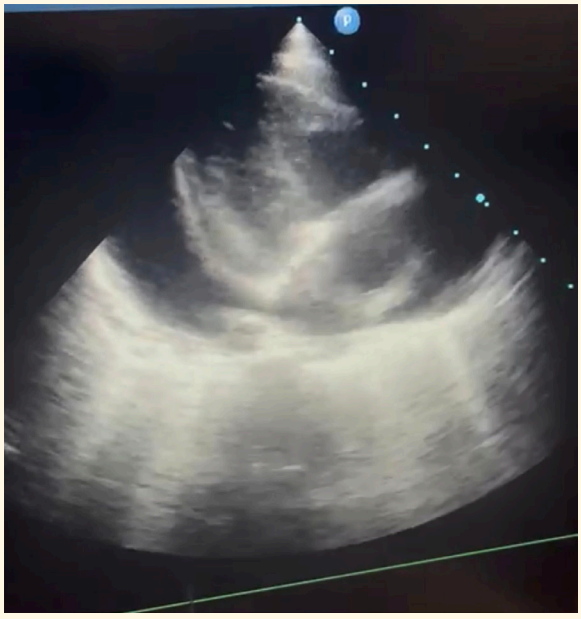
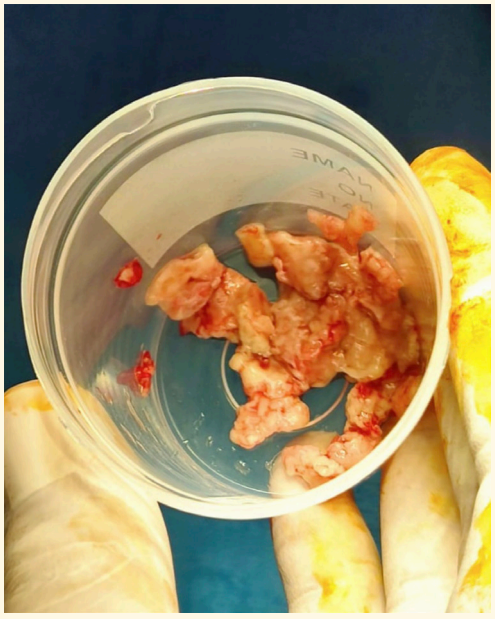
Year: September 2024 Volume: 11 Issue: 3

E-ISSN: 2587-2478

The Journal of Pediatric Research





galenos Publishing House

JPR
The Journal of Pediatric Research

Official Journal of Ege University Children's Hospital

EDITORIAL BOARD

The Journal of Pediatric Research is the official publication of Ege University Faculty of Medicine, Department of Pediatrics and Ege Children's Foundation.

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publication Date: September 2024
E-ISSN: 2587-2478
International scientific journal published quarterly.

JPR
The
Journal of Pediatric Research
Official Journal of Ege University Children's Hospital

EDITORIAL BOARD

JPR
The Journal of Pediatric Research

Official Journal of Ege University Children's Hospital

Scientific Advisory Board

JPR
The Journal of Pediatric Research

Official Journal of Ege University Children's Hospital

Please refer to the journal's webpage **(https://jpedres.org/)** for "Aims and Scope", "Instructions to Authors" and "Ethical Policy".

The editorial and publication processes of the Journal of Pediatric Research are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

The Journal of Pediatric Research is indexed in **Emerging Sources Citation Index (ESCI), Embase, Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, ProQuest, CABI, Gale/Cengage Learning, Ulakbim TR Dizin, TurkMedline, J-GATE, IdealOnline, Hinari, GOALI, ARDI, OARE, AGORA** and **Türkiye Citation Index**.

The journal is published online.

Owner: Ege University and Ege Children's Foundation

Responsible Manager: Özgür ÇOĞULU

JPR
The
Journal of Pediatric Research
Official Journal of Ege University Children's Hospital

Contents

JPR
The
Journal of Pediatric Research
Official Journal of Ege University Children's Hospital

Editorial

Dear JPR Readers,

We are proud and happy to announce that the third issue of "The Journal of Pediatric Research" in 2024 has been published.

In this issue, we present to you 10 articles, including 8 Original Researches and 2 Case Reports. In an article, the authors evaluated the role of platelets in lung inflammation in patients with cystic fibrosis. Another study in this issue examined permanent tooth development and associated risk factors in patients treated for cancer before the age of six. There is also a single-center study reporting results evaluating the clinical features and outcomes of recurrent sacrococcygeal germ cell tumors.

This issue also includes articles titled "Hyponatremia as a Biochemical Marker of Complicated Acute Appendicitis: A Retrospective Cohort Study", "An Evaluation of Previously Undiagnosed Childhood Primary Headache Cases Through Their EEG and MR Findings", "Clinical Value of Systemic Immune Inflammation and Panimmune Inflammation in Adenoid Hypertrophy", "Evaluation of Patients with Tall Stature Applying to Pediatric Endocrinology Clinic", and "Investigating the Use of Therapeutic Hypothermia in Partially Eligible Infants: A Single-Center Experience". Thus, readers will have the opportunity to read articles on different topics related to childhood. They will be able to access two featured case reports.

The Journal of Pediatric Research is indexed in Emerging Sources Citation Index (ESCI), Embase, Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, ProQuest, CABI, Gale/Cengage Learning, Ulakbim TR Dizin, TurkMedline, J-GATE, Ideal Online, Hinari, GOALI, ARDI, OARE, AGORA and Türkiye Citation Index. We thank the authors, referees, editorial team, and Galenos Publishing House for their support in the preparation of this issue. We look forward to your contributions to our future issues.

Best wishes

İpek KAPLAN BULUT

J Pediatr Res 2024;11(3):129-35
DOI: 10.4274/jpr.galenos.2024.67984

Original Article

An Evaluation of Previously Undiagnosed Childhood Primary Headache Cases Through Their EEG and MR Findings

Selcan Öztürk[1], Erdal Komut[2]

[1]Hitit University Faculty of Medicine, Department of Pediatrics and Child Health, Division of Pediatric Neurology, Çorum, Turkey
[2]Hitit University Faculty of Medicine, Department of Radiology, Çorum, Turkey

ABSTRACT

Aim: Headaches are a major cause of presentations to pediatric neurology clinics, the majority being primary. Although diagnosis is mostly based on medical history and physical examination, imaging methods and electroencephalography (EEG) are used for differential diagnosis or identifying accompanying conditions. We evaluated cases of primary headache presenting to a newly established pediatric neurology clinic in July-December 2022 and compared their magnetic resonance imaging (MRI) and EEG findings.

