enzymes involved in glycogenolysis causes defective glycogen breakdown and results in exercise intolerance, muscle cramps, and rhabdomyolysis in muscle glycogenosis. If the absent enzyme is also en enzyme expressed in tissues other than liver and skeletal muscle, other clinical manifestations such as neutropenia, hemolytic anemia, or proximal tubular dysfunction may occur depending on the affected tissue. The first diagnostic tool is, if available, a demonstration of glycogen storage and enzyme deficiency in the liver or muscle. Molecular analyses confirm the diagnosis.[9,10]

GSD type V (Myophosphorylase deficiency, McArdle disease)

The GSD type V is the most common and well-known type of muscle glycogenosis. GSD type V is also known as McArdle disease. Myophosphorylase deficiency results in defective glycogenolysis in skeletal muscle. Typical symptoms are exercise intolerance with myalgia and stiffness of exercising muscles, which are relieved by rest. This clinical issue is named "second wind phenomenon". Two types of effort are more responsible for symptoms: brief, intense isometric exercise, such as lifting heavy weights, or constant

Table 1. Causes of pediatric rhabdomyolysis

Infections	Mycoplasma pneumoniae
	Primary (acute) q fever
	Enterovirus
	Human parainfluenza viruses
	West Nile encephalitis
	Inflammatory bowel disease
	Bacillus cereus
	COVID-19
Fluid and electrolyte imbalances	Water intoxication
	Hypokalemia
	Hyponatremia
	Hypophosphatemia
Muscle strain/excessive activity/trauma	Burns
	Prolonged immobilization
	Electrical injury
	Blunt trauma and crush injuries
Medications	Propofol
	Cholesterol-lowering drugs
	Levetiracetam
	Daptomycin
	Colchicine
	Lithium
	Synthetic marijuana
Inherited neuromuscular disorders	Malignant hyperthermia-susceptibility
	Anoctaminopathy-5
	Duchenne muscular dystrophy
	Becker muscular dystrophy
	Limb-girdle muscular dystrophy (2B and 2I)
	Marinesco-Sjogren syndrome
	Pontocerebellar hypoplasia type 2
Inborn errors of metabolism	(see Table 3)

COVID-19: Coronavirus disease-2019

Table 2. Causes of red urine without RBCs

Heme positive	
Hemoglobinuria	Hemolytic anemias
	Hemolytic-uremic syndrome
	Cystitis
Myoglobinuria	Rhabdomyolysis
Heme negative	
Drugs	Adriamycin
	Chloroquine
	Deferoxamine
	Hydroxycobalamin
	Ibuprofen
	Iron sorbitol
	Levodopa
	Metronidazole
	Nitrofurantoin
	Phenytoin
	Quinine
	Rifampin
	Salicylates
	Sulfasalazine
Foods	Beets
	Blackberries
	Paprika
	Red food coloring
Porphyrinuria	Disorders of "Heme" metabolism

RBCs: Red blood cells

dynamic exercise, such as running fastly or climbing uphill.[9,11] Clinical examination is usually normal between rhabdomyolysis episodes, but a proximal muscle or scapulohumeral weakness and wasting may occur in the fourth decade of life. Baseline CK levels are high, and CK can increase to more than 100,000-1,000.000 UI/L during episodes of rhabdomyolysis, causing a risk of developing AKI. Myoglobinuria occurs in about half of the patients. The ischaemic forearm exercise test (IFET) was first used as a diagnostic tool. The abnormal increase in ammonia and the absence of lactate elevation during exercise support GSD-V diagnosis. Due to the risk of rhabdomyolysis, the standardized non-ischaemic FET has replaced the ischaemic test. Muscle biopsy shows storage and negative myophosphorylase staining. Muscle biopsy should be performed several weeks after a rhabdomyolysis episode. Recently, muscle biopsy may be avoided if sequencing of *PYGM* gene is available.[10]

Table 3. Inborn errors of metabolism to consider in rhabdomyolysis

Glycogen storage diseases	GSD type V
	GSD type Ixd
Disorders of glycolysis	ALDOA deficiency
	LDH deficiency
	Muscle phosphofructokinase deficiency
	PGK deficiency
Disorders of mitochondrial fatty acid oxidation	Carnitine transporter deficiency
	Carnitine palmitoyltransferase II deficiency
	VLCAD deficiency
Mitochondrial disorders OXPHOS deficiencies	
Others	Lipin-1 deficiency
	TANGO2

ALDOA: Aldolase A, GSD: Glycogen storage disease, LDH: Lactate dehydrogenase, PGK: Phosphoglycerate kinase, VLCAD: Very long-chain acyl-CoA dehydrogenase, OXPHOS: Oxidative phosphorylation system, TANGO2: Transport and Golgi organization 2

There is no grateful therapy for GSD-V. Oral sucrose, ribose, or glucose ingestion together with abundant hydration before exercise is recommended to prevent rhabdomyolysis.[12,13] Recently, a pilot study showed that a modified ketogenic diet might improve symptoms and exercise tolerance in patients with GSD-V.[12]

GSD type IXd (Muscle phosphorylase kinase deficiency)

GSD type IXd is caused by muscle phosphorylase kinase deficiency. Muscle phosphorylase kinase deficiency is an X-linked disorder caused by mutations in PHKA1, which encodes the α1 subunit. GSD-IXd is a cause of cramps, exercise intolerance and raised CK. The second wind phenomenon occurs. These symptoms are similar to GSD-V. They are usually milder and present anytime from childhood to adulthood. Rhabdomyolysis has been reported in patients with GSD-IXd. There is a variable lactate response with the non-ischaemic FET. Symptoms should be managed as in other muscle glycogenosis.[10,13,14]

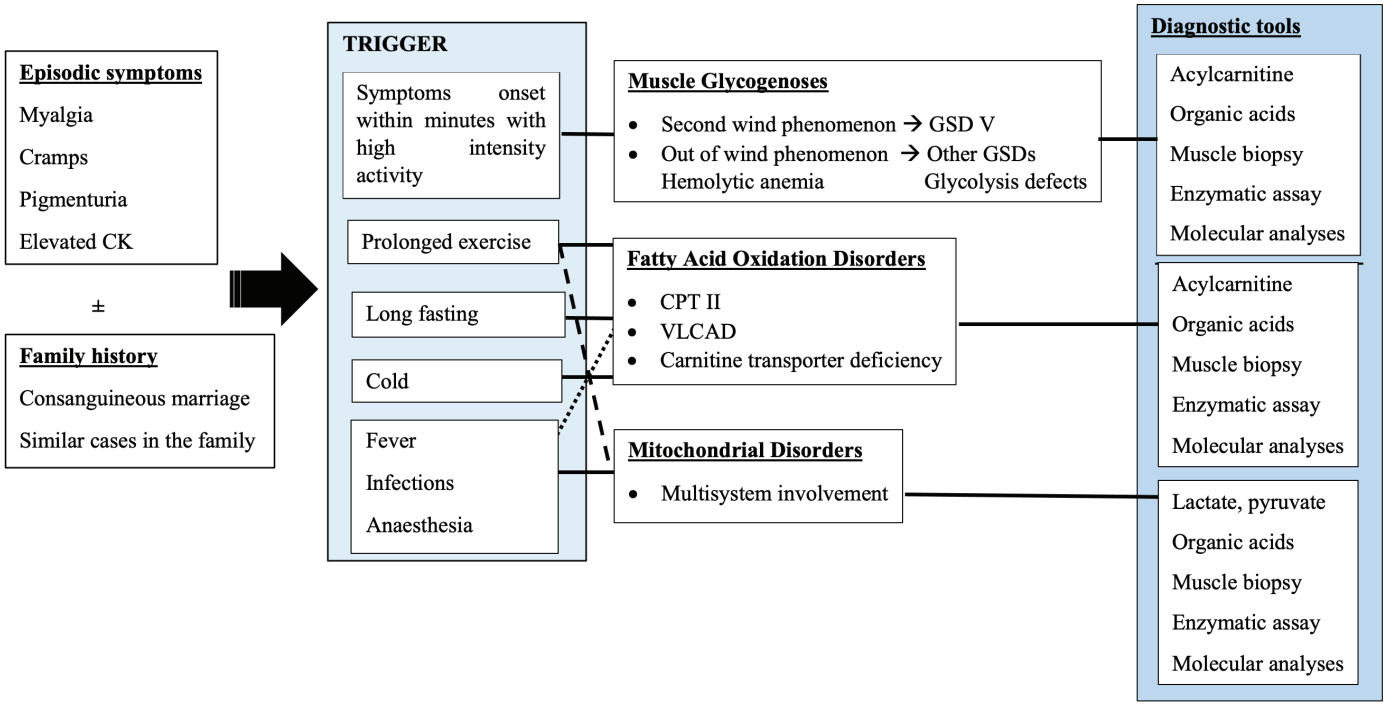


Figure 1. Algorithm for metabolic etiologies of rhabdomyolysis

CK: Creatine kinase, GSD: Glycogen storage disease, CPT: Carnitine palmitoyltransferase, VLCAD: Very long-chain acyl-CoA dehydrogenase

Disorders of Glycolysis

ALDOA deficiency (GSD type XII)

Aldolase catalyzes the reversible conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate in glycolysis. Aldolase A (ALDOA) is a predominant isoform of aldolase in skeletal muscle and erythrocytes. Single cases with very variable symptoms are reported very rarely. The main clinical findings are hemolytic anemia, recurrent episodes of rhabdomyolysis, usually precipitated by fever, and mental retardation. CK levels are normal or elevated at rest. Muscle biopsy usually reveals non-specific alterations and biochemical studies performed in muscle or erythrocytes show diminished ALDOA activity.[15]

There is no specific treatment. Avoiding vigorous exercise that may cause rhabdomyolysis is the main principle of management.[16]

LDH deficiency (GSD type XI)

Lactate dehydrogenase (LDH) has two subunits, namely muscle (M) and heart (H). There are five isoenzymes (LDH1-5) consisting of these two subunits. *LDHA* and *LDHB* genes encode the M and H proteins, respectively. LDHA mutations result in the deficiency of the LDH and they are very rare. It mainly affects skeletal muscles because skeletal LDH has all M-subunits.[17] In addition to muscle symptoms, a few affected patients suffered from skin rashes.[16,18] In patients with myoglobinuria, LDH deficiency should be kept in mind in the presence of low LDH despite elevated CK.[16]

Muscle phosphofructokinase deficiency (GSD type VII, Tarui disease)

There are three isoforms of phosphofructokinase; muscle, liver, and platelet isoforms. Muscle phosphofructokinase has the main role in glycolysis and the conversion of fructose 6-phosphate to fructose 1,6-bisphosphate. In GSD-VII, there is blockage of glycolysis resulting from a deficiency of the enzyme muscle phosphofructokinase due to mutations in the *PFKM* gene. The main clinical symptom is exercise intolerance, same as in GSD-V. The onset of classic form is usually in childhood. The main clinical features are muscle cramps, exercise intolerance, rhabdomyolysis, and myoglobinuria, often associated with hemolytic anemia and hyperuricemia but without the second wind phenomenon. Patients with late-onset form suffer from myalgia later in life. Infantile onset form may present as floppy infants. Infantile onset patients have no hemolytic anemia.[11,16]

The CK at rest is typically raised in GSD-V but may be normal in GSD-VII. A flat lactate curve, a normal increase of ammonia in non-ischaemic FET, and increased bilirubin and reticulocyte counts are helpful for differentiation from GSD-V. Biochemical assay of the muscle phosphofructokinase level and *PFKM* gene analysis are required for diagnosis.[11,16]

No specific treatment exists. The patients should avoid a high carbohydrate diet and strenuous exercise, as glucose cannot be metabolized. According to a recent, 5-year follow-up study, ketogenic diet can benefit.[19]

Muscle Phosphoglycerate Kinase Deficiency

Phosphoglycerate kinase (PGK) deficiency is a rare X-linked metabolic disorder caused by mutations in the *PGK1* gene. There are three main clinical presentations; non-spherocytic hemolytic anemia, myopathy, or the combination of anemia and central nervous system involvement. The myopathic form is indistinguishable from PFK deficiency and is characterized by recurrent episodes of exercise-induced cramps and myoglobinuria. The onset is usually in childhood.

Definitive diagnosis requires a biochemical assay of the PGK enzyme activity in muscle and/or erythrocytes and *PGK1* gene analysis.[20]

No specific treatment or cure exists. Management primarily consists of avoiding strenuous exercise. Symptoms typically resolve with rest.[16]

Disorders of Mitochondrial Fatty Acid Oxidation

Carnitine transporter deficiency

Carnitine transporter deficiency, also called systemic carnitine deficiency, is caused by a lack of the sodium-dependent carnitine transporter protein OCTN2. Carnitine cannot pass through the plasma membrane. Therefore, entry of Acyl-CoA esters, transported by binding to carnitine, into the mitochondrial fatty acid oxidation cycle is disrupted. Carnitine which cannot be transported into the cell is lost through the kidneys, and plasma and intracellular carnitine levels decrease. For plasma, carnitine levels of patients are <5 μM/L, while the normal range is 25-50 μM/L. The most fundamental clinical features are progressive cardiomyopathy and myopathy. Hypoglycemia and encephalopathy attacks may occur. It can cause sudden infant death. Older children have rhabdomyolysis, even in the absence of myopathy and cardiomyopathy. Asymptomatic or mild patients diagnosed by using neonatal screening were reported.Plasma carnitine level is tried to be kept above 10 μM/L with high-dose carnitine support (100-300 mg/kg/day). Response to treatment is good.[21,22]

Carnitine palmitoyltransferase II deficiency

Long-chain fatty acids do not cross the bilayer mitochondrial membrane. Thus, carnitine palmitoyltransferase (CPT) I and II afford long-chain fatty acids transport into the mitochondrial compartment. CPT II protein is in the inner mitochondrial membrane. CPT II deficiency is an autosomal recessive disorder of long-chain fatty acid oxidation.