Materials and Methods: Individuals presenting with headaches were first classified as primary or secondary headaches, and patients with primary headaches were included as migraine or tension-type headaches (TTH). Two hundred four patients presented but only fifty migraines and 50 TTH patients, who had EEG and MRI, met the study criteria.

Results: Greater photophobia, phonophobia, and family histories were present in the migraineurs, while attack frequencies were higher and durations shorter in the TTH group (p=0.025, p=0.001, respectively). Pain was generally throbbing in character in the migraine patients and compression in the TTH cases. No pathology was encountered in the MRIs of 90% of the migraine patients and 94% of the TTH group. While no pathology was detected at EEG in most cases, sharp spike-wave activity was determined in 10% of the migraine patients and in 2% of the TTH group.

Conclusion: MRI and EEG are not generally required in the diagnosis of primary headaches once a detailed history and physical examination have been performed. While the majority of brain MRI requests are of no particular diagnostic value, unnecessarily requested EEGs can lead to misdiagnoses. It is crucially important to ensure that patients are closely monitored and that unnecessary requests are avoided.

Keywords: Electroencephalography, migraine, pediatric neurology, primary headache, tension-type headache

Introduction

Headaches, a frequently seen entity in children and adolescents, represent one of the principal causes of presentations to pediatric neurology clinics (1). It is particularly important to establish whether childhood headache is primary or secondary, because these pains can derive from potentially life-threatening central nervous system pathologies, and can also be symptoms of other diseases. Due to the differing etiologies involved, headaches may cause decreased quality of life, absenteeism from school, and restrictions in education (1,2). It generally impacts adversely on children's school and social activities and the work performance of their parents (2).

Address for Correspondence
Selcan Öztürk, Hitit University Faculty of Medicine, Department of Pediatrics and Child Health, Division of Pediatric Neurology, Çorum, Turkey
Phone: +90 364 219 30 00 **E-mail:** drselcanozturk@gmail.com **ORCID:** orcid.org/0000-0002-3517-2983
Received: 18.04.2024 **Accepted:** 31.07.2024

Headaches are divided into three groups according to The International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta), primary and secondary headaches, and cranial neuropathy (3). Primary headaches are those not associated with causes such as tumors, meningitis, encephalitis, head trauma, intoxication, or pseudotumor cerebri (4). Diagnosis is based on medical history and a detailed physical examination (5). In addition to blood pressure measurement and fundoscopic examination, the determination of family history and risk factors is highly important for evaluation. Brain imaging and electroencephalography (EEG) must be performed for differential diagnosis when required.

Primary headaches are more common in children, particularly during school-age. Headaches can be associated with several underlying neurological conditions, such as epilepsy. Studies have reported an increased prevalence of epilepsy in children and adolescents with headache, and also greater headaches in patients followed-up due to epilepsy, than in the normal population (5,6). At the same time, headaches may be an epilepsy aura or a postictal symptom of clinical seizures which families are unable to clearly identify. Although EEG findings are not always specific, they can sometimes yield useful information. Ictal changes indicating abnormal electrical activity are observed at EEG during headache attacks, particularly when the headache is associated with seizures, while interictal epileptiform activity may be detected at EEG in some migraine patients.

Magnetic resonance imaging (MRI) of the brain is not normally required when the headache is evaluated as primary. However, MRI is recommended for differential diagnosis in the presence of "red flag" findings following a detailed history directed toward the headache and examination findings. Unnecessary MRIs can sometimes be performed in the absence of detailed evaluations. The purpose of this retrospective study was to evaluate the EEG and MRI findings of previously undiagnosed children presenting with headaches to a newly established pediatric neurology clinic and diagnosed with primary headaches.

Materials and Methods

This single-center, cross-sectional study was performed at the Hitit University Çorum Erol Olçok Training and Research Hospital, Turkey. This study was approved by the Hitit University Faculty of Medicine Clinical Research and Ethics Committee (decision no.: 2022-105, dated: 14.12.2022). Individuals presenting with headaches as outpatients to the pediatric neurology clinic between July and December 2022 were included in this research. The patients' medical records were examined in detail, and their demographic characteristics such as age and sex, duration and frequency of headache, its character and localization, and any accompanying symptoms such as nausea, and vomiting, photophobia, and phonophobia were evaluated. The cases were first classified as primary or secondary headaches. Those patients with primary headaches were included in the evaluation as migraine or tension-type headache (TTH) according to ICHD-III beta criteria. Those patients with histories of head trauma, aged under six, those with histories of brain surgery by neurosurgery, with neurological diseases such as epilepsy or cerebral palsy, and those previously diagnosed with migraine and TTH and using preventive treatment were not included in this study. The brain MRIs which some patients had undergone as a neuroradiological examination before presenting to the pediatric neurology outpatient clinic, and the brain MRI and EEG findings following presentation to the outpatient clinic for differential diagnosis and to investigate accompanying conditions were evaluated. All scans were performed using Neuron Spectrum 5 (Neurosoft, Ivanovo, Russia) EEG devices with 21 electrodes and a 10-20 system attached to the scalp with paste. The patients' EEG findings were classified as either normal or pathological by the same pediatric neurologist.

Informed consent was waived due to the retrospective nature of this study.

Statistical Analysis

Statistical analyses of the data obtained from patients with primary headaches diagnosed as migraine or TTH were performed on SPSS version 22 software (IBM, Armonk, NY, USA). The chi-square test was employed to compare frequencies between the two groups, the t-test for mean comparisons, and the Mann-Whitney U test was used for non-normally distributed data. Statistical significance was set at $p<0.05$.

Results

Two hundred and four patients presented to our clinic with headaches during the study period. Primary headaches were determined in 153 patients following detailed neurological and systemic examinations, while 51 cases were assessed as secondary headaches. Eighty-one (53%) of the patients with primary headaches were followed up as migraine cases and 61 (40%) as TTH. Unclassifiable primary headache was considered in 11 patients (7%). Fifty-five of the migraine cases were regarded as migraine without

aura and 26 as migraine with aura. EEG was especially planned for migraine patients during aura, while some patients followed-up with TTH also underwent EEG with preliminary diagnoses of epilepsy in terms of comorbidity. These patients' brain MRI images obtained concurrently were also examined. We learned that the great majority of our patients with headaches (54%, n=110) had already undergone brain MRI or brain computed tomography before presenting to the child neurology outpatient clinic.

One hundred patients aged 5-17 years, with a mean age of 149.7±36.5 months, diagnosed with migraine (n=50) and TTH (n=50) were enrolled in this study. The mean age of the migraine group was 147.2±35.3 months and that of the TTH group was 152.2±37.8 months. This difference was not statistically significant (p=0.49). Girls represented 66% (n=33) of the patients with migraine and 62% (n=31) of those diagnosed with TTH. There was no significant gender difference between the groups (p=0.68). A comparison of the duration of symptoms showed that these had generally persisted for three months or 3-6 months in the TTH group, while in the migraine group, they had more frequently been present for more than six months, and sometimes even longer than 24 months. The difference between the groups was statistically significant (p=0.01). These items are presented in Table I and Table II. In the tables, categorical variables are expressed as n (%).

No significant differences were observed in this study between the migraine and TTH groups in terms of the demographic variables of age and sex. However, more family histories were found in the migraineurs (p=0.025). A significant difference was observed between the two groups in terms of attack frequencies and durations (p=0.001). The attack duration in TTH was generally 1-3 hours, while among the migraineurs, the duration usually exceeded three hours. Significant differences were observed between the migraine and TTH groups in terms of photophobia (72% vs. 52%, n=36 vs. n=26, respectively) and phonophobia (70% vs. 28%, n=35 vs. n=14, respectively) (p=0.039 and p=0.001) (Table III).

The patients were also classified on the basis of normal or abnormal EEGs. The descriptive statistics are shown in Table IV, and analysis revealed a significant variation between them (p=0.048). Focal/hemispheric sharp spike waves were observed in four (8%) of the patients followed up due to migraine, and generalized spike and sharp wave activity in one (2%). Focal sharp wave activity was observed in only one of the patients with TTH, and no bilateral sharp wave activity was present in any. Bilateral slow wave activity and background rhythm irregularity were seen in two (4%) of the migraine patients, while focal slowdown at EEG was observed in one in the TTH group.

Our patients' brain MRIs were evaluated. The MRI results were compared between the migraine and TTH groups. Arachnoid cyst was detected in 4% of the migraine patients, non-specific white matter anomaly in 2%, septal deviation in 2%, and adenoid vegetation in 2%. Non-specific white matter anomaly was detected in 2% of the patients followed up due to TTH and septal deviation in 2%. No significant differences were determined between the two groups in terms of their MRI images. These data are shown in Table IV and Table V.

Table I. Demographic characteristics of the children with migraine and tension-type headache

Demographic characteristics	**Migraine n (%)**	**Tension-type headache n (%)**	**p value**
Female	33 (66)	31 (62)	0.068
Male	17 (34)	19 (38)	
Age groups (years)			
6-8	5 (10)	4 (8)	
9-10	11 (22)	10 (20)	
11-14	20 (40)	16 (32)	
15-18	14 (28)	20 (40)	
Family history of headache	26 (52)	15 (30)	0.025*
Accompanying disease	9 (18)	9 (18)	
Using medication	3 (6)	2 (4)	

*p<0.05

Table II. Headache characteristics of children with migraine and tension-type headaches			
	Migraine n (%)	**Tension-type headache n (%)**	**p value**
Localization			
Frontal	18 (36)	23 (46)	0.09
Temporal	26 (52)	17 (34)	
Occipital	-	4 (8)	
Vertex	6 (12)	6 (12)	
Duration since onset			
3-6 month	5 (10)	14 (28)	0.001*
7-12 months	13 (26)	10 (20)	
13-24 months	13 (26)	5 (10)	
Longer than 24 months	16 (32)	7 (14)	
Frequency			
Every day	5 (10)	21 (42)	0.001*
Less than three times a week	35 (70)	22 (44)	
Less than four times a month	10 (20)	7 (14)	
Attack duration			
1-3 hours	15 (30)	44 (88)	0.001*
4-6 hours	24 (48)	6 (12)	
7-12 hours	7 (14)	-	
13-24 hours	3 (6)	-	
Longer than 24 hours	1 (2)	-	
Character of pain			
Throbbing	46 (92)	23 (46)	0.001*
Compression	3 (6)	22 (44)	
Stabbing	1 (2)	5 (10)	
*p<0.05			

Table III. Symptoms accompanying headaches			
	Migraine n (%)	**Tension-type headache n (%)**	**p value**
Nausea	41 (84)	31 (62)	0.026*
Vomiting	11 (22)	7 (14)	0.298
Photophobia	36 (72)	26 (52)	0.039*
Phonophobia	35 (70)	14 (28)	0.001*
Waking at night	8 (16)	6 (12)	0.564
*p<0.05			

Table IV. EEG findings in headaches			
	Migraine n (%)	**TTH n (%)**	**p value**
Normal	42 (84)	48 (96)	0.048*
Abnormal			
Bilateral/generalized spike/sharp wave activity	1 (2)		
Focal/hemispheric spike/sharp wave activity	4 (8)	1 (2)	
Bilateral slow wave activity or background rhythm irregularity	2 (4)		
Focal slowdown	1 (2)	1 (2)	
*p<0.05, EEG: Electroencephalography			

Table V. MRI findings in headaches			
	Migraine n (%)	**Tension-type headache n (%)**	**p value**
Normal	45 (90)	47 (94)	0.059
Abnormal			
Arachnoid cysts	2 (4)	1 (2)	
Non-specific white matter abnormalities	1 (2)	1 (2)	
Septal deviation	1 (2)	1 (2)	
Adenoid vegetation	1 (2)		
*p<0.05, MRI: Magnetic resonance imaging			

Table VI. Causes of secondary headache in our study	
	Number n (%)
Upper respiratory tract infections (sinusitis, otitis)	33/51 (64.7)
Discopathy (accompanied by neck pain)	4/51 (7.8)
Hypertension	2/51 (3.95)
Dental decay	3/51 (5.9)
Trauma	2/51 (3.95)
Refractive errors (astigmatism)	4/51 (7.8)
Benign intracranial hypertension	3/51 (5.9)

Discussion

Headaches are pains resulting from infectious, physical causes, or chemical causes which affect the pain-sensitive structures inside and outside the head. In order for headaches to be defined as primary, no underlying pathological finding must be identified. Primary headaches are an important public health problem which adversely affect the individuals concerned, their families, and even the entire community, in the majority of cases. The prevalence of primary headaches in adults is approximately 42%. The figure among the pediatric population is unclear, although a significant increase has been determined in recent years (7). Approximately 60% of children and adolescents experience headaches at least once in their lives. Headaches before the age of four years is very rare, although their prevalence rises thereafter (2,8).

Two hundred four patients presented to the pediatric neurology clinic due to headaches during the short, six-month study period. A large part, approximately 75% of these cases, were evaluated as primary headaches. Our patients were asked 'red flag' questions when taking about their histories. Secondary headache should initially be considered when the patient is young (particularly younger than six years), when there are systemic symptoms such as fever, when the pain alters the character of an already existing headache, when there is a history of trauma or neoplasm, when the pain rouses the patient from their sleep, when there is a worsening of pain during coughing, sneezing, exercising, or the Valsalva maneuver or when waking in the morning and in the presence of abnormal neurological findings (9).