There are three clinical phenotypes in CPT II deficiency; lethal neonatal form, severe infantile hepatocardiomuscular form, and myopathic form.[23] Lethal neonatal form manifests with hypoketotic hypoglycemia, liver failure, cardiomyopathy, respiratory distress, and/or cardiac arrhythmias. Liver and brain calcifications, cystic dysplastic kidneys, and neuronal migration defects have been reported.[24,25] Severe infantile hepatocardiomuscular form presents with hypoketotic hypoglycemia, liver failure, cardiomyopathy, and peripheral myopathy.[25,26]

The myopathic form is usually mild and can manifest from infancy to adulthood. The unbalanced sex distribution was reported in previous studies. More than 75% of patients reported were male thus far.[27] It is clinically characterized by recurrent episodes of muscle pain, muscle weakness, and rhabdomyolysis. These episodes are triggered mainly through exercise, prolonged fasting, exposure to cold, fever, infection, menstruation, emotional stress. Affected individuals generally do not have muscle weakness in between the attacks. Renal failure requiring hemodialysis due to acute tubular necrosis is also occasionally reported during rhabdomyolysis attacks. The overall increase of C12 to C18 acylcarnitines will support the diagnosis of CPT II deficiency. The increases in C16+C18: 1 and (C16+C18:1)/C2 ratios are more specific than other acylcarnitine measurements. The absence of the typical acylcarnitine profile does not exclude the diagnosis of CPT II deficiency, especially the mild myopathic form.[28,29] Decreased CPT II activity and histopathological changes consisting lipid accumulation can be detected in muscle biopsy. Previous reports showed that muscle biopsies might be normal and showed non-specific changes or lipid deposition.[30] The diagnosis should be confirmed by *CPT II* gene analysis.[23] CPT II deficient patients should avoid prolonged fasting and excessive muscle exercise in long-term treatment. Dietary therapy should be suggested to provide energy based on fractionated meals rich in carbohydrates and medium-chain triglyceride (MCT).[31]

Very long-chain acyl-CoA dehydrogenase deficiency

Very long-chain acyl-CoA dehydrogenase (VLCAD) plays a role in mitochondrial β-oxidation of long-chain fatty acids. There are three phenotypes reported. The severe or early-onset form typically presents within the first few months of life. It is characterized by hypertrophic or dilated cardiomyopathy and arrhythmias, hypotonia, hepatomegaly, and intermittent hypoglycemia. The moderate form typically presents during late infancy or early childhood with episodes of hypoketotic hypoglycemia and hepatomegaly. Cardiomyopathy is much less likely in moderate than in severe phenotypes. The mild or late-onset form is typically present in adolescence or early adulthood and is characterized by exercise intolerance and rhabdomyolysis. Episodic rhabdomyolysis may be provoked by infection, cold, fasting, exercise, or emotional stress.[22,25] The specific marker for VLCAD from dried blood spots is an elevation of C14:1 acylcarnitine. Other long-chain acylcarnitines and/or abnormal ratios of C14:1 and other acylcarnitines support the diagnosis of VLCAD deficiency. The acylcarnitine profile can be completely normal in patients with mild VLCAD, which should be kept in mind. There is usually dicarboxylic aciduria, especially during severe metabolic decompensation. Muscle biopsy may show lipid storage, and the electromyography is often myopathic. Clinical and acylcarnitine profiles may be confused with CPT II deficiency. Enzyme analysis can be done for diagnosis. Diagnosis needs to be confirmed by enzyme assay of VLCAD or by mutation analysis of *ACADVL* encoding VLCAD.[25]

Prolonged fasting should be avoided in patients in order to prevent acute metabolic decompensation. Frequent, regular feeds which are high carbohydrate-low fat are recommended. For providing a source of energy; MCT, by-passing the enzymatic block in β-oxidation is preferable. A bolus of MCT before exercise can prevent rhabdomyolysis in patients with myopathic VLCAD deficiency.[25,32] Triheptanoin (C7 odd-chain fatty acid) can substitute for MCT in patients with VLCAD deficiency.[33]

Rhabdomyolysis attacks may result in life-threatening events such as acute renal failure requiring hemodialysis. Generally, the treatment of rhabdomyolysis is conservative such as intravascular volume expansion, urinary alkalinization.[34]

Mitochondrial oxidative phosphorylation system disorders

The oxidative phosphorylation system (OXPHOS) is the final step in the aerobic production of adenosine triphosphate. The OXPHOS consists of 5 protein complexes (Complex I-V) and 2 electron carriers embedded in the inner mitochondrial membrane. Defects in OXPHOS can be caused by a mutation in either mitochondrial DNA or nuclear DNA.

Most patients with mitochondrial disorders present with a multisystem disorder at any age, and the symptoms are almost progressive. The most commonly affected organs are the brain, kidney, heart, and skeletal muscle, all of which require the most energy.[35,36]

Mitochondrial myopathies lead to muscle energy failure due to dysfunction of the mitochondrial respiratory chain, coded by both mitochondrial and nuclear genome. It can be a non-progressive disease, but life-threatening episodes of rhabdomyolysis may occur. There is no effective treatment available for mitochondrial myopathies.[37-39]

Others

Muscle phosphatidic acid phosphatase deficiency (Lipin-1 deficiency)

Lipin-1 (LPIN1) is a phosphatidic acid phosphohydrolase that catalyzes the dephosphorylation of phosphatidic acid to diacylglycerol and inorganic phosphate. It regulates critical metabolic pathways, such as adipocyte differentiation and lipid metabolism, nuclear envelope and mitochondrial dynamics, and vacuole fusion. LPIN1 encodes Lipin-1.

LPIN1 deficiency is one of the leading metabolic causes of recurrent rhabdomyolysis episodes in children. Deficiency of this enzyme causes potentially fatal rhabdomyolysis triggered by infection. It should be kept in mind if normal acylcarnitines are detected in patients with recurrent rhabdomyolysis. Despite the known roles of LPIN1 in lipid biosynthesis and transcriptional regulation, the pathogenic mechanisms causing rhabdomyolysis are unclear.

There is no known effective treatment for LPIN1 deficiency. Symptomatic treatment of rhabdomyolysis, high energy intake from carbohydrates, and monitoring for hyperkalemia and cardiac arrhythmias are reported in the management of rhabdomyolysis.[40-42]

TANGO2 Deficiency

The Transport and Golgi Organization protein 2 (TANGO2) protein regulates the organization of the Golgi apparatus and the endoplasmic reticulum. Mutations in TANGO2 have been recently described in episodic rhabdomyolysis. Clinical findings are hypoglycemia, hyperammonemia, and susceptibility to life-threatening cardiac tachyarrhythmias. Neurologic abnormalities, developmental delay, and intellectual disability are other accompanying clinical courses of patients. Other clues for suspicion of TANGO2 deficiency are hypothyroidism, QT prolongation, or abnormalities of long-chain acylcarnitines and urine dicarboxylic acids. TANGO2 deficiency mimics fatty acid oxidation defects, except for ketosis.[43-45]

There is no specific known treatment for TANGO2 deficiency. Treatment of rhabdomyolysis and organic complications (e.g., hyperammonemia, seizures, arrhythmias) is fundamental in managing attacks. Anabolizing management, treatment with vitamin B1, B2, and carnitine were reported to stabilize metabolic decompensation.[46]

CONCLUSION

Pediatricians should consider IEMs in the differential diagnosis of rhabdomyolysis. It should not be forgotten that IEMs have high prevalence due to the high rate of consanguineous marriages in our country. The road to diagnosis starts with the suspicion of the clinician and a thorough clinical evaluation.

Ethics

Peer-reviewed: Externally peer-reviewed.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Gardner HM, Askenazi DJ, Hoefert JA, Helton A, Wu CL. Acute kidney injury among children admitted with viral rhabdomyolysis. Hosp Pediatr. 2021;11:878-85.
2. Scalco RS, Gardiner AR, Pitceathly RD, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015;10:1-15.
3. Saudubray JM, Baumgartner M, Walter J. Clinical approach to inborn errors of metabolism in pediatrics. Inborn metabolic diseases. In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn Metabolic Diseases. Springer, Berlin, Heidelberg, 2016;3-70.
4. Lockwood GM, Storm DW. Urine Testing in Children: Little People, Big Challenges. Urine Tests: Springer; 2020:259-80.
5. Pan C, Avner E. Clinical evaluation of the child with hematuria. Nelson textbook of pediatrics 20th Int ed Elsevier Saunders, Philadelphia, 2016;2494.
6. Schiff M, Mochel F, Dionisi-Vici C. Emergency Treatments. In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn Metabolic Diseases. Springer, Berlin, Heidelberg, 2016;109-17.
7. El-Gharbawy A, Vockley J. Inborn errors of metabolism with myopathy: defects of fatty acid oxidation and the carnitine shuttle system. Pediatr Clin North Am. 2018;65:317-35.
8. Chan EK, Kornberg AJ, Ryan MM. A diagnostic approach to recurrent myalgia and rhabdomyolysis in children. Arch Dis Child. 2015;100:793-7.
9. Scalco RS, Lucia A, Santalla A, et al. Data from the European registry for patients with McArdle disease and other muscle glycogenoses (EUROMAC). Orphanet J Rare Dis. 2020;15:330.
10. Walter J, Labrune PA, Laforet P. The glycogen storage diseases and related disorders. In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn metabolic diseases. Springer, Berlin, Heidelberg, 2016;121-37.
11. Lucia A, Martinuzzi A, Nogales-Gadea G, Quinlivan R, Reason S. Clinical practice guidelines for Glycogen Storage Disease V & VII (McArdle Disease and Tarui Disease) from an international study group. Neuromuscul Disord. 2021;31:1296-310.
12. Løkken N, Hansen KK, Storgaard JH, Ørngreen MC, Quinlivan R, Vissing J. Titrating a modified ketogenic diet for patients with McArdle disease: A pilot study. J Inherit Metab Dis. 2020;43:778-86.
13. Santer R, Klepper J, Smit GPA. Disorders of carbohydrate metabolism and glucose transport. In: Blau N, Duran M, Gibson KM, Dionisi-Vici K. Physician's Guide to the Diagnosis, Treatment, And Follow-Up Of Inherited Metabolic Diseases. Springer, Berlin, Heidelberg, 2014;265-301.
14. Kishnani PS, Goldstein J, Austin SL, et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21:772-89.
15. Papadopoulos C, Svingou M, Kekou K, et al. Aldolase A deficiency: Report of new cases and literature review. Mol Genet Metab Rep. 2021;27:100730.
16. Wamelink MM, Valayannopoulos V, Garavaglia B. Disorders of glycolysis and the pentose phosphate pathway. In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn Metabolic Diseases. Springer, Berlin, Heidelberg, 2016;149-60.
17. Farhana A, Lappin S. Biochemistry, Lactate Dehydrogenase.[Updated 2020 May 17]. StatPearls [Internet] Treasure Island (FL): StatPearls Publishing 2021.
18. Kanno T, Maekawa M. Lactate dehydrogenase M-subunit deficiencies: clinical features, metabolic background, and genetic heterogeneities. Muscle Nerve Suppl. 1995;18:S54-S60.
19. Similä ME, Auranen M, Piirilä PL. Beneficial effects of ketogenic diet on phosphofructokinase deficiency (glycogen storage disease type VII). Front Neurol. 2020;11:57.
20. Echaniz-Laguna A, Nadjar Y, Béhin A, et al. Phosphoglycerate kinase deficiency: a nationwide multicenter retrospective study. J Inherit Metab Dis, 2019;42:803-8.
21. Longo N. Primary carnitine deficiency and newborn screening for disorders of the carnitine cycle. Ann Nutr Metab. 2016;68:5-9.
22. Spiekerkoetter U, Duran M. Mitochondrial fatty acid oxidation disorders. In: Blau N, Duran M, Gibson KM, Dionisi-Vici K. Physician's Guide to the Diagnosis, Treatment, And Follow-Up Of Inherited Metabolic Diseases. Springer, Berlin, Heidelberg, 2014;247-64.
23. Joshi PR, Zierz S. Muscle carnitine palmitoyltransferase II (CPT II) deficiency: a conceptual approach. Molecules. 2020;25:1784.
24. Boemer F, Deberg M, Schoos R, et al. Diagnostic pitfall in antenatal manifestations of CPT II deficiency. Clin Genet. 2016;89:193-7.
25. Morris AA, Spiekerkoetter U. Disorders of mitochondrial fatty acid oxidation & riboflavin metabolism. In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn metabolic diseases. Springer, Berlin, Heidelberg, 2016;201-13.
26. Vladutiu GD, Quackenbush EJ, Hainline BE, Albers S, Smail DS, Bennett MJ. Lethal neonatal and severe late infantile forms of carnitine palmitoyltransferase II deficiency associated with compound heterozygosity for different protein truncation mutations. J Pediatr. 2002;141:734-6.
27. Joshi PR, Deschauer M, Zierz S. Carnitine palmitoyltransferase II (CPT II) deficiency: genotype-phenotype analysis of 50 patients. J Neurol Sci. 2014;338:107-11.
28. Gempel K, Kiechl S, Hofmann S, et al. Screening for carnitine palmitoyltransferase II deficiency by tandem mass spectrometry. J Inherit Metab Dis. 2002;25:17-27.