Some children with primary headaches may experience paroxysmal altered states of consciousness, or episodic symptoms and abnormal movements reminiscent of epileptic seizures. In many cases, EEG can help establish whether these attacks are caused by underlying epilepsy or else represent symptoms of a primary headache disorder.

Headache can be seen before, after, or during epileptic seizures (10). However, the relationship between headache and epilepsy has not been adequately investigated. Headache and epileptic seizures are known to share several pathophysiological mechanisms. Ion channel disorders and neurotransmitters in particular are thought to be responsible for these mechanisms. Cortical spreading depression and neuronal hyperexcitability are thought to be responsible for the relationship between migraine and epilepsy in society, especially in children. However, no genetic or environmental risk factor has to date been identified between the two diseases.

The prevalence of epilepsy in the community is 0.5-1.5% but ranges between 1% and 17% in patients with migraine. The prevalence of migraine in the community is 5-18% but ranges between 8% and 24% in patients with epilepsy. A possible relationship has been suggested between these two diseases due to the increased prevalence of both primary headache and epilepsy in the normal population. Indeed, this comorbidity condition has been reported to be more common in some types of epilepsy.

Routine interictal EEG is not recommended for patients with headache. However, EEG can be performed for differential diagnosis in cases of a history of suspected epilepsy. Ictal EEG is thought to be potentially beneficial in some forms of migraine (basilar or hemiplegic).

Evaluation of our patients' EEGs revealed no pathology in 84% (n=42) of those with migraine and 96% of those with TTH. Epileptiform discharge was observed in 10% (n=5) of those patients with migraine and focal slowing in 6% (n=3). While no specific EEG abnormality is expected in migraine, studies have reported that focal slowing may be seen during aura, but the findings are usually normal (10,11). These abnormalities may appear on a transient basis during the ictal phase of the migraine aura, and specific EEG changes may not always be seen during aura. This is thought to be associated with cortical spreading depression and the complex physiopathology of migraine.

According to the current literature, routine imaging is not recommended for children presenting with recurrent headaches if neurological examinations are normal (12). The probability of a space-occupying lesions in the brain in these patients is reported to be low, especially if the children's complaints persist for longer than one month, in the absence of a history of seizure or abnormal gait findings, and if migraine is also present in a member of the family (12). Unfortunately, however, in the majority of cases, MRI or brain tomography are performed for the purpose of lowering parental anxiety and in order not to overlook a potential intracranial pathology. As reported in the present study, brain MRI or computed tomography were assessed by pediatricians in order to ensure that severe conditions such as brain tumors were not overlooked or due to parental anxiety. Repeat evaluations of the MRI results revealed abnormalities such as arachnoid cyst, septal deviation, adenoid vegetation, and non-specific white matter lesions. These are known to be incidental findings and do not generally require any specific medical treatment.

Evaluation of secondary headaches revealed upper respiratory tract infection findings in 33 of the 51 patients, discopathy accompanied by neck pain in four, elevated blood pressure in two, headache associated with dental decay in three, and headache secondary to recent trauma in two. The patients were asked whether they had presented to an ophthalmologist in the previous six months. Refractive error (astigmatism) was detected in four patients and benign intracranial hypertension findings in three. The causes of secondary headaches in our study are shown in Table VI.

In patients presenting to our clinic due to primary headache, no evident pathology was encountered in the MRIs of 90% of the migraine patients and 94% of those with TTH in this study. The existing literature concludes that routine imaging is not indicated when the neurological examinations of children presenting to the clinic with headaches are normal (12). The likelihood of a space-occupying lesion in the brain is reported to be low, particularly if the children's complaints persist for longer than one month, without any history of seizure or abnormal gait findings, or if a migraineur is present in the family (11). Unfortunately, in the majority of cases, MRI or tomography of the brain is performed in order to reduce parental anxieties rather than to exclude an intracranial pathology.

Study Limitations

One particular strength of this research is that it involved previously undiagnosed patients. The principal limitations are the fact that it was conducted in a newly established center, with a relatively small number of patients, and with a shorter follow-up period than in other studies. Despite these limitations, however, our data are promising due to their similarity to those of other studies.

Conclusion

Headaches represent one of the most frequent reasons for admission to pediatric neurology clinics. MRI and EEG are not generally required in the diagnosis of primary headaches

once a detailed history and physical examination have been performed. While the majority of brain MRI requests are of no particular diagnostic value, unnecessarily requested EEGs can lead to misdiagnoses. It is therefore crucially important to ensure that patients are closely monitored and that unnecessary requests are avoided. In order to enhance our current understanding of this subject, we recommend that normal and abnormal EEGs be compared with larger patient numbers and with longer follow-up times, such as five to ten years.

Ethics

Ethics Committee Approval: This study was approved by the Hitit University Faculty of Medicine Clinical Research and Ethics Committee (decision no.: 2022-105, dated: 14.12.2022).

Informed Consent: Informed consent was waived due to the retrospective nature of this study.

Authorship Contributions

Surgical and Medical Practices: S.Ö., Concept: S.Ö., Design: S.Ö., Data Collection and/or Processing: S.Ö., E.K., Analysis and/or Interpretation: S.Ö., E.K., Literature Search: S.Ö., E.K., Writing: S.Ö., E.K.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Gofshteyn JS, Stephenson DJ. Diagnosis and Management of Childhood Headache. Curr Probl Pediatr Adolesc Health Care. 2016; 46:36-51.
2. Nieswand V, Richter M, Gossrau G. Epidemiology of Headache in Children and Adolescents-Another Type of Pandemia. Curr Pain Headache Rep. 2020; 24:62.
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38:1-211.
4. Kabbouche MA, Kacperski J, O'Brien HL PS, Powers SW, Hershey AD. Headache in Children and Adolescents. In: Swaiman KF A, S, Ferriero DM, Schor NF E, editors. Swaiman's Pediatric Neurology Neurology. Sixth. Elsevier Saunders, UK/USA; 2018. p. 647-55.
5. Rho YI, Kim SH, Kang HC, Lee YJ, Kim YO, Kim SK. EEG Characteristics and Diagnostic Implications in Childhood Headache: A Multi-Center Study. Front Neurol. 2020; 11:569486.
6. Kim S. Pediatric headache: a narrative review. J Yeungnam Med Sci. 2022; 39:278-84.
7. Baglioni V, Orecchio S, Esposito D, Faedda N, Natalucci G, Guidetti V. Tension-Type Headache in Children and Adolescents. Life. 2023; 13:825.
8. Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain. 2014; 15:15.
9. Park EG, Yoo IH. The diagnostic values of red flags in pediatric patients with headache. Brain Dev. 2022; 44:512-9.
10. Bauer PR, Tolner EA, Keezer MR, Ferrari MD, Sander JW. Headache in people with epilepsy. Nat Rev Neurol. 2021; 17:529-44.
11. Canpolat M, Topcu A, Kardas F, et al. An assessment of the relation between vitamin D levels and electroencephalogram (EEG) changes in migraine patients. Bratisl Lek Listy. 2022; 123:92-9.
12. Martens D, Oster I, Gottschling S, et al. Cerebral MRI and EEG studies in the initial management of pediatric headaches. Swiss Med Wkly. 2012; 142:w13625.

J Pediatr Res 2024;11(3):136-41
DOI: 10.4274/jpr.galenos.2024.45556

Original Article

Evaluation of Patients with Tall Stature Applying to a Pediatric Endocrinology Clinic

Aşan Önder Çamaş[1], Inara Eldarova[2], Burçin Çiçek[1], Sibel Ergin Şahin[1], Merve Nur Hepokur[1]

[1]İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Pediatric Endocrinology, İstanbul, Turkey
[2]İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Pediatrics, İstanbul, Turkey

ABSTRACT

Aim: Tall stature, defined as a height greater than 2 standard deviation score (SDS), affects 2.3% of children. Our study aimed to explore the causes of tall stature in children and assess the long-term outcomes for these cases.

Materials and Methods: This study included 393 children with tall stature who applied to a pediatric endocrinology clinic between 2015-2024. The patients' medical histories, physical examinations, laboratory findings and hormonal profiles were recorded.

Results: Two hundred and forty-seven girls (62.8%) and 146 boys (37.2%) with a mean age of 9.0±2.8 (0.7-16.8) years were included. The majority of the cases presented with obesity and tall stature (25.2%), early onset of puberty signs and tall stature (18.8%), and early onset of puberty signs (12%). Tall stature was not reported as a complaint in 32.7% of the patients. At the initial visit, the height SDS was 2.6±0.5 (2.0-6.2), the mid parenteral height (MPH) SDS was 0.1±0.8 [(-1.9)-3.6] and the predicted adult height (PAH)-MPH was 8.5±7.8 [(-8.5)-39.0] cm. Considering their diagnoses, the majority were familial tall stature (39.9%), obesity + tall stature (32.3%), and central precocious puberty (13.5%). Cranial imaging was performed in 33 cases, and pathology was detected in 10. 95 of the cases had reached their final height. There was a statistically significant difference between the final height SDS and the patients' initial height SDS and MPH SDS values ($p<0.001$). There was no difference between their PAH and final height values ($p=0.481$).

Conclusion: Those individuals with tall stature required fewer hospital admissions than those with short stature. Obesity, precocious puberty, and genetic potential were found to be the most significant triggering factors, so they should not be overlooked.

Keywords: Tall stature, children, final height

Introduction

In children, height >2 standard deviation score (SDS) according to age and gender is defined as tall stature. If the difference between a child's height SDS and mid parenteral height (MPH) SDS is more than 2 SDS, this child can be also defined as a tall child. 2.3% of all children are tall. Tall stature has unfortunately never been a reason for referral as short stature is (1-4).

Height is affected by multiple factors such as nutrition, genetic, hormonal and environmental factors. Growth can be evaluated in four different stages. The first phase is the intrauterine phase and growth in this phase is associated with maternal factors, placental function, maternal nutrition and growth stimulating factors. In the second phase, which includes the first 2-3 years of life, growth is regulated mainly by nutrition. Growth hormone (GH) and

Address for Correspondence
Aşan Önder Çamaş, İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Pediatric Endocrinology, İstanbul, Turkey
Phone: +90 532 510 29 96 **E-mail:** asanonder@yahoo.com **ORCID:** orcid.org/0000-0002-5730-3198
Received: 27.04.2024 **Accepted:** 21.07.2024

thyroid hormones play a primary role during childhood in the third phase. In the 4th phase (puberty), a pubertal height spurt is achieved due to the effects of sex steroids along with GH (2).

In the differential diagnosis of tall stature, familial tall stature (FTS) should first be considered (4-8). In tall children without dysmorphic findings, the growth rate must be evaluated first. Healthy obesity, aromatase deficiency or estrogen resistance can be considered in those with normal growth rate and height SDS-MPH SDS>2 SDS. If the difference between MPH SDS and height SDS is less, FTS is particularly considered. If a tall child has an increased height velocity, evaluations should be made for puberty precocious, hyperthyroidism, constitutional tall stature, and GH excess. In tall children with dysmorphic findings, overgrowth syndromes such as Sotos, Weaver, Fragile X, Simpson-Golabi-Behmel (proportionate types) and Marfan, Klinefelter, Beckwith-Wiedemann, Triple X (disproportionate types) must be kept in mind (1-3,9,10).

Tallness is not always benign. There is also the possibility that it may be accompanied by some complications. Cardiovascular system diseases and metabolic disorders, psychiatric problems, vertebral deformities and an increased tendency of breast, prostate and colon cancer are sometimes detected in tall people (4,11,12).

In our study, we aimed to investigate the etiology of children with tall stature who were admitted to the pediatric endocrinology clinic and to evaluate the follow-up of these cases.

Materials and Methods

This study was conducted by accessing the records of 393 tall children (height>2 SDS) who were admitted to our clinic between 2015 and 2024. The patients' complaints at presentation, date of birth, gender, calendar age at the time of admission, weight, height, body mass index (BMI) measurements, bone ages, pubertal stages, final heights and final height SDS, GH suppression test results, pituitary and cranial magnetic resonance imaging (MRI) findings, and the treatments they received were recorded. Data regarding the family history of the patients (birth height, birth weight, MPH, consanguinity, presence of tall individuals in the family, presence of pituitary pathology in the family) were obtained from the hospital database.

Body weight was checked with the same electronic device, and the measurements were taken with the patients wearing just their underwear. The heights of all cases were measured by the same person using a Harpenden Stadiometer. Measurements in the supine position were applied to younger children (under 2 years of age). Height and weight SDS and the height age of the cases were calculated using our country's references (13) and the "CHILD METRICS" program (14). The estimated adult heights of the patients according to their bone ages (predicted adult height=PAH) were calculated via the Bayley-Pinneau method (15). Those cases with a bone age of >14 years in girls and a bone age of >16 years in boys and an annual growth rate of <2 cm were considered to have reached their final heights (16). The heights of the parents were measured and MPH was calculated according to the formula below by using CHILD METRICS:

For girls= [mother's height (cm) + father's height (cm)-13]/2

For boys= [mother's height (cm) + father's height (cm)+13]/2

Tanner staging was used to evaluate pubertal status. Testicular volume was measured with a Prader orchidometer in boys. Testicular volume exceeding 4 mL and breast development in girls at Tanner stage II were considered as entering puberty (17,18). The appearance of secondary sexual characteristics before the age of 8 years on girls and 9 years in boys was considered as precocious puberty (19).