29. Anichini A, Fanin M, Vianey-Saban C, et al. Genotype-phenotype correlations in a large series of patients with muscle type CPT II deficiency. Neurol Res. 2011;33:24-32.
30. Angelini C, Nascimbeni AC, Cenacchi G, Tasca E. Lipolysis and lipophagy in lipid storage myopathies. Biochimic Biophys Acta. 2016;1862:1367-73.
31. Ivin N, Della Torre V, Sanders F, Youngman M. Rhabdomyolysis caused by carnitine palmitoyltransferase 2 deficiency: a case report and systematic review of the literature. J Intensive Care Soc. 2020;21:165-73.
32. Van Calcar SC, Sowa M, Rohr F, et al. Nutrition management guideline for very-long chain acyl-CoA dehydrogenase deficiency (VLCAD): an evidence- and consensus-based approach. Mol Genet Metab. 2020;131:23-37.
33. Norris MK, Scott AI, Sullivan S, et al. Tutorial: triheptanoin and nutrition management for treatment of long-chain fatty acid oxidation disorders. JPEN J Parenter Enteral Nutr.2021;45:320-8.
34. Merritt JL, MacLeod E, Jurecka A, Hainline B. Clinical manifestations and management of fatty acid oxidation disorders. Rev Endocr Metab Disord. 2020;21:479-93.
35. de Laat P, Rodenburg R, Smeitink J. Mitochondrial oxidative phosphorylation disorders. In: Blau N, Duran M, Gibson KM, Dionisi-Vici K. Physician's Guide to the Diagnosis, Treatment, And Follow-Up Of Inherited Metabolic Diseases. Springer, Berlin, Heidelberg, 2014;337-59.
36. Rahman S, Mayr JA. Disorders of oxidative phosphorylation. In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn metabolic diseases. Springer, Berlin, Heidelberg, 2016;223-42.
37. Andreu A, Bruno C, Dunne T, et al. A nonsense mutation (G15059A) in the cytochrome b gene in a patient with exercise intolerance and myoglobinuria. Annal Neurol. 1999;45:127-30.
38. Andreu AL, Hanna MG, Reichmann H, et al. Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA. N Engl J Med. 1999;341:1037-44.
39. Olimpio C, Tiet MY, Horvath R. Primary mitochondrial myopathies in childhood. Neuromuscul Disord. 2021;31:978-87.
40. Pizzamiglio C, Lahiri N, Nirmalananthan N, et al. First presentation of LPIN1 acute rhabdomyolysis in adolescence and adulthood. Neuromuscul Disord. 2020;30:566-71.
41. Topal S, Demir M, Hasan A, et al. A neglected cause of recurrent rhabdomyolysis, LPIN1 gene defect: a rare case from Turkey. Turk J Pediatr Dis. 2020;62:647-51.
42. Lamari F, Saudubray J-M, Mitchell GA. Disorders of Intracellular Triglyceride and Phospholipid Metabolism In: Saudubray J-M, Garcia-Cazorla A (eds). Inborn metabolic diseases. Springer, Berlin, Heidelberg, 2016;477-91.
43. Schymick J, Leahy P, Cowan T, et al. Variable clinical severity in TANGO2 deficiency: Case series and literature review. Am J Med Genet A. 2021 Oct 19. doi: 10.1002/ajmg.a.62543. Epub ahead of print
44. Bérat CM, Montealegre S, Wiedemann A, et al. Clinical and biological characterization of 20 patients with TANGO2 deficiency indicates novel triggers of metabolic crises and no primary energetic defect. J Inherit Metab Dis. 2021;44:415-25.
45. Dines JN, Golden-Grant K, LaCroix A, et al. TANGO2: expanding the clinical phenotype and spectrum of pathogenic variants. Genet Med. 2019;21:601-7.
46. Mingirulli N, Pyle A, Hathazi D, et al. Clinical presentation and proteomic signature of patients with TANGO2 mutations. J Inherit Metab Dis. 2020;43:297-308.

DOI: 10.4274/TP.galenos.2021.69775
Trends in Pediatrics 2021;2(4):154-158

Original Article

Phenylalanine Levels of Patients with Classical Phenylketonuria According to Eating Habits of Caregivers

Pelin Teke Kısa[1], **Abdurrahman Çiçek**[2], **Hüseyin Karagöz**[2], **Mahmut Dağ**[2], **Arda Güneş**[2], **Gülşah Yavaş**[2], **Nur Arslan**[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Pediatric Metabolism and Nutrition, İzmir, Turkey
[2]Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

Cite this article as: Teke Kısa P, Çiçek A, Karagöz H, Dağ M, Güneş A, Yavaş G, Arslan N. Phenylalanine levels of classical phenylketonuria patients according to eating habits of caregivers. Trends in Pediatrics 2021;2(4):154-158

ABSTRACT

Objective: Diet is the main component in the treatment of classical phenylketonuria (PKU). Living in the same house as a PKU patient affects the lifestyle of family members in many ways. The present study examines the dietary habits of the parents of PKU patients.

Methods: The parents of 32 PKU patients were asked about their socio-demographic characteristics, family dietary patterns (mealtimes; frequency of meals with the PKU patient; content of foods at mealtimes, etc.) the parental dietary regimen and any food allergies.

Results: The mean age of the PKU patients was 11.5±4.3 years, and 14 (44%) were female. The mean plasma phenylalanine (Phe) level over the previous year was 732.4±339.0 µmol/L in the patient group. Within the study sample, 2 (6%) families prepared only low-protein meals in the home, and the Phe levels of the two PKU patients in these families never exceeded >600 µmol/L, and 26 (81%) parents prepared separate meals for the PKU patient and for the other family members every day. The 28 (88%) parents had no special dietary regimen, with a mean Phe level of 774.8±345.4 µmol/L (p=0.055). Finally, 26 (81%) of the parents were careful about the foods they consumed while eating with the PKU patient, opting especially for foods that are low in Phe.

Conclusion: Diet is an indispensable part of the treatment of PKU and can affect the dietary patterns also of parents. Phe levels are lower in the children of parents who adopt a protein-restricted diet as a lifestyle, such as vegan and pescetarian. Large-scale studies are needed to investigate the physical, social and psychological effects of parents' dietary habits on PKU patients.

Keywords: Phenylketonuria, mealtime, parents, phenylalanine, diet, family

INTRODUCTION

Phenylketonuria (PKU) is the most common inborn error of the amino acid metabolism globally. In PKU, phenylalanine (Phe), an essential amino acid, cannot be converted into tyrosine due to a deficiency of phenylalanine hydroxylase enzyme activity in the liver. The most severe form of this disorder is known as classical PKU. Classical PKU occurs when phenylalanine hydroxylase activity is severely reduced or absent. Phe accumulates and the production of phenylketones is increased, resulting in high Phe levels in the blood and brain. Consequently, high blood levels of Phe have neurotoxic effects, and can lead to such serious neurological and psychiatric symptoms as microcephaly, mental retardation, epilepsy, behavioral disorder, hyperactivity and autism.[1] Although the exact pathogenesis of neurocognitive dysfunction yet to be clearly explained,[2] the goal with all available treatments is to reduce blood Phe levels, since it is known that high blood levels of Phe are strongly associated with neurocognitive dysfunction. The

P. Teke Kısa: 0000-0001-6481-3172; **A. Çiçek:** 0000-0003-0392-1932; **H. Karagöz:** 0000-0001-6012-2024; **M. Dağ:** 0000-0001-7581-6918; **A. Güneş:** 0000-0001-8594-3152; **G. Yavaş:** 0000-0001-6928-533X

Address for Correspondence: Nur Arslan
Dokuz Eylül University Faculty of Medicine, Department of Pediatric Metabolism and Nutrition, İzmir, Turkey
E-mail: nur.arslan@deu.edu.tr **ORCID-ID:** 0000-0001-6481-3172
Received: 11.06.2021 **Accepted:** 02.09.2021 **Publication date:** 04.01.2022

target is to maintain a blood Phe level of <360 µmol/L in children under 12 years of age, while the target blood level of Phe is <600 µmol/L in older children.[1]

The mainstay treatment is a lifelong Phe-restricted diet,[3] which has three main features: (a) natural protein is restricted, (b) Phe-free-L-amino acid supplements are used to provide the necessary protein, and (c) low-protein foods are consumed.[1] The diet lacks high protein foods such as meat, chicken, fish, eggs, cheese and milk, with the calories that the patients need being provided by foods that are rich in carbohydrates and low in protein, such as fruit, vegetables and grains.[3] Especially, children with classical PKU usually only tolerate Phe levels between 200 -500 mg day.[1]

The importance of family meals has been well established, however dining with a dieter can lead to changes in the eating habits and also in food preferences of other family members. To date, there has been a lack of studies investigating the eating habits of families of patients with classical PKU. The present study analyzes the eating habits of family members with a child with classical PKU so as to identify the strategies followed by families to cope with the associated problems.

MATERIALS and METHODS

This prospective study was conducted at Dokuz Eylül University Faculty of Medicine, a specialized PKU clinic. All the patients were diagnosed as having classical PKU (Phe >1200 µmol/L, Phe tolerance <20 mg/kg/day) via Newborn Screening Program and their treatments were initiated immediately after their diagnosis. Phe levels were monitored based on recommendations of European guidelines on PKU (Frequency of blood Phe levels fortnightly at 1-12 years; monthly after the age of 12 years).[1] Among the 37 eligible families, five caregivers declined to participate in the study, and so a total of 32 caregivers of children with classical PKU were enrolled in the study, who were asked to complete four questionnaires, and thus to provide details of:

1) The socio-demographic characteristics of the child and the caregivers; child's age, gender and dietary compliance; parent's age, sex, marital status, educational level, occupation,

2) Family dietary patterns (mealtimes; frequency of meals with the patient with PKU; content of foods at mealtimes, number of variety, frequency of foods consumed, etc.),

3) The parental dietary regimen (whether a pescatarian, vegetarian or vegan dietary regimen was followed),

4) Any food allergies (whether families were following a special diet).

Statistical Analysis

The data analysis was performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 22.0 (SPSS IBM, Armonk, NY, USA). The normality of the sample distribution was tested using the Kolmogorov-Smirnov test. Numerical variables were expressed as mean ± standard deviation or median (minimum-maximum), depending on the normality of distribution; and categorical variables were expressed as numbers and percentages (%). Since the Phe levels were normally distributed; the Student's t-test and one-way ANOVA was used to compare the parameters between the groups. The level of statistical significance was set at a p-value of <0.05.

Ethical Consideration

The protocol of the present study was designed to be in compliance with the 1964 Declaration of Helsinki. The study was initiated, and data collection began after approval was granted by the Ethics Committee of the Dokuz Eylül University Faculty of Medicine, Non-Interventional Research Ethics Committee (approval number: 2018/09-24). Informed consent was obtained from all parents enrolled in the study.

RESULTS

Demographic and Clinical Features

Included in the study were 32 patients with classical PKU diagnosed during newborn screening. The median age at the time of diagnosis was 10 days (range: 2-16 days), and all diagnoses were made based on biochemical and genetic analyses (Phe >1200 µmol/L for all). The mean age of the patients was 11.5±4.3 years, and 14 (44%) were female and 18 (56%) were male. All of the patients had been on a strict low-Phe diet since the newborn period (10 g/day of natural protein), and all were receiving Phe-free L-amino acid supplements in 3-4 servings/day. The mean plasma Phe level over the previous year was 732.4±339.0 µmol/L in all patients. Demographic characteristics of the 32 caregivers are presented in Table 1.

Family Dietary Patterns

The meals were prepared together by the mother and father in one family, while the mother was the only person preparing the meals in all other families. Considering the eating habits of the families, only low-protein meals were prepared at home for the 2 patients with PKU who had no siblings and who were living only with their parents, and all members of these 2 (6%) families were undergoing Phe-restricted diet therapy. The mean Phe level over the last year was 351.1±68.3 µmol/L and 308.7±52.2 µmol/L in the children with PKU of these 2 families, and the Phe level of these 2 patients with PKU never exceeded 600 µmol/L. In 26 (81%) families, the parents prepared separate meals for the patient with PKU and for the other family members every day, and these patients had a mean Phe level of 744.5±332.9 µmol/L. Four (12%) parents were not preparing Phe-restricted diet meals at home. Low-Phe foods were given to the patient with PKU from the same table, while protein-rich foods were shared among other family members. These patients had a mean Phe level of 859.6±520.6 µmol/L. When the 3 eating habits were compared, no statistically significant difference could be established in the respective Phe levels (p=0.086). Of the total, 3 (9%) patients with PKU did not eat their meals with their families, and did not sit at the same table,

and the mean Phe level of these 3 respondents was 889.8±351.1 µmol/L. The children with PKU of 29 (91%) parents who shared the same table with other family members had a mean Phe level of 720.3±284.5 µmol/L (p=0.407).

When the content of the foods included in the meals of families with a patient with PKU was examined, 20 (62%) families consumed meat once a week or less, and the mean Phe level was 768.8±302.6 µmol/L in the children with PKU of this group, compared to 678.0±411.6 µmol/L in the children with PKU of families who consumed meat more often than once a week. An examination of vegetable consumption in the home revealed that 19 (59%) families ate vegetables every day, and 8 (25%) families every other day. The mean Phe levels of the children with PKU in these families were 714.3±357.1 µmol/L and 835.4±332.9 µmol/L, respectively. Vegetables were consumed less frequently in 5 (16%) families, and the mean Phe level of the children with PKU in these families was 743.5±387.4 µmol/L.