The results of the laboratory parameters in the hospital database [thyroid functions, GH, prolactin, cortisol, insulin like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), and GH suppression test] were evaluated. Thyroid functions, cortisol and prolactin levels were studied via the chemiluminescent microparticle immunoassay method by Abbott Architect on an I2000 SR device. GH, IGF-1 and IGFBP-3 were studied via the CLIA (chemiluminescent immunoassay) method on a Siemens Immulite 2000 device. IGF-1 and IGFBP-3 SDS values were calculated using CHILD METRICS. Oral glucose tolerance test (OGTT) was performed on those cases with basal IGF-1 and IGFBP-3 >2 SDS, without pre-pubertal/FTS clinics, and/or on those whose height velocity was >1 SDS. GH suppression test was performed by administering 1.75 g/kg glucose orally and then measuring GH levels at 0, 30, 60, 90 and 120 minutes. A GH value of <1 ng/mL was considered as being suppressed (20).

Left wrist radiography of the cases were evaluated and bone age was calculated according to Greulich-Pyle atlas (21). Cases with rapidly progressing puberty, those diagnosed with precocious puberty under the age of 7, and those without precocious puberty but with increased growth rates were evaluated via MRI. The cranial and

pituitary MRI results of the patients were investigated using the data in the records.

Ethical permission was obtained from the Scientific Research Ethics Committee of University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital (approval no.: 79, date: 28.03.2024). A written informed consent form was obtained from the parents of participants.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27 for Windows (IBM SPSS, Chicago, IL). Descriptive statistics are expressed as mean ± standard deviation for variables with a normal distribution, and as median (minimum-maximum) for variables without a normal distribution. Normal distribution was assessed by the Kolmogorov-Smirnov test. The significance of difference between two pairs was assessed using the Paired Samples t-test. One-way ANOVA was used to compare the means of more than two groups when there was one independent variable. Statistical significance was set at $p<0.05$.

Results

Two hundred and forty-seven girls (62.8%) and 146 boys (37.2%) with an average age of 9.0±2.8 (0.7-16.8) years were included in this study. The majority of the cases presented with obesity with tall stature (25.2%), early onset of puberty signs with tall stature (18.8%), or just early onset of puberty signs (12%). Tall stature was not reported as a complaint in 32.7% of the patients. Birth length was 51.5±2.3 (44.0-58.0) cm and MPH SDS was 0.1±0.8 [(-1.9)-3.6] SDS. There was consanguinity in 19.3% of the participants, and a total of 66.4% stated that there were taller individuals in their family. Additionally, it was learned that 2.3% of the cases had a family history of pituitary pathology. The anthropometric/clinical evaluations of the cases at admission are given in Table I. Considering the diagnoses, the majority were FTS (39.9%), obesity with tall stature (32.3%), and central precocious puberty (CPP) (13.5%). Syndromic tall stature was detected in 1.03% of all cases (4 Marfan, 1 Klinefelter Syndrome) (Table II). There was no significant difference in initial height SDS according to the diagnostic groups (p=0.191).

When the initial laboratory data of the patients were evaluated, no thyroid dysfunction, excess or deficiency of cortisol/prolactin was detected in any of them. OGTT was performed in 68 patients and GH levels were suppressed in all but one (diagnosed with GH secreting adenoma). For the whole study group, IGF-1 SDS was 2.4±2.9 [(-2.4)-21.9] and IGFBP-3 SDS was 1.2±1.1 [(-1.9)-5.6]. When corrected for height age, this data was 0.6±1.5 [(-3.3)-6.4] SDS and 0.6±1.0 [(-1.8)-3.7] SDS, respectively. Cranial imaging was performed in 33 cases, and pathology was detected in 10 of them (2.5% of the entire study group). 8/10 were non-functional microadenomas, 1/10 was GH-secreting microadenoma and 1/10 was hypothalamic hamartoma.

Table I. Anthropometric/clinical evaluations of the cases at admission

Age (year) (min.-max.)	9.0±2.8 (0.7-16.8)
Gender Female (%) Male (%)	 247 (62.8) 146 (37.2)
Height (cm) (min.-max.)	148.1±19.1 (77.5-198.0)
Height SDS (min.-max.)	2.6±0.5 (2.0-6.2)
Weight (kg) (min.-max.)	53.1±21.5 (10-132)
Weight SDS (min.-max.)	2.6±1.0 [(-0.7)-5.5]
BMI (kg/cm^2) (min.-max.)	23.2±5.4 (13.2-45)
BMI SDS (min.-max.)	1.7±1.2 [(-2.9)-4.7]
Pubertal status/Tanner stage Stage 1 Stage 2 Stage 3 Stage 4 Stage 5	 39.4% 26.9% 13.2% 6.2% 14.2%
Bone age (months) (min.-max.)	82.7±62.1 (6.0-204.0)
PAH (cm) (min.-max.)	176.6±11.2 (154.0-207.0)
Height SDS - MPH SDS (min.-max.)	2.5±0.9 [(-1.5)-5.1]
PAH-MPH (cm) (min.-max.)	8.5±7.8 [(-8.5)-39.0]

SDS: Standard deviation score, BMI: Body mass index, PAH: Predicted adult height, MPH: Mid parenteral height, min.: Minimum, max.: Maximum

Table II. Diagnosis of the patients

Diagnosis	**Number (%)**
CPP	53 (13.5)
Obesity	127 (32.3)
FTS	157 (39.9)
Obesity + CPP	25 (6.4)
Marfan syndrome	4 (1)
Obesity + FTS	16 (4.1)
GH secreting adenoma	1 (0.3)
Congenital adrenal hyperplasia	2 (0.5)
Normal variant puberty	7 (1.8)
Klinefelter syndrome	1 (0.3)

CPP: Central precocious puberty, FTS: Familial tall stature, GH: Growth hormone

Table III. Clinical findings of those patients who had reached their final height	
Gender	
Female (%) Male (%)	49 (51.9) 46 (48.4)
Diagnosis	
Obesity +FTS (%) FTS (%) Marfan syndrome (%) CPP (%) Obesity + CPP (%) GH secreting adenoma (%) Klinefelter syndrome (%)	26 (27.4) 60 (63.2) 3 (3.2) 2 (2.1) 2 (2.1) 1 (1) 1 (1)
Final height (cm) (min.-max.)	180.9±9.7 (162.0-210.0)
Final height SDS (min.-max.)	1.8±0.9 [(-0.0)-5.4]
Final height SDS-MPH SDS (min.-max.)	2.4±1.0 [(-1.0)-4.4]
Final height SDS-initial height SDS (min.-max.)	(-0.6)±0.7 [(-2.8)-1.1]
Final height-PAH (cm) (min.-max.)	(-0.2)±6.1 [(-13.4)-23.5]
CPP: Central precocious puberty, FTS: Familial tall stature, GH: Growth hormone, SDS: Standard deviation score, PAH: Predicted adult height, MPH: Mid parenteral height, min.: Minimum, max.: Maximum	

In the follow-up of the patients; gonadotropin-releasing hormone analog treatment was started in 53 patients due to CPP, hydrocortisone treatment was started in two patients due to congenital adrenal hyperplasia, and somatostatin treatment was started in one patient due to GH-secreting adenoma.

It was found that 95 of the cases had reached their final height. The clinical findings of these patients are shown in Table III. There was a statistically significant difference between the final height SDS and the patient's initial height SDS and MPH SDS values ($p<0.001$). We did not find any difference between the PAH and final height values ($p=0.481$). Final heights of both the obesity and FTS groups were found to be higher than the familial target heights. Final height SDS - MPH SDS were 1.51±1.26 in the obesity group and 1.39±0.94 in FTS group. The final height SDS values were lower than initial height SDS levels in these two groups (-0.67±0.74 in the obesity group and -0.64±0.79 in FTS group).

Discussion

In the evaluation of growth, monitoring the height, height velocity and determining whether there are deviations from the normal are very important in the early diagnosis of the presence of any underlying pathological causes (22,23). The evaluation of a tall child begins with creating their medical history. Birth height, weight and head circumference must be investigated. Afterwards, it is crucial to learn about the possible presence of tall individuals in the family, pubertal timing and the auxological parameters of the parents. It is mandatory to have information regarding the child's history of hypo-hyperglycemia, cardiac defects, joint laxity, obesity, nutritional problems, ocular defects and neurodevelopmental disorders. In the physical examination, it is important to evaluate height, weight, head circumference, BMI, sitting height and arm-span (in terms of the differential diagnosis of proportional/disproportionate tall stature) as well as pubertal stage. Also, a detailed examination should be performed in order to detect dysmorphic findings, cardiac murmur, and skeletal deformities. Among our cases, only five patients with syndromic tallness had disproportionately tall stature. For this reason, arm-span and sitting height measurements could not be made in all cases. It is also important to evaluate bone age. In the presence of obesity and early puberty, bone age is advanced; whereas in the presence of FTS, it is normal or retarded. Gonadotropins, GH and IGF-1 levels can be helpful in the differential diagnosis of puberty precocious and GH excess. If disorders of hypothalamic-pituitary axis are considered, detailed hormonal profiles and cranial imaging are useful. Genetic evaluation should be performed in the presence of dysmorphic findings and disproportionate tall stature (1-4,11).

Given that tallness is considered a normal condition, it is not frequently cited as a reason for admission. As a result, patients are often diagnosed late and have an increased likelihood of developing complications (1,2). In 32.3% of our patients, tall stature was not reported as a presenting complaint. The majority of diagnoses were FTS, obesity, and CPP. Consistent with existing literature, the largest group in our study comprised cases with FTS (4,23). FTS was observed in 44% of our patients, and it was noted that 66.4% of all study patients had tall family members. Other studies have reported a frequency of 66-80% for the diagnosis of FTS in children with idiopathic tall stature (24,25).

Obesity and precocious puberty are other frequent causes of tall stature. In our study, 42.8% of the cases had obesity. 19.9% of all cases were followed up with CPP, and two cases were followed up with peripheral precocious puberty. Wang (26) put forward that the prevalence of BMI increased subcutaneous fat tissue and that obesity was higher in girls with early pubertal development than in girls with normal/late pubertal development. Another study reported that increased BMI was associated with early pubertal development and triggered the early onset

of puberty by 0.7 years in girls and 0.6 years in boys (27). In obesity, IGF-1 values are found to be normal/increased due to the effects of high insulin levels. However, the GH response to different stimuli is blunted. Therefore, an increase in height velocity occurs with high IGF-1 levels (28,29). It has also been shown that higher IGF-1 levels in mid-childhood are associated with earlier puberty onset (30). The initial IGF-1 values of our patients were found to be increased, even when it was corrected for height age. However, the GH levels in OGTT were suppressed in all but one individual. The diagnosis of CPP and obesity in a significant portion of our cases may explain the high IGF levels. Except for those case with GH excess, GH suppression in the others indicates that IGF levels may not be sufficient for diagnosis/monitoring. In summary, obese children tend to be 4-5 cm taller than their normal-weight peers. They also tend to have advanced bone age and early pubertal signs (28). When our patients were evaluated, 25 (14%) of 168 obese patients had CPP.

In the differential diagnosis of tall stature, genetic syndromes should be suspected especially if they are accompanied by findings such as dysmorphic findings, disproportionately tall stature and/or pubertal arrest (31,32). The diagnosis rate using molecular genetic methods is 43% in tall cases with syndromic features, but it decreases to 8% in those cases without dysmorphic findings (33). In our study, after clinical and genetic examinations, five patients (1%) were diagnosed with primary growth disorder. 80% of primary growth disorder cases were Marfan Syndrome. Consistent with our findings, in the study conducted by Kärkinen et al. (24), Marfan syndrome was the most common primary growth disorder in extremely tall children with a frequency of 2.3%. Also, it was observed that half of the cases with primary growth disorder had height SDS >3.9 (24). Therefore, as height increased, the probability of primary growth disorder diagnosis increased. The initial height SDS values of our Marfan syndrome cases were 3.18±0.99.

Cranial imaging should be performed especially in the presence of neurological findings and if there is an organic CPP etiology, dysfunction of hypothalamic-pituitary axis should be considered (10). In this study, hypothalamic hamartoma was detected in a male patient who was diagnosed with CPP, and pituitary microadenoma was detected in a female patient who was diagnosed with GH excess.

When the 95 cases who had reached their final height were evaluated, final height SDS was significantly lower than the initial height SDS. However, it was still high compared to the MPH SDS. The fact that the majority of the cases were diagnosed with FTS and obesity may have caused this. Final height data were available for only two CPP cases. Therefore, we could not make an analysis. If treatment for CPP is started earlier and before bone age progresses, it is less likely that there will be a loss in final height (34,35).