Table 1. Socio-demographic data of 32 phenylketonuria caregivers

	Caregivers
	n (%)
Sex	
Female	20 (62)
Male	12 (37)
Age (years)	
Mean ± SD	40.0±8.2
20-29	2 (6)
30-39	18 (56)
40-49	6 (19)
50-59	6 (19)
Domicile	
Town	18 (56)
Village	9 (28)
Rural	5 (15)
Educational	
Elementary/occupational school	26 (81)
Upper secondary school	4 (12)
University	2 (6)
Number of children	
1	3 (9)
2	15 (47)
3	10 (31)
≥4	4 (13)
Household, n (%)	
≤4	17 (53)
>4	15 (47)
Employment status	
Full-time or part-time work	7 (22)
Unemployed	25 (78)

SD: Standard deviation

Parental Dietary Regimen

When the parental dietary regimens were examined, 3 (9%) families described themselves as vegan and 1 (3%) as pescatarian. The children with PKU in these families had a mean Phe level of 429.8±115.0 µmol/L over the previous year. Among the total parent sample, 28 (88%) had no special dietary regimen, and the children with PKU in these families had a mean Phe level of 774.8±345.4 µmol/L. The difference between the two groups was statistically insignificant (p=0.055).

Twenty-six (81%) were careful about the foods they consumed while eating with the patient with PKU, opting especially for foods that were low in Phe. The mean Phe level over the preceding year was 762.7±351.1 µmol/L in the children with PKU of the parents who were careful about the foods they consumed while eating with the patient with PKU, compared to 599.3±308.7 µmol/L in the children of the parents who paid no such attention (p=0.392).

Food Allergies

None of the parents had a history of food allergy.

DISCUSSION

The parents of patients with PKU pay attention to the foods they consume when eating in the presence of their children. Some parents prepare only Phe-restricted diet meals at home, meaning that all family members follow a protein-restricted diet. The mean Phe level is at the target value of <360 µmol/L specified in the PKU guidelines in patients with PKU of these parents. The Phe levels were lower in these families than in the other families, but statistical significance could not be obtained due to the small sample size. Some families opted not to share the same table with the patient with PKU and eat their meals at separate times or in a different room.

It has long been known that living with a child with a chronic condition imposes a psychosocial burden on families,[4,5] and that lifelong diet therapy affects the quality of life of both the patient and the family.[6] Parents believe that the preservation of neurocognitive functions in their children with PKU depends on successful dietary therapy[7] and so families may change their lifestyles to fully comply with the diet therapy. After diagnosis, parents may change their employment attributes, preferring to work shorter hours, or quitting their job completely[8] and social isolation is common in the families of a person with PKU.[9] Most of the parents in the study opted to prepare separate meals for their children with PKU every day. Parents of patients with PKU spend an average of 3 hours a day preparing meals[8] and struggle to find time for themselves. In the present study, the person who prepared the meals in the families of patients with PKU was

usually the mother. Mothers work harder than fathers, and the daily lives of mothers of patients with classical PKU is affected to a greater degree than the fathers, and mothers also experience more anxiety and depression.[10]

Different diets evoke different feelings in patients with PKU. Especially during the adolescence, 30% of patients feel shame at not being able to consume all types of food, and their parents experience similar feelings.[11] Parents who worry that their children may feel different because of the PKU diet are in a constant struggle.[7] When preparing meals for their children with PKU, they try to make meals that are similar to what the other members of the family are eating. They may also modify their lifestyles such as by not consuming foods that are rich in Phe and not going to restaurants.[7,9] In addition to these strategies, it was reveled in the present study that most parents imitated their children with PKU in their food preferences.

When the Phe values were examined according to the frequency of consumption of meat and vegetables in the meals of the families, no statistical difference was found. Phe level in the patients with PKU of families who consumed vegetables every day was detected slightly less than patients with PKU in families who consumed vegetables every other day or less frequently. However, Phe values were unexpectedly slightly lower in families that consumed meat more frequently than in other families. Many factors including small sample size in this study, socio-economic levels of families, diet adherence of patients with PKU, etc might cause this contradictory result.

It was a well-known fact that the food preferences of parents influenced those of their children,[12,13] although in the present study it was noted that the parents adjusted their food preferences to suit those of the child with PKU in the family. Although the food preferences and food neophobias in the families of patients with PKU were found to have only a limited effect on the children's eating habits,[14] the Phe levels were under control in the 2 families who followed a Phe-restricted diet as a family. When the parents opted a Phe-restricted diet, such as pescatarian, vegan or vegetarian regimens, their children with PKU had lower Phe levels than other individuals.

Study Limitations

There were certain limitations in our study, the most significant of which was the small sample size. Another limitation was that the eating habits of the sample were not compared with those with family members with healthy children. A study investigating the eating habits of all family members may be helpful in making a clear assessment of the different eating habits within the family.

CONCLUSION

Living with a patient with classical PKU places a considerable burden on the parents, affecting many different areas. While diet is a vital element in PKU treatment, it may also affect the dietary patterns of the child's parents. Large-scale studies are needed to identify the physical, social and psychological effects of parents' dietary habits on patients with classical PKU.

Ethics

Ethics Committee Approval: Ethic approval was granted by the Ethics Committee of the Dokuz Eylül University Faculty of Medicine, Non-Interventional Research Ethics Committee (approval number: 2018/09-24).

Informed Consent: Informed consent was obtained from all parents enrolled in the study.

Peer-reviewed: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.T.K., N.A., Concept: P.T.K., N.A., Design: P.T.K., N.A., Data Collection or Processing: P.T.K., A.Ç., H.K., M.D., A.G., G.Y., Analysis or Interpretation: P.T.K., N.A., Literature Search: P.T.K., N.A., Writing: P.T.K., N.A.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12:162.
2. de Groot MJ, Hoeksma M, Blau N, Reijngoud DJ, van Spronsen FJ. Pathogenesis of cognitive dysfunction in phenylketonuria: Review of hypotheses. Mol Genet Metab. 2010;99:S86-S89.
3. MacDonald A, Van Wegberg AMJ, Ahring K, et al. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis. 2020;15:171.
4. Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. J Child Psychol Psychiatry. 1998;39:29-46.
5. Raina P, O'Donnell M, Rosenbaum P, et al. The health and well-being of caregivers of children with cerebral palsy. Pediatrics. 2005;115:e626 LP-e636.
6. Fabre A, Baumstarck K, Cano A, et al. Assessment of quality of life of the children and parents affected by inborn errors of metabolism with restricted diet: preliminary results of a cross-sectional study. Health Qual Life Outcomes. 2013;11:158.
7. Carpenter K, Wittkowski A, Hare DJ, et al. Parenting a Child with Phenylketonuria (PKU): an Interpretative Phenomenological Analysis (IPA) of the Experience of Parents. J Genet Couns. 2018;27:1074-86.
8. MacDonald A, Smith TA, de Silva S, Alam V, van Loon JMT. The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK. Mol Genet Metab Reports. 2016;9:1-5.
9. Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Reports. 2018;17:57-63.
10. Gunduz M, Arslan N, Unal O, Cakar S, Kuyum P, Bulbul SF. Depression and anxiety among parents of phenylketonuria children. Neurosciences (Riyadh). 2015;20:350-6.
11. Witalis E, Mikoluc B, Motkowski R, et al. Phenylketonuria patients' and their parents' knowledge and attitudes to the daily diet - multi-centre study. Nutr Metab (Lond). 2017;14:57.

12. Pearson N, Biddle SJH, Gorely T. Family correlates of fruit and vegetable consumption in children and adolescents: a systematic review. Public Health Nutr. 2009;12:267-83.
13. Damiano SR, Hart LM, Paxton SJ. Correlates of parental feeding practices with pre-schoolers: parental body image and eating knowledge, attitudes, and behaviours. Appetite. 2016;101:192-98.
14. Evans S, Daly A, Chahal S, Ashmore C, MacDonald J, MacDonald A. The influence of parental food preference and neophobia on children with phenylketonuria (PKU). Mol Genet Metab Rep. 2017;14:10-4.

DOI: 10.4274/TP.galenos.2021.35229
Trends in Pediatrics 2021;2(4):159-164

Original Article

A Study on Pediatric Nurses' Pain Management Knowledge and Practices in Turkey

Ayşegül Şimşek[1], **Duygu Gözen**[2]

[1]İstinye University Faculty of Health Sciences, Department of Midwifery, İstanbul, Turkey
[2]İstanbul University-Cerrahpaşa, Florence Nightingale Faculty of Nursing, Department of Child Health and Diseases Nursing, İstanbul, Turkey

Cite this article as: Şimşek A, Gözen D. A Study on Pediatric Nurses' Pain Management Knowledge and Practices in Turkey. Trends in Pediatrics 2021;2(4):159-164

ABSTRACT

Objective: With a child's less developed ability to express oneself when compared to adults, it is a more challenging task to manage pain in children. Nurses, as those who spend the most time with patients, need to have sufficient knowledge about assessing and managing pain in children. The aim of this study is to determine the knowledge and pediatric practices of nurses working in pediatric clinics on pain management in children.

Methods: This descriptive study was completed with 134 nurses. Study data were captured through using a questionnaire drafted, and rearranged in line with specialist advice, by the researchers. Data were electronically evaluated with percentage, Kruskal-Wallis H and Mann-Whitney U tests using analysis system.

Results: It was determined that 81.3% of nurses had not been trained on pain management in children. It was established that nurses preferred pharmacological methods to non-pharmacological, that 54.5% of them used a combination of pharmacological and non-pharmacological methods to relieve pain in children, and that 16.4% mentioned difficulty in pain management due to lack of time. Nurses' knowledge of pain management was found to be slightly above the average (maximum 22 points; median ± standard deviation=16.50±2.74; minimum-maximum: 9-21).

Conclusion: The study established that nurses' level of knowledge about pain management was inadequate, that nurses encountered various challenges in pain management arising from the workplace setting, and that rate of use of non-pharmacological pain treatment methods, an independent function of nursing, is significantly low.

Keywords: Children, non-pharmacological treatment, pain management

INTRODUCTION

The Taxonomy Committee of the International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[1-3] Assessment of pain takes an individual's age and physical, psychological, social, and environmental factors into consideration.[2,4] The major problem in the assessment of pain in children is an imprecise verbal account of pain experienced by children due to inadequate language development.[3] Untreated pain leads to biological, psychological, social, developmental, and behavioral problems in children.[4] The first step in pain management is clarifying the level, severity, and location of the pain. Many pain scales [visual analog scales (VAS), "Face, Legs, Activity, Cry, Consolability", Wong-Baker] are applied to obtain the presence of pain. These scales are used according to age, responsiveness, medical diagnosis, and treatment of the child and can be effectively used to make pain concrete. After defining the pain level with scales, the next step is to relieve the pain or reduce its severity. At this stage, pharmacological and non-pharmacological methods can be used alone or in combination. While analgesics are the most preferred pharmacological method,

D. Gözen: 0000-0001-9272-3561

Address for Correspondence: Ayşegül Şimşek
İstinye University Faculty of Health Sciences, Department of Midwifery, İstanbul, Turkey
E-mail: aysegul.simsek@istinye.edu.tr **ORCID-ID:** orcid.org/0000-0002-2166-1778
Received: 30.07.2021 **Accepted:** 17.09.2021 **Publication date:** 04.01.2022

many non-pharmacological methods including distraction, massage, and oral sucrose can also be preferred.[3,5,6]

Effective pain management takes correct information, attitude, appraisal, and therapeutic intervention skills.[7] There are several aspects differentiating nurses in pain management from other medical staff members: prolonged interaction with the patient; early awareness of pain; observation of patient's previous pain experience and methods to cope with pain; implementation of planned treatment and observation of effects and results of such treatment; guidance and support to a family with an empathetic approach.[2,8]

While pain is sometimes an indicator of an existing problem, it sometimes becomes an aggravating factor for this problem. Therefore, it should be detected, evaluated, and remedied as early as possible. Relieving the pain of a child is one of the most familiar issues for pediatric nurses. Nurses should know every stage of pain management within the scope of care and should relieve pain. When the literature is evaluated, it is seen that there are many studies on the knowledge of pain management of nurses and that these studies examine the pain infornation of nurses and the methods they use to relieve pain.[2,3,9,10] Despite many studies, there is still insufficient information on pain management, and the origin of these deficiencies is wondered.[1,3,8,9] In the light of this information, we aimed to determine the knowledge and practices of nurses working in pediatric clinics on pain management in children.

Study Questions

What is the level of knowledge of pediatric nurses about pain management in children?

What is the rate of pediatric nurses knowing and using pain assessment tools in children?

Which methods do pediatric nurses use in children's pain management?

MATERIALS and METHODS

Study Design

This descriptive study was conducted in all private, state, and university hospitals in a city.

Participants

The research population consisted of 184 nurses working in pediatric clinics in all hospitals in a city. In the sample calculation, it was concluded that 123 nurses should be reached with a sampling error of ±0.05 and a 95% confidence interval. One nurse could not participate in the study because she was on unpaid leave, and one nurse was in the military. The study was completed with 134 nurses who met the inclusion criteria.

The study was carried out in one university hospital, one maternity and children's hospital, one training and research hospital, eight state hospitals, and four private hospitals. The participants of this study were pediatric nurses working in pediatrics, pediatric surgery, pediatric emergency, pediatric intensive care, and neonatal intensive care units of these hospitals.

Data Collection Tools

In the collection of data, a data collection form consisting of,[1,10-14] 62 open and closed-ended questions prepared in line with the literature was used. The questionnaire consisted of 3 sections, the first of which contained 16 questions to solicit information on nurses' socio-demographic characteristics, professional status, and experience. The second of which contained 24 questions concerning nurses' practices aiming to manage pain and factors affecting these practices. The third section consisted of 22 questions prepared to assess nurses' level of knowledge about pain management. This section was sent to 5 specialists in pediatric nursing in terms of content and relevance. An evaluation form, in which the appropriateness of each question item, and the opinions and comments could be included, was used to obtain expert opinions about the applicability of the survey questions. The questions were revised in line with the information obtained. Nurses giving correct answers to all the questions in this section scored 22. Data were collected through interviews conducted by the researcher with nurses in person.

Statistical Analysis

Data gathered in the study were analyzed using Statistical Package for the Social Sciences version 18 software program (IBM Company). While the median and standard deviation values were calculated in the analysis of continuous data, numbers and percentages were calculated in the analysis of categorical data such as age and gender. In the comparison of pain knowledge score and descriptive information, non-parametric tests were used by looking at the normality distribution. Mann-Whitney U test was performed to compare the pediatric willingness to work in the clinic and institution variables with pain management knowledge. The Kruskal-Wallis test was used to compare the working style and hours, and the knowledge of pain management of the nurses. Findings were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

Ethical Considerations

Before the study, written approval was obtained from the provincial health directorate and the directorates of the hospitals where the study would be conducted, and the local ethics committee approval was obtained from Kocaeli University Clinical Research Ethic Committee (approval number: KAEK 12/1, date: 20.10.2011). Because only one hospital had a local ethics committee among all hospitals included in the study, ethics committee approval was obtained from this committee. Before the study, the participants were informed about the study, and the written and verbal consents were obtained.

RESULTS

Information on the introductory characteristics of nurses is given in Table 1. It was found that 51.5% of the nurses were undergraduate graduates, most of the nurses had less than 5 years of nursing experience and the duration of experience in the pediatric clinic was less than 1 year. While 84.3% of the nurses worked in shifts, 74.6% stated that they did not choose to work in the pediatric clinic, and 68.7% were satisfied with working in the pediatric clinic. However, it was determined that more than half of them did not follow professional publications and did not attend scientific meetings.

It was defined that 18.7% of the nurses had previously received training on pain management in children, and about half of them did not record the presence of pain in the patient file. Information on nurses' knowledge and use of the pediatric pain scale is given in Table 2. It was found that 33.3% used distraction, 28.3% used hot/cold dressing, and 11.7% used massage as a non-pharmacological method. Relaxation techniques, kangaroo care, repositioning, landscaping, pacifier use, and individualized care were other methods used. Nurses reported that 16.4% did not practice non-pharmacological methods due to lack of time, 9.6% due to communication problems with the patient and their relatives, and 9% due to communication problems with the team.Nearly half of the nurses reported that they needed information on pain assessment and management and 13.4% on non-pharmacological methods. The median value of the pain scores of the nurses was 16±2.74 [minimum (min)-maximum (max); 9-21] points (Table 3).

While 89.5% of the nurses reported that they did not know that pain is a vital sign; 29% stated that they accepted the presence of pain if the child and their parents reported pain. While 28% reported that newborns/infants perceived pain, 40% stated that the child's pain is not always a symptom of the disease. When the knowledge levels of nurses on pain management were evaluated, it was determined that the knowledge scores of the nurses working in university [16.70±1.64 (min-max; 13-20)] and state hospitals [15.47±3.19 (min-max; 9-21)] were higher than the nurses working in private hospitals [16.12±2.94 (min-max; 11-21)], and the difference was statistically significant (p=0.03). When the nurses' work patterns and pain management knowledge scores were compared, it was found that the scores of those who worked during the daytime were higher, but there was no statistical difference between them (p>0.05). While the pain management knowledge scores of nurses who worked 40-48 hours a week [16.72±2.16 (min-max; 11-21)] were higher than those who worked for 48 hours and above a week [15.39±3.07 (min-max; 9-21)], a statistical difference was found between working time and pain management knowledge scores (p=0.01).

Table 1. Socio-demographic characteristics of nurses (n=134)

Characteristics	Groups	n	%
Age	20-24 years	64	47.8
	25-29 years	36	26.8
	30-34 years	23	17.2
	35 years and older	11	8.2
Gender	Male	6	4.5
	Female	128	95.5
Marital status	Married	69	51.5
	Single	65	48.5
Having a child	Yes	45	33.6
	No	89	66.4
Level of education	High school	38	28.4
	Associate degree	27	20.1
	Undergraduate	69	51.5
Total		134	100

Table 2. Nurses' awareness and use of a pediatric pain assessment scale

Characteristics		n	%
Awareness of any assessment scale	Yes	56	41.8
	No	78	58.2
Known assessment scales*	VAS	24	18
	Wong-Baker	32	23.8
Use of any assessment scale at the clinic	Yes	40	29.8
	No	94	70.2
Assessment scales used at the clinic*	VAS	7	5.2
	FLACC	3	2.2
	Wong-Baker	30	22.4
Personal use of any assessment scale	Yes	19	14.2
	No	115	85.8
Assessment scales personally used*	VAS	3	2.2
	Wong-Baker	16	12
Interventions of nurses to relieve pain	Pharmacological practices	48	35.8
	Non-pharmacological practices	13	9.7
	Pharmacological and non-pharmacological practices	73	54.5

*Those refraining from answering relevant questions were not considered
VAS: Visual analogue scale, FLACC: Face, Legs, Activity, Cry, Consolability

Table 3. Distribution of nurses' median scores of pain management knowledge

Level of knowledge about pain management	Number of items	Correct		Min - Max
		n	%	
General pain knowledge	6	14	10.4	1-6
Pain assessment	12	11	8.2	4-12
Pain treatment	4	26	19.4	0-4
Total	22	51	38	9-21

Min: Minimum, Max: Maximum

When the nurses' willingness to work in the pediatric clinic and their pain management knowledge scores were examined, it was determined that the knowledge scores of those who wanted to work in the pediatric clinic were higher and there was no statistical difference between them (p>0.05) (Table 4).

DISCUSSION

Effective and comprehensive implementation of pain management can be achieved by adding the experience of nurses in the clinics they work after graduation, on top of the theoretical knowledge they received during their undergraduate education. No matter how comprehensive the theoretical knowledge is, the place of clinical skills and postgraduate scientific studies and courses is undeniable. In line with the information obtained from this study and the literature, it is concluded that pain management in school and after working life is not emphasized enough.[7,10,11,15-18]

Besides the factors related to nurses, the institution, institution policies, the satisfaction of the nurses from the clinics they work, the communication within the team, the working order, and the weekly working hours can also affect pain management in clinics.[1,6,19]

To increase knowledge and be aware of current practices during the clinical study in pain management, the continuation of scientific publications, meetings, and training should be ensured. In our study, it was seen that a small part of the nurses received pain management training, and in line with the other data obtained, it was suggested that the working population could not provide a comprehensive and effective management process in pain management.

When pain management is considered, detection of pain presence, determination of pain level, relieving pain with pharmacological and non-pharmacological methods, and recording pain by regular follow-up are the most prominent steps in pain management.[3,8,13]

Accepting the presence of pain and determining the level of pain are the main principles in pain management. Scales are used to determine the level of pain.[20] While 67.9% of nurses considered themselves competent in pain management, when asked if they knew of a pain assessment scale, 58.2% answered negatively. Pain assessment scales provide nurses with convenience in appraising pain.[3,14] It was found that very few of the nurses knew and used pain assessment scales in our study. The procedures adopted by the institution also play a role in the use of pain assessment scales as well as the personal approach of nurses. Study findings led us to the conclusion that nurses neglected to use pain assessment scales, and that usage of scales was not widespread across clinics (29.8%) or enforced through protocols. One study reported that pain management should be included in in-hospital procedures and standard pain management protocols should be established.[3] Thus, the pain will become a visible and tangible notion.[21]

As a result of numerous studies conducted, several pain assessments scales have been developed taking the age of the patient and involved clinic into consideration and made available for use after necessary validity/reliability tests.[4,5,10] However, the fact that enrolled nurses were aware of only two pain assessment scales (VAS and Wong-Baker) was an indication of the education gap or difficulties experienced by nurses in accessing conducted studies. The best-known tools for assessing pain are Wong-Baker and VAS. These scales have been used for many years and are reliable, effective, and easy-to-use scales. Similarly, several studies conducted in the country also reported that nurses were not using any pain assessment scales.[6,21,10] In the present study, we interviewed with nurses from all hospital groups (private, state, university), and the level of knowledge of nurses working at university hospitals about pain management was found to be significantly higher than that of nurses working at other hospitals. This result, like the Finnish example,[2] is the expected outgrowth of the fact that nurses working at university hospitals are more knowledgeable than nurses from other hospitals as university hospitals in the country are primarily research- and education-oriented hospitals. In the studies that the knowledge of nursing students about pain management and non-pharmacological practices was examined, it was reported that their knowledge level

Table 4. Comparison of nurses' working conditions and their level of knowledge

Working conditions		n (%)	Level of knowledge about pain management	
			Min - Max	Test value/p
Institution	University hospital	49 (36.6)	13-20	3,429*/0.03
	State hospital	69 (51.5)	9-21	
	Private hospital	16 (11.9)	11-20	
Working order	Consistently daytime	21 (15.7)	12-20	1.400*/2.37
	By shifts	113 (84.3)	9-21	
Working hours (/a week)	40 to 48 hours	65 (48.5)	11-21	-2,569**/0.01
	48 hours and above	69 (51.5)	9-21	
Whether employment with pediatric clinic is voluntary	Yes	34 (25.4)	12-21	-1.316**/0.188
	No	100 (74.6)	9-21	

*Kruskal-Wallis test, **Mann-Whitney U test, Min: Minimum, Max: Maximum

was not sufficient.[19] This result also confirmed that neither nursing students nor graduate nurses were sufficiently knowledgeable about the implementation of non-pharmacological interventions or knew that interventions which they implemented might be considered as non-pharmacological interventions similar to the results of the present study. When we look at the studies on pain management with nurses in the literature, although there are many studies in which pain is addressed, it is seen that the level of knowledge is still not sufficient.[3,11,13] In many studies conducted, non-pharmacological methods were reported to be effective in mitigating pain.[15,16,21] In our study, and other studies, it was seen that nurses knew pharmacological practices.[2,3,8,9] In our study, it was found that nurses were aware of non-pharmacological methods which had independent functions in pain management. Nurses cannot carry out non-pharmacological practices effectively because of personal factors and working conditions. The findings we obtained were similar to the literature.[6,16]

While the clinical use of pain as the fifth vital sign was included in the literature, it was seen in our study that the number of nurses who accepted pain as a vital sign was low. Although the frequency of studies on this subject increased, it was seen that nurses still did not know the routine evaluation of pain.[21] In our study, the pain scores of the nurses were found to be above the median value, while it was reported to be in average values in other studies.[6,20] This result might be a consequence of the facilitation of access by nurses to information in the period from the former study to date and frequent emphasis put on pain in recent years. Elimination of pain is a human right, and the pain of a patient should be relieved or mitigated to an acceptable level, regardless of the age of the patient. Especially, children should not be expected or required to endure pain.[1,3,6,10] The intermediate knowledge level of nurses about the treatment of pain in the present study leads us to the conclusion that the knowledge deficiency of nurses is not only about assessment but also about the treatment of pain in children.

Study Limitations

The main limitation of the research was that the population and sample of the research are only pediatric nurses working in hospitals located in a city constituted the population and sample of the research. The findings of the study were limited to the scope of the data collection form used and the answers given by the nurses in the sample group.

CONCLUSION

It was concluded that the knowledge level of nurses on pain management was moderate. It was determined that even if the nurses did not receive training on pain management, they used pain assessment scales and non-pharmacological applications to a small extent in the units they worked. It was concluded that the biggest obstacle to the nurses' inability to concentrate on pain management was the lack of time. Nurses should provide care for children experiencing pain based on scientific facts. To active this, we concluded that pain should be cited among routine vital signs in hospital protocols, and that nurses' knowledge of pain management should be consolidated through training.

Ethics

Ethics Committee Approval: The local ethics committee approval was obtained from Kocaeli University Clinical Research Ethic Committee (approval number: KAEK 12/1, date: 20.10.2011).

Peer-reviewed: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ş., D.G., Concept: A.Ş., D.G., Design: A.Ş., D.G., Data Collection or Processing: A.S., Analysis or Interpretation: A.Ş., Literature Search: A.Ş., D.G., Writing: A.Ş., D.G.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Manworren RC, Stinson J. Pediatric pain measurement, assessment, and evaluation. Semin Pediatr Neurol. 2016;23:189-200.
2. Peirce D, Brown J, Corkish V, Lane M, Wilson S. Instrument validation process: a case study using the Paediatric Pain Knowledge and Attitudes Questionnaire. J Clin Nurs. 2016;25:1566-75.
3. Wuni A, Salia SM, Ibrahim MM, et al. Evaluating knowledge, practices, and barriers of paediatric pain management among nurses in a tertiary health facility in the northern region of ghana: a descriptive cross-sectional study. Pain Res Manag. 2020;2020:8846599.
4. Akkaya A. The effect of using pacifier and dextrose pacifier on pain reduction during orogastric tube placement in newborns. Unpublished master's thesis. Uludağ University Institute of Health Sciences. 2020, Bursa
5. Akpolat R, Şişman H, Alptekin D, Gökçe E, Gezer D, Arslan S. Evaluation of approaches to pain after surgery. Cukurova Med J. 2021;46:670-6.
6. Kodama Y, Fukahori H, Tse M, Yamamoto-Mitani N. Pain Prevalence, Pain Management, and the Need for Pain Education in Healthcare Undergraduates. Pain Manag Nurs. 2021;22:408-13.
7. Akdemir N, Akyar I, Görgülü Ü. Approaches of nurses to the pain problem of patients hospitalized in physical therapy and rehabilitation clinics or admitted to outpatient clinics. Turk J Phys Med Rehab. 2008;54:157-63.
8. Hroch J, Van Den Kerkhof EG, Sawhney M, Sears N Gedcke-Kerr L. Knowledge and Attitudes about Pain Management among Canadian Nursing Students. Pain Manag Nurs. 2019;20:382-9.
9. Staveski SL, Boulanger K, Erman L, et al. The Impact of Massage and Reading on Children's Pain and Anxiety after Cardiovascular Surgery: A Pilot Study. Pediatr Crit Care. 2018;19:725-32.
10. Peng N, Lao AH, Chen C, et al. Knowledge and attitudes of pediatric clinicians regarding pediatric pain management. J Spec Pediatr Nurs. 2020;25:e12302.
11. Al-Taweel D, Awad A. Development, and validation of medication assessment tools to evaluate prescribing adherence to evidence-based guidelines for secondary prevention of coronary heart disease in post-acute coronary syndromes patients in Kuwait. Plos One. 2020;15:e0241633.
12. Kemar D, İşler Dalgıç A. Evidence-Based Nonpharmacological Nursing Practices Used in Pain Management in Newborns. BAUN Health Sci J. 2020;9:197-204. Available online at: https://dergipark.org.tr/tr/pub/balikesirsbd

13. Nydahl P, Egerod I, Hosey MM, Needham DM, Jones C, Bienvenu OJ. Report on the Third International Intensive Care Unit Diary Conference. Crit Care Nurse. 2020;40:e18-e25.
14. Kia Z, Allahbakhshian M, Ilkhani M, Nasiri M, Allahbakhshian A. Nurses' use of non-pharmacological pain management methods in intensive care units: A descriptive cross-sectional study. Complement Ther Med. 2021;58:102705.
15. Hunter OO, Pharm AW, Leng J, Mariano ER. Educating Nurses on Intravenous Lidocaine for Postoperative Pain Management. Pain Manag Nurs. 2021;22:94-9.
16. Tano PF, Apiribu F, Tano EK, Boamah Mensah AB, Dzomeku VM, Boateng I. Predicting factors that determine patients' satisfaction with post-operative pain management following abdominal surgeries at Komfo Anokye Teaching Hospital, Kumasi, Ghana. PLos One. 2021;16:e0251979.
17. Campbell E. Faculty perspectives of teaching pain management to nursing students. Pain Manag Nurs. 2020;21:179-86.
18. Laekeman M, Schäfer A, Moog ME, Kuss K. Recommendations for a Pediatric Pain Education Curriculum for Physical and Occupational Therapists: Scoping Review and Survey. Children. 2021;8:390.
19. Chatchumni M, Eriksson H, Monir Mazaher A. Scoping Review of Pain Management Education Programs (PMEPs): Do They Prepare Nurses to Deal with Patients' Postoperative Pain? Hindawi Pain Research and Management. 2020;1-7.
20. Maestro-Gonzalez A, Mosteiro-Diaz P, Fernandez-Garrido J, Zuazua-Rico D. Determinants of Knowledge of Pain among Nurses in a Tertiary Hospital in Spain. Pain Management Nursing. 2021;22:394-401.
21. Erzincanli S, Sayin Kasar K. Effect of Hand Massage on Pain, Anxiety, and Vital Signs in Patients Before Venipuncture Procedure: A Randomized Controlled Trial. Pain Management Nursing. 2021;22:356-60.

DOI: 10.4274/TP.galenos.2021.25238
Trends in Pediatrics 2021;2(4):165-169

Original Article

The Effects of Growth Hormone Treatment in Patients with Isolated Growth Hormone Deficiency on Hematological Parameters

Derya Şengün[1], **Atilla Çayır**[2]

[1]Private Çorlu Reyap Hospital, Clinic of Child Health and Diseases, Erzurum, Turkey
[2]Erzurum Training and Research Hospital, Clinic of Pediatric Endocrinology, Erzurum, Turkey

Cite this article as: Şengün D, Çayır A. The Effects of Growth Hormone Treatment in Patients with Isolated Growth Hormone Deficiency on Hematological Parameters. Trends in Pediatrics 2021;2(4):165-169

ABSTRACT

Objective: A small number of studies were reported regarding the direct and indirect effects of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) especially on the erythrocyte series. The purpose of this study was to examine the effects of GH treatment (GHT) used in patients with isolated GH deficiency (IGHD) on hematological parameters.

Methods: The records of the patients who were diagnosed as having IGHD in our clinic and received GHT for at least two years between 2013 and 2019 were retrospectively examined. Height, height standard deviation scores (SDS), weight, weight SDS, IGF-1, annual growth rates, and changes in blood count parameters before and after the GHT were recorded. The statistical analyses were made using SPSS v.20 Package Program, and the significance level was accepted as $p<0.05$.

Results: A total of 37% (n=23) of the 62 patients that were included in the study were female, and 63% (n=39) were male. It was determined that the age of the patients was between 2-16 years at the time of diagnosis, and the median age at diagnosis was 10.8. After the GHT, a significant increase was detected in the distribution and volume of hemoglobin, hematocrit, and red sphere count ($p<0.05$). A statistically significant but clinically insignificant decrease was detected in the platelet count and there was an increase in the platelet volumes ($p<0.001$). A clinically significant decrease was detected in the number of white sphere, lymphocyte and neutrophil counts ($p<0.05$).

Conclusion: It was determined that GHT had a stimulating effect on erythropoiesis in IGHD. It was also shown that GHT caused a number of changes on the platelet count, white sphere count, and the lymphocyte and neutrophil parameters, which were not clinically important. We believe that studies at *in vitro* and molecular level are needed to explain the effects of GHD and GHT on the hematopoietic system.

Keywords: Growth hormone, isolated growth hormone deficiency, growth hormone therapy, hematological parameters, child

INTRODUCTION

Growth hormone deficiency (GHD) is a significant cause of short stature, seen in approximately 1/4,000 to 1/10,000 of the patients.[1,2] Isolated GHD (IGHD) can be defined as the deficiency of GH that is independent of other pituitary hormone deficiencies and the presence of an organic lesion.[3] GHD can be either congenital or acquired, while the height and weight of patients at birth are in the normal range. The children with GHD are expected to have regular growth during the first six months, while the growth slows down later in life. A proportionally short height ensues and the weight increases relative to the height, leading to delayed bone age.[2]

Treatment of GHD involves the use of biosynthetic human growth hormone produced by recombinant gene technologies (rhGH). The

D. Şengün: 0000-0003-4772-731X

Address for Correspondence: Atilla Çayır
Erzurum Training and Research Hospital, Clinic of Pediatric Endocrinology, Erzurum, Turkey
E-mail: dratillacayir@gmail.com **ORCID-ID:** orcid.org/0000-0001-9776-555X
Received: 23.07.2021 **Accepted:** 08.11.2021 **Publication date:** 04.01.2022

rhGH is safely used with very rare side effects. Growth hormone has been shown to have metabolic effects related to several systems besides its effects on height. Carbohydrate, fat, and protein metabolisms are adversely affected, body composition deteriorates, bone health is adversely affected, quality of life decreases, and cardiovascular morbidity increases in GHD.[4,5]

It is known that GH and insulin-like growth factor-1 (IGF-1) have effects on the hematopoietic system. GH and IGF-1 regulate hematopoiesis and cytokine production via bone marrow. GH plays a role in platelet production and differentiation. GH contributes to the regulation of erythropoiesis by increasing renal erythropoietin (EPO) production. It has been shown that erythropoiesis is slowed down due to GHD in hypophysectomized rats, recombinant GH treatment leads to an increase in EPO and stimulation of erythropoiesis, and GH increases IGF-1, which directly and indirectly stimulates erythropoiesis.[4,6]

There are few studies on the effect of long-term GH therapy on hematological parameters. This study aimed to investigate the changes in auxological and hematological parameters of patients who received GHT for IGHD.

MATERIALS and METHODS

Study Design

In this retrospective cross-sectional study, STROBE guideline was used for reporting purposes.[7] The study protocol was approved by the Local Ethics Committee at University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital (IRB number: 2019/07-60, date: 15.04.2019).

Setting and Participants

The study was conducted in the Pediatric Endocrinology outpatient clinics between May 2013 and May 2019.

Out of the 187 patients, who presented with short stature to the center during the study period, 62 patients with IGHD, who received recombinant GH treatment for at least two years and attended regular follow-up visits, were included in the study. The exclusion criteria of the study were the presence of other endocrine or chronic diseases (n=1), receiving therapy with B12 or iron for anemia (n=2), and use of non-GH therapeutics with potential effects on hematological parameters (n=1) (Figure 1).

The IGHD is defined as a condition of GHD not associated with any organic lesion and also other pituitary hormone deficiencies.[8]

Variables

The demographic and clinical data were obtained from patient files such as age, sex, height and weight of the patients. The primary outcome of the study was set as the blood hemoglobin (Hb) level. Other variables investigated were the age, gender, height at the time of diagnosis, weight, standard deviation scores (SDS), annual growth rate after GH treatment, white blood cell count (WBC), total lymphocyte count (LYM), absolute neutrophil count (NEU),

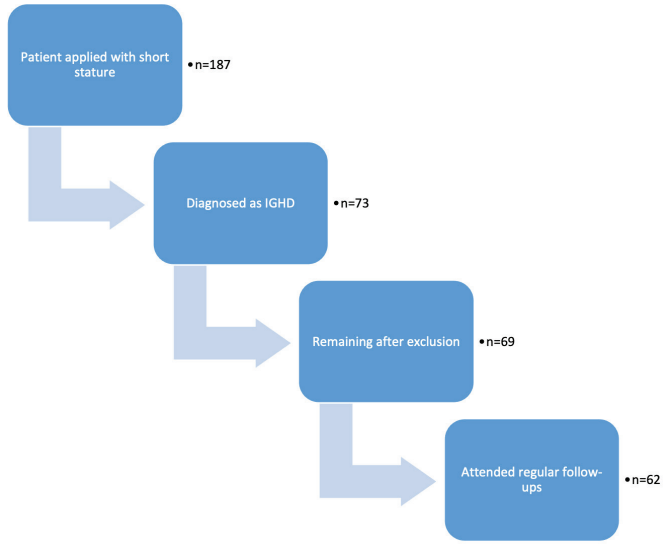


Figure 1. Participant flow diagram
IGHD: Isolated growth hormone deficiency

hematocrit (HCT), erythrocyte count (RBC), erythrocyte red cell distribution width (RDW), erythrocyte mean corpuscular volume (MCV), platelet count (PLT), mean platelet volume (MPV), and IGF-1 levels. The hematological parameters included in the complete blood count were measured via a Sysmex XN-1000 device (Sysmex Ltd, Turkey) using the WNR, WDF, RET, DCL, SLS, and PLT kits.

Anthropometric measurements were performed using a calibrated device (Seca, 216, Hamburg, Germany) that measured weight and height in ±100 gram and ±0.1 cm sensitivity SDs. Growth charts for Turkish children prepared by Neyzi et al.[9] were used to evaluate height, weight, and SDS.

The patients were subcutaneously administered with 0.025-0.035 mg/kg/day recombinant biosynthetic GHT in the evenings.[10] The values obtained at the onset of the therapy were compared with those in the 6th, 12th, 18th, and 24th months after the start of the GHT.

Study Size

The sample size was calculated based on the primary outcome, Hb level, using the GPower program.[11] Considering the effect size as 0.15 (small), α error as 0.05, power as 85%, the number of groups as 1, the number of repeated measurements as 5, correlations among repeated measures as 0.5, and non-sphericity correction as 1, a total of 61 participants were determined for inclusion in the study group.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 20.0, Chicago, IC, USA). Results were presented as mean, SD, median, minimum, maximum, percentage, and numbers. The normal distribution of continuous variables was examined with the Shapiro-Wilk test. When the normal distribution could not be met for some

variables, the Friedman test was used to compare more than two dependent group variables. The threshold for statistical significance was accepted as p<0.05.

RESULTS

Of the 62 patients included in the study, 37% (n=23) were female and 63% (n=39) were male. The age at the time of diagnosis ranged between 2 and 16 years, with a median of 10.8 years (9.9 for girls, 11.3 for boys).

The auxological and hematological parameters of all patients before and after GHT and the results of different gender groups are shown in Table 1, Table 2, and Table 3.

DISCUSSION

Our study showed that there were significant changes in some of the hematological parameters of patients with idiopathic GHD after two years of GHT and follow-up compared to the baseline. It is known that the GH/IGF-1 axis has a role in the regulation of hematopoiesis. The facts that erythropoiesis is impaired in adults with GHD, and Hb and hematopoietic precursor cells increase after the GHT also support this relationship.[12,13]

It was found that the mean Hb values of the patients in our study increased significantly after the treatment compared to the baseline. Kawa et al.[14] compared the hematological parameters of patients receiving GHT at baseline and in the 3rd and 6th months

Table 1. Comparison of the repeated measurements in all patients (n=62)

	Baseline Mean ± SD	6th month Mean ± SD	12th month Mean ± SD	18th month Mean ± SD	24th month Mean ± SD	p
Height SDS	-2.96±1.03	-2.66±1.07	-2.43±1.05	-2.22±1.10	-2.14±1.05	<0.001
Weight SDS	-2.10±1.38	-2.07±1.33	-1.96±1.37	-1.85±1.34	-1.80±1.35	0.003
Hb (g/dL)	13.74±1.18	13.89±1.07	13.96±1.19	14.61±3.65	14.17±1.21	<0.001
HCT (%)	41.00±3.30	42.01±3.26	42.25±3.30	42.04±4.76	42.32±3.14	0.006
RBC (10^{12}/L)	5.03±0.98;	5.17±0.42.	5.20±0.44;	5.19±0.39;	5.31±0.69;	0.028
MCV (fL)	79.98±3.98	80.88±4.18	80.47±4.20	80.92±4.15	80.99±4.08	0.046
RDW (%)	12.54±1.54	12.18±1.03	12.20±1.12	12.50±1.14	12.70±1.10	0.005
PLT (10^9/L)	319.48±84.93	344.05±97.94	333.24±88.49	323.15±71.95	317.52±74.03	0.001
MPV (fL)	7.42±1.75	7.69±1.98	8.29±1.96	9.58±7.38	8.94±1.74	<0.001
WBC (10^9/L)	9.02±3.25	8.57±2.30	8.22±3.14	7.94±2.50	7.46±1.85	<0.001
LYM (10^9/L)	3.12±1.01	3.10±0.97	2.96±0.96	2.95±1.08	2.79±0.79	0.023
NEU (10^9/L)	5.12±3.29	4.80±2.46	4.26±2.72	4.11±2.35	4.28±2.06	0.035

SD: Standard deviation, SDS: SD scores, HCT: Hematocrit, RBC: Erythrocyte count, MCV: Mean corpuscular volume, RDW: Red cell distribution width, PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cell, LYM: Lymphocyte count, NEU: Neutrophil count

Table 2. Comparison of the repeated measurements in males (n=39)

	Baseline Mean ± SD	6th month Mean ± SD	12th month Mean ± SD	18th month Mean ± SD	24th month Mean ± SD	p
Height SDS	-2.93±1.1	-2.61±1.11	-2.37±1.05	-2.19±1.09	-2.13±1.03	<0.001
Weight SDS	-2.22±1.38	-2.14±1.36	-2.05±1.37	-1.94±1.35	-1.91±1.36	0.035
Hb (g/dL)	13.71±1.11	13.85±1.11	14±1.26	14.24±1.12	14.35±1.2	<0.001
HCT (%)	40.96±3.28	41.94±3.36	42.71±3.54	42.85±3.15	43.02±3.17	<0.001
RBC (10^{12}/L)	5.12±0.98	5.24±0.38	5.32±0.41	5.25±0.39	5.48±0.77	0.014
MCV (fL)	79.48±3.84	79.9±4.24	79.61±4.25	80.2±4.35	80.73±4.19	0.065
RDW (%)	12.63±1.61	12.32±1.13	12.33±1.1	12.66±1.23	12.69±1.11	0.171
PLT (10^9/L)	297.87±84.66	326.43±97.67	321.25±95.26	310.02±69.57	297.07±70.33	0.001
MPV (fL)	7.72±1.71	7.99±1.9	8.3±1.92	8.61±1.82	9.03±1.75	0.262
WBC (10^9/L)	9.08±3.43	8.74±2.47	8.27±3.36	8.04±2.55	7.2±1.45	<0.001
LYM (10^9/L)	3.05±0.97	3.13±0.99	2.93±0.92	3.08±1.02	2.88±0.65	0.359
NEU (10^9/L)	5.05±2.99; 4.4 (1.75-17.3)	4.74±2.41; 4.01 (1.8-12.1)	4.07±2.65; 3.4 (1.33-18)	3.64±1.39; 3.5 (1.37-8.8)	4.06±1.58; 3.8 (2-9.4)	0.044

SD: Standard deviation, SDS: SD scores, HCT: Hematocrit, RBC: Erythrocyte count, MCV: Mean corpuscular volume, RDW: Red cell distribution width, PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cell, LYM: Lymphocyte count, NEU: Neutrophil count

Table 3. Comparison of the repeated measurements in females (n=23)

	Baseline Mean ± SD	6th month Mean ± SD	12th month Mean ± SD	18th month Mean ± SD	24th month Mean ± SD	p
Height SDS	-3±0.92	-2.73±1	-2.5±1.06	-2.27±1.12	-2.15±1.08	<0.001
Weight SDS	-1.89±1.37	-1.95±1.29	-1.79±1.37	-1.67±1.34	-1.6±1.34	0.130
Hb (g/dL)	13.78±1.3	13.94±1.02	13.89±1.08	15.23±5.83	13.85±1.18	0.572
HCT (%)	41.07±3.38	42.13±3.15	41.46±2.74	40.66±6.52	41.12±2.76	0.254
RBC (10^{12}/L)	4.87±0.97	5.02±0.44	4.99±0.41	5.07±0.37	5.01±0.39	0.525
MCV (fL)	80.82±4.15	82.52±3.59	81.92±3.74	82.13±3.54	81.4±3.92	0.157
RDW (%)	12.38±1.42	11.92±0.76	11.96±1.12	12.22±0.92	12.7±1.08	0.028
PLT (10^9/L)	356.13±73.41	373.91±92.93	353.56±73.12	345.39±71.9	352.17±68.24	0.670
MPV (fL)	6.9±1.71	7.16±2.03	8.27±2.06	11.2±11.86	8.79±1.75	<0.001
WBC (10^9/L)	8.91±2.96	8.27±20	8.13±2.79	7.76±2.45	7.9±2.34	0.242
LYM (10^9/L)	3.22±1.07	3.05±0.93	2.99±1.03	2.7±1.15	2.62±0.98	0.020
NEU (10^9/L)	5.24±3.81	4.89±2.57	4.58±2.86	4.88±3.29	4.65±2.68	0.640

SD: Standard deviation, SDS: SD scores, HCT: Hematocrit, RBC: Erythrocyte count, MCV: Mean corpuscular volume, RDW: Red cell distribution width, PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cell, LYM: Lymphocyte count, NEU: Neutrophil count

of treatment and showed that GHT increased the erythroid cell line. Bergamaschi et al.[15] found that GHT improved normochromic normocytic anemia in prepubertal children and patients receiving GHT in adulthood. Miniero et al.[16] emphasized that among patients with idiopathic GHD, those with anemia before the GHT had a significant increase in Hb-SDS after 12 months of GHT, and normal Hb values were achieved in all of the children. It has also been mentioned that GH and IGF-1 directly modulate hematopoiesis through their proliferative and anti-apoptotic effects and indirectly through regulating cytokine production.[17] Considering these studies together, the effect of GH on hematopoiesis is obvious, but its role in hematopoiesis and the mechanisms that keep the balance are still not clear.

It was found that the mean HCT and RBC of the patients in our study increased significantly after the GHT compared to the baseline. In a study by Esposito et al.[18] 12 patients with GHD were diagnosed as having normocytic anemia, and Hb, HCT, and RBC of these patients were found to increase in the first two years of GHT. They also showed that the anemia improved in all of these patients in the 5th year of their treatment. In our study, 2 patients were found to have anemia before the GHT, and their anemia improved after 2 years of treatment, with a significant increase in RBC counts. Pankratova et al.[19] emphasized that the RBC counts were lower in children with GHD before treatment, which increased after 12 months of GHT.

The GHT indirectly increases Hb by increasing EPO production in the kidneys in the early period and by enhancing the effect of EPO at the receptor level. In addition, IGF-1 stimulates the maturation and proliferation of erythroid cell lines with an EPO-like effect by acting on its own receptors expressed on erythroid precursors. GH stimulates the production of IGF-1 by inducing the hematopoietic progenitor cells, and the increased IGF-1 stimulates erythropoiesis by inducing autocrine and paracrine effects in the hematopoietic system.[14,15,20,21] One of the limitations of our study was that it was done retrospectively; therefore, the EPO levels could not be measured, and no data could be obtained to evaluate this relationship. The fact that there was an increase in Hb, HCT, RBC, RDW, and MCV, which were among the parameters related to the erythroid cell line, after the GHT compared to the baseline supported the hypothesis that GHT stimulated erythropoiesis.

With regard to the platelet parameters, it was found that platelet values were not at levels that would be a risk factor for bleeding or thrombosis at the baseline or during the treatment, and the variations were not considered to be clinically significant. Xu et al.[22] showed that GH positively affected platelet production and differentiation *in vitro*. Similar to our study, Esposito et al.[18] did not detect a significant difference between the patient and control group in terms of PLTs before and after GHT. No effect of GHT has been shown on PLT in a small number of human studies.

In our study, it was found that the MPV increased significantly during the GHT compared to the baseline ($p<0.001$). There is no study in the literature examining the relationship between MPV and GHT. It was found that, in adults with acromegaly (with excess GH), MPV was higher before treatment compared to the control group, and MPV decreased with the decrease in GH levels after the treatment.[23,24] This finding is consistent with those of our study, which can be explained by the fact that GH increases platelet activation.

In our study, WBC, lymphocyte, and NEUs were significantly lower at baseline compared to those after the treatment. No previous study has been found about the effects of GHT on the WBC, lymphocyte, and neutrophil levels and their functions in children with GHD. In studies evaluating the hematological parameters, it was reported that GH had no effect on leukocyte count.[14,18,21] Positive effects of GHT have been demonstrated in children with GHD and phagocytic dysfunction.[25] It has been stated that treatments aimed at reducing GH in patients with acromegaly can reduce NEUs. However, a clear distinction could not be made regarding whether this is due to the decrease in GH levels or a drug-related side effect.[26]

In our study, WBC, lymphocyte, and NEUS were not below the limits in any of the patients at the baseline or during the 2-year treatment and follow-up, and the differences did not lead to any clinically significant change. The fact that our study did not evaluate the functions of erythrocytes, leukocytes, and thrombocytes, although the effect of GHT on the level of these cells was investigated, was a limitation of our study.

CONCLUSION

In conclusion, no significant hematological abnormality was detected before GHT in idiopathic GHD. GHT was found to have erythropoiesis stimulatory effects. In addition, it was shown that GHT was associated with some clinically insignificant changes on platelet, WBC, lymphocyte, NEUs and MPV. We think that *in vitro* and molecular studies to explain these effects of GHD and GHT may help clarify the subject matter.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee at University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital (IRB number: 2019/07-60, date: 15.04.2019).

Informed Consent: Retrospective cross-sectional study.

Peer-reviewed: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.Ç., Design: A.Ç., Data Collection or Processing: D.Ş., Analysis or Interpretation: D.Ş., Literature Search: A.Ç., D.Ş., Writing: A.Ç., D.Ş.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah growth study: growth standards and the prevalence of growth hormone deficiency. J Pediatr. 1994;125:29-35.
2. Stanley T. Diagnosis of growth hormone deficiency in childhood. Curr Opin Endocrinol Diabetes Obes. 2012;19:47-52.
3. Bianchi A, Giampietro A, Pontecorvi A, De Marinis L. Isolated growth hormone deficiency: clinical entity? J Endocrinol Invest. 2008;31(9 Suppl 9):12-5.
4. Jørgensen AP, Fougnnger KJ, Ueland T, et al. Favorable long-term effects of growth hormone replacement therapy on quality of life, bone metabolism, body composition and lipid levels in patients with adult-onset growth hormone deficiency. Growth Horm IGF Res. 2011;21:69-75.
5. Follin C, Thilén U, Osterberg K, Björk JK, Erfurth EM. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab. 2010;95:3726-35.
6. Kurtz A, Zapf J, Eckardt KU, et al. Insulin-like growth factor I stimulates erythropoiesis in hypophysectomized rats. Proc Natl Acad Sci U S A. 1988;85:7825-9.
7. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guildelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-9.
8. Hernández LM, Lee PDK, Camacho-Hübner C. Isolated growth hormone deficiency. Pituitary. 2007;10:351-7.
9. Neyzi O, Bundak R, Gökçay G, et al. Reference values for weight, height, head circumference, and body mass index in Turkish Cchildren. J Clin Res Pediatr Endocrinol. 2015;7:280-93.
10. Ranke MB. Pediatric growth hormone deficiency (GHD) in the recombinant human GH (rhGH) Eera. Pediatr Endocrinol Rev. 2018;16 (Suppl 1):63-9.
11. Lenth R. Java Applets for Power and Sample Size [Computer software]. Russ Lenth - Department of Statistics and Actuarial Science - University of Iowa, 2009.
12. Eugster EA, Fisch M, Walvoord EC, DiMeglio LA, Pescovitz OH. Low hemoglobin levels in children with in idiopathic growth hormone deficiency. Endocrine. 2002;18:135-6.
13. Vihervuori E, Sipilä I, Siimes MA. Increases in hemoglobin concentration and iron needs in response to growth hormone treatment. J Pediatr. 1994;125:242-5.
14. Kawa MP, Stecewicz I, Piecyk K, et al. The impact of growth hormone therapy on the apoptosis assessment in CD34+ hematopoietic cells from children with growth hormone deficiency. Int J Mol Sci. 2017;18:111.
15. Bergamaschi S, Giavoli C, Ferrante E, et al. Growth hormone replacement therapy in growth hormone deficient children and adults: effects on hemochrome. J Endocrinol Invest. 2006;29:399-404.
16. Miniero R, Altomare F, Rubino M, et al. Effect of recombinant human growth hormone (rhGH) on hemoglobin concentration in children with idiopathic growth hormone deficiency-related anemia. J Pediatr Hematol Oncol. 2012;34:407-11.
17. Hanley MB, Napolitano LA, McCune JM. Growth hormone-induced stimulation of multilineage human hematopoiesis. Stem Cells. 2005;23:1170-9.
18. Esposito A, Capalbo D, De Martino L, et al. Long-term effects of growth hormone (GH) replacement therapy on hematopoiesis in a large cohort of children with GH deficiency. Endocrine. 2016;53:192-8.
19. Pankratova M, Yusipovich A, Vorontsova M, et al. One-year recombinant growth hormone therapy does not improve hemoglobin state and morphology of erythrocytes in growth hormone deficient children. Pathophysiology. 2018;25:13-17.
20. Sohmiya M, Kanazawa I, Kato Y. Effect of recombinant human GH on circulating granulocyte colony-stimulating factor and neutrophils in patients with adult GH deficiency. Eur J Endocrinol. 2005;152:211-5.
21. Meazza C, Bonomelli I, Pagani S, et al. Effect of human recombinant growth hormone therapy on circulating levels of erythropoietin and granulocyte-colony stimulating factor in short children. J Pediatr Endocrinol Metab. 2009;22:837-43.
22. Xu Y, Wang S, Shen M, et al. hGH promotes megakaryocyte differentiation and exerts a complementary effect with c-Mpl ligands on thrombopoiesis. Blood. 2014;123:2250-60.
23. Demirpence M, Yasar HY, Colak A, et al. Mean platelet volume and platelet function analysis in acromegalic patients before and after treatment. Acta Endocrinol (Buchar). 2016;12:401-6.
24. Unüubol M, Güuney E, Tüure M, Eryıilmaz U. Mean platelet volume and arterial stiffness in patients with acromegaly. Anatol J CardiolAnadolu Kardiyoloji Derg. 2014;14:456-63.
25. Kotzmann H, Riedl M, Clodi M, et al. The influence of growth hormone substitution therapy on erythroid and myeloid progenitor cells and on peripheral blood cells in adult patients with growth hormone deficiency. Eur J Clin Invest. 1996;26:1175-81.
26. Manfredi R, Tumietto F, Azzaroli L, et al. Growth hormone (GH) and the immune system: impaired phagocytic function in children with idiopathic GH deficiency is corrected by treatment with biosynthetic GH. J Pediatr Endocrinol. 1994;7:245-51.

DOI: 10.4274/TP.galenos.2021.96168
Trends in Pediatrics 2021;2(4):170-172

Case Report

Central Anticholinergic Syndrome Following Excessive Mydriatic Use in an Eight-Year-Old Patient

Nazan Kaymaz[1], **Mehmet Erdem Uzun**[2], **Fatih Battal**[1], **Yusuf Güzel**[1], **Hakan Aylanç**[1]

[1]Çanakkale Onsekiz Mart University Hospital, Department of Pediatrics, Çanakkale, Turkey
[2]University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Resarch Hospital, Clinic of Child Psychhiatry, Bursa, Turkey

Cite this article as: Kaymaz N, Uzun ME, Battal F, Güzel Y, Aylanç H. Central Anticholinergic Syndrome Following Excessive Mydriatic Use in an Eight-Year-Old Patient. Trends in Pediatrics 2021;2(4):170-172

ABSTRACT

Cyclopentolate hydrochloride, belonging to a class of drugs known as anticholinergics, is an ophthalmic solution frequently used in ophthalmology clinics because of its cycloplegic and mydriatic effects in both refractions as well as fundus examinations. After application, the maximum cycloplegic effect begins approximately after 30-60 min, which can further continue up to 24 h. Due to a dose-dependent relationship, cyclopentolate hydrochloride's side effects can be observed both in an ocular and systemic manner which may occur if solutions more than 0.5% concentration are used. Herein, we report central anticholinergic syndrome due to the administration of excessive amounts of cyclopentolate hydrochloride in a child.

Keywords: Child, mydriatics, cyclopentolate, ophthalmic solutions, dilatation

INTRODUCTION

A refractory ophthalmological examination is extremely crucial for children aiming at an early diagnosis of likely refractive errors and potential eye disorders that might hinder a child's normal growth. Cyclopentolate hydrochloride eye drops are commonly used as potential cycloplegic and mydriatic agents to assist in several refractive evaluations and are systemically absorbed from the conjunctiva as well as the nasal mucosa. Although rare, several side effects may develop as a result of inadequate dose individualization and excessive systemic absorption leading to the active ingredient's unwanted bioavailability. Since intoxication symptoms appear 30 min after the drug's administration, they usually persist for 4-8 hours and then resolve without significant sequelae,[1] but certain patients may experience few symptoms like ataxia, dysarthria, disorientation, hallucination, euphoria, unreasonable laughter, agitation, increased motor activity, confusion, and delirium during this period.[2] Herein, we describe an eight-year-old male child with central anticholinergic syndrome caused by an excessive dosage of cyclopentolate hydrochloride.

CASE REPORT

An eight-year-old male patient, without any previous systemic health issues, was referred to our pediatric emergency clinic with symptoms of disorganized speech, hallucinations, and periods of hyperactivity. After obtaining the patient's medical history, it was revealed that the patient who previously wore glasses due to hyperopia, underwent an annual follow-up examination in an ophthalmology outpatient clinic that had prescribed cyclopentolate hydrochloride to create mydriasis half an hour before the examination. Additionally, his mother was also explained the entire drug dispensing procedure and thereby was asked to administer the eye drops to the patient, but due to a gross misunderstanding of the drug dosage, it was applied incorrectly as a repetition of one drop in each eye with

N. Kaymaz: 0000-0002-3962-4799; **ME. Uzun:** 0000-0003-4311-2670; **Y. Güzel:** 0000-0002-1241-3561; **H. Aylanç:** 0000-0002-8907-3809

Address for Correspondence: Fatih Battal
Çanakkale Onsekiz Mart University Hospital, Department of Pediatrics, Çanakkale, Turkey
E-mail: battalfatih@hotmail.com **ORCID-ID:** orcid.org/0000-0001-9040-7880
Received: 17.11.2021 **Accepted:** 21.12.2021 **Publication date:** 04.01.2022

an interval of five minutes for approximately one hour until the examination time thus, a total of 12 drops was instilled in each eye. The patient visited our pediatric emergency clinic for a follow-up visit due to aggravated adverse symptoms including disorganized speech, hallucinations, and hyperactive periods, caused by copious drug administration. His vital signs were as follows: body temperature, 37.3 °C; blood pressure, 110/60 mmHg; heart rate, 95 beats/minute; respiratory rate, 20 breaths/minute; and oxygen saturation, 97% at room air. He had dry oral mucosa and a rash on his face with dilated pupils and a negative response to light reflex. Additionally, the patient also exhibited various symptoms like dysarthria, ataxic gait, disorientation of place, time and person, significantly increased motor activity as well as psychomotor agitation. It was observed that he was talking too fast in meaningless context accompanied by visual hallucinations and a lack of attention while other systemic and neurological physical examination findings were not detected. There was no history suggesting infection or fever, central nervous system infection, and no history suggesting electrolyte disturbances that may might occur due to fluid loss such as vomiting or/and diarrhea. The patient was monitored and followed up in the emergency department after considering the diagnosis of central anticholinergic syndrome due to excessive usage of cyclopentolate hydrochloride. Normal sinus rhythm was observed in the electrocardiogram while the blood pressure and heart rate evaluations were normal. All possible complications of mydriatic intoxication were properly monitored. As his symptoms returned to normal after 4 hours, he was discharged after 8 hours of follow-up.

DISCUSSION

In this case report, an eight-year-old boy diagnosed as having central anticholinergic syndrome following excessive cyclopentolate hydrochloride dosage as a mydriatic agent for a regular ophthalmic examination was presented. Abnormal examination findings found in the patient were dry oral mucosa, prolonged mydriatic state, lack of attention, increased motor activity, and visual hallucinations.

Systemic side effects of cyclopentolate hydrochloride can be classified into two groups as neuropsychiatric and non-neuropsychiatric. Non-neuropsychiatric side effects like hypertension, tachycardia, arrhythmia, respiratory distress, and tremors develop more frequently, while the most common neuropsychiatric side effects observed are ataxia, hallucinations, confusion, disorientation, meaningless speech and behaviors as well as psychomotor agitation. Sometimes an adverse effect known as acute toxic psychosis occurs very rarely in pediatric patients.[3] Due to the widespread usage of 1% cyclopentolate hydrochloride solution as a cycloplegic agent for refractory examinations, it has been reported that several systemic side effects may occur while using solutions more than 0.5% concentrations in the pediatric patient population[4] due to the fact that children are extremely prone to systemic toxicity due to their lower body weight as well as the presence of an immature blood-brain barrier for drug metabolism. Moreover, as maximum side effects have been reported while using these drops in infants, therefore it is recommended that infants undergoing retinopathy of prematurity examination should be kept under observation for the next 24 h after the examination is carried out.[5]

Since the risk of side effects of cyclopentolate hydrochloride is greater at higher concentrations and doses, it can be observed that the side effects of cyclopentolate hydrochloride are not only dose-dependent but can also develop with routine drug usage at an appropriate concentration or dose.[6] Nevertheless, it was also suggested that the incidence of side effects increased in those patients having a prior systemic disease;[7] however, this was not applicable in our patient, as he exhibited many side effects without the presence of any systemic disease.

As there are no specific laboratory tests for the diagnosis of the central anticholinergic syndrome; some other drug intoxications such as opioids and benzodiazepines, respiratory disorders, fluid and electrolyte imbalances, hormonal imbalance as well as psychiatric illness could be considered in the differential diagnosis. In our patient, no laboratory tests were conducted due to a high suspicion of drug intoxication. Therefore, it was suggested that if the patient's presenting symptoms did not improve or worsen during the follow-up, then necessary investigations would be carried out. Owing to the fact that other treatment modalities were only indicated when the symptoms of central anticholinergic syndrome either became subjectively evident or a life-threatening situation occurred as in our patient, our patient was provided symptomatic treatment which led to the improvement of the patient's symptoms in about 4 hours. To conclude, although cyclopentolate hydrochloride is a frequently used drug in ophthalmologic examinations, it also has some serious systemic side effects when given in inappropriate doses. Since unrestrained drug administration may cause an increase in the incidence of potential side effects, utmost care should be taken that the drug should always be administered by trained health personnel. As our case report highlighted the importance of correct usage of topical ophthalmic preparations in children, it also proved that although the side effects improved without the need for medical intervention, sometimes an early recognition of systemic toxicity symptoms as well as initiation of required interventions were essential for optimal recovery of patients. It is also recommended that during the application of such drugs, the nasolacrimal duct openings should be closed by pressing the eye's inner corners with a finger to prevent the ophthalmic solution from leaking in the nose, passing through the nasolacrimal duct, and finally to the systemic circulation to avoid any adverse reactions.

Ethics

Informed Consent: Parents of the patient provided informed consent to publish the report.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.K., F.B., Concept: M.E.U., H.A., Design: N.K., H.A., Data Collection or Processing: Y.G., Analysis or Interpretation: M.E.U., F.B., Literature Search: Y.G., N.K., Writing: N.K., M.E.U., F.B., Y.G., H.A.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Bhatia SS, Vidyashankar C, Sharma RK, Dubey AK. Systemic toxicity with cyclopentolate eye drops. Indian Pediatr. 2000;37:329-31.
2. V Pooniya, N Pandey. Systemic toxicity of topical cyclopentolate eyedrops in a child. Eye (Lond). 2012;26:1391-2.
3. Derinoz O, Er A. Inability to walk, disequilibrium, incoherent speech, disorientation following the instillation of 1% cyclopentolate eyedrops: Case report. Pediatr Emerg Care. 2012;28:59-60.
4. Ağın H, Gerçek H, Kutlu A, Gülez N, Atlıhan F. Topikal siklopentolat kullanımına bağlı gelişen deliryum tablosu: Bir vaka takdimi. Çocuk Sağlığı ve Hastalıkları Derg. 2008;51:39-42.
5. Laws DE, Morton C, Weindling M, Clark D. Systemic effects of screening for retinopathy of prematurity. Br J Ophthalmol. 1996;80:425-8.
6. Awan KJ. Adverse systemic reactions of topical cyclopentolate hydrochloride. Ann Ophthalmol. 1976;8:695-8.
7. Mirshahi A, Kohnen T. Acute psychotic reaction caused by topical cyclopentolate use for cycloplegic refraction before refractive surgery: case report and review of the literature. J Cataract Refract Surg. 2003;29:1026-30.

Abdullah Barış Akcan
Ahu Kara Aksay
Alper Köker
Alper Ozcan
Anıl Er
Atilla Çayır
Ayhan Abacı
Ayşe Anık
Ayşe İpek Polat
Balahan Makay
Ceren Günbey
Çimen Olguner
Deniz Kor
Eda Didem Kurt Şükür
Edip Ünal
Elif Kıymet
Emel Ulusoy
Emine Hafize Erdeniz
Erdal Eren
Fatih Mehmet Azık
Funda Tüzün Erdoğan
Gönül Çatlı
Hatice Eke Güngör
Havva Nur Peltek Kendirci
Hüsniye Çalışır
İbrahim Murat Hirfanoğlu
İhsan Esen
Ihsan Turan
İlker Devrim
İlknur Çağlar
Korcan Demir
Mediha Akcan
Mehmet Ağın
Mehmet Gündüz
Melek Yıldız
Meral Torun Bayram
Muammer Büyükinan
Müge Ayanoğlu
Nur Arslan
Onur Akın
Osman Alphan Küpesiz
Özgür Çağlar
Özlem Ünal Uzun
Pelin Teke Kısa
Rahmi Özdemir
Samim Özen
Seçil Arslansoyu Çamlar
Selda Ayça Altıncık
Selim Dereci
Sema Kalkan Uçar
Sercan Öztürk
Serkan Fazlı Çelik
Serkan Kırık
Serpil Özgen
Soner Sertan Kara
Sultan Aydın Köker
Tolga Ünüvar
Tuba Tuncel
Yılmaz Ay

2021 AUTHOR INDEX

2021 SUBJECT INDEX