PAH values calculated according to the initial bone ages of all cases were compatible with the final height. This highlights the importance of initial bone age assessment.

Study Limitations

When considering the limitations of this study, approximately just a quarter of the cases had reached their final height. There were only two CPP patients who had reached their final height. Therefore, the effect of the treatment on final height could not be evaluated in CPP patients. The annual height velocity of the patients, changes in IGF-1 levels and the relationship of these factors with the final height according to the diagnostic groups also could not be evaluated.

Conclusion

In conclusion, tall stature required fewer hospital admissions than short stature as it was not considered pathological. Obesity, precocious puberty and genetic potential were found to be the most significant triggering factors. Tall stature should not be overlooked by clinicians and possible clinical pathologies should be excluded via detailed evaluations.

Ethics

Ethics Committee Approval: Ethical permission was obtained from the Scientific Research Ethics Committee of University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital (approval no.: 79, date: 28.03.2024).

Informed Consent: A written informed consent form was obtained from the parents of participants.

Authorship Contributions

Surgical and Medical Practices: A.Ö.Ç., I.E., B.Ç., S.E.Ş., M.N.H., Concept A.Ö.Ç., I.E., Design: A.Ö.Ç., I.E., Data Collection and/or Processing: B.Ç., S.E.Ş., M.N.H., Analysis and/or Interpretation: I.E., B.Ç., M.N.H., Literature Search: A.Ö.Ç., I.E., S.E.Ş., Writing: A.Ö.Ç., I.E.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Corredor B, Dattani M, Gertosio C, Bozzola M. Tall Stature: A Challenge for Clinicians. Curr Pediatr Rev. 2019; 15:10-21.
2. Meazza C, Gertosio C, Giacchero R, Pagani S, Bozzola M. Tall stature: a difficult diagnosis? Ital J Pediatr. 2017; 43:66.
3. Baron J, Sävendahl L, De Luca F, et al. Short and tall stature: a new paradigm emerges. Nat Rev Endocrinol. 2015; 11:735-46.
4. Leung AKC, Leung AAC, Hon KL. Tall Stature in Children. Adv Pediatr. 2019; 66:161-76.
5. Lui JC, Baron J. Epigenetic Causes of Overgrowth Syndromes. J Clin Endocrinol Metab. 2024; 109:312-20.
6. Lui JC, Baron J. CNP-related Short and Tall Stature: A Close-knit Family of Growth Disorders. J Endocr Soc. 2022; 6:bvac064.
7. Weiss B, Ott T, Vick P, et al. Identification of novel genes including NAV2 associated with isolated tall stature. Front Endocrinol (Lausanne). 2023; 14:1258313.
8. Weiss B, Eberle B, Roeth R, et al. Evidence That Non-Syndromic Familial Tall Stature Has an Oligogenic Origin Including Ciliary Genes. Front Endocrinol (Lausanne). 2021; 12:660731.
9. Edmondson AC, Kalish JM. Overgrowth Syndromes. J Pediatr Genet. 2015; 4:136-43.
10. Banerjee S, Bajpai A. Precocious Puberty. Indian J Pediatr. 2023; 90:582-9.
11. Sada V, Puliani G, Feola T, et al. Tall stature and gigantism in transition age: clinical and genetic aspects-a literature review and recommendations. J Endocrinol Invest. 2024; 47:777-93.
12. Singh J, Wanjari A. Cardiac Complications in Marfan Syndrome: A Review. Cureus. 2022; 14:e29800.
13. Neyzi O, Furman A, Bundak R, Gunoz H, Darendeliler F, Bas F. Growth references for Turkish children aged 6 to 18 years. Acta Paediatr. 2006; 95:1635-41.
14. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol. 2017; 9:182-4.
15. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr. 1952; 40:423-41.
16. Finkelstein BS, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, Cuttler L. Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. Arch Pediatr Adolesc Med. 2002; 156:230-40.
17. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969; 44:291-303.
18. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970; 45:13-23.
19. Gangat M, Radovick S. Precocious puberty. Minerva Pediatr. 2020; 72:491-500.
20. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014; 99:3933-51.
21. P.S. Greulich W. Radiographic atlas of skletal development on the hand and wrist. 2nd Ed. Stanford Univ. Press. p. 53,1959.
22. Urakami T. Tall stature in children and adolescents. Minerva Pediatr. 2020; 72:472-83.
23. Leung AK, Robson WL. Evaluating tall children. Can Fam Physician. 1995; 41:457-8.
24. Kärkinen J, Sorakunnas E, Miettinen PJ, Raivio T, Hero M. The aetiology of extreme tall stature in a screened Finnish paediatric population. EClinicalMedicine. 2021; 42:101208.
25. Stalman SE, Pons A, Wit JM, Kamp GA, Plötz FB. Diagnostic Work-up and Follow-up in Children with Tall Stature: A Simplified Algorithm for Clinical Practice. J Clin Res Pediatr Endocrinol. 2015; 7:260-7.
26. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics. 2002; 110:903-10.
27. He Q, Karlberg J. Bmi in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res. 2001; 49:244-51.
28. Albuquerque EVA, Scalco RC, Jorge AAL. Management Of Endocrine Disease: Diagnostic and therapeutic approach of tall stature. Eur J Endocrinol. 2017; 176:R339-53.
29. Al-Samerria S, Radovick S. Exploring the Therapeutic Potential of Targeting GH and IGF-1 in the Management of Obesity: Insights from the Interplay between These Hormones and Metabolism. Int J Mol Sci. 2023; 24:9556.
30. Baier I, Pereira A, Ferrer P, Iñiguez G, Mericq V. Higher Prepubertal IGF-1 Concentrations Associate to Earlier Pubertal Tempo in Both Sexes. Horm Res Paediatr. 2023; 96:404-11.
31. Zeigler SM, Sloan B, Jones JA. Pathophysiology and Pathogenesis of Marfan Syndrome. Adv Exp Med Biol. 2021; 1348:185-206.
32. Butler G, Srirangalingam U, Faithfull J, Sangster P, Senniappan S, Mitchell R. Klinefelter syndrome: going beyond the diagnosis. Arch Dis Child. 2023; 108:166-71.
33. Vasco de Albuquerque Albuquerque E, Ferreira de Assis Funari M, Pereira de Souza Quedas E, et al. Genetic investigation of patients with tall stature. Eur J Endocrinol. 2020; 182:139-47.
34. Knific T, Lazarevič M, Žibert J, et al. Final adult height in children with central precocious puberty - a retrospective study. Front Endocrinol (Lausanne). 2022; 13:1008474.
35. Chu ZL, Jiang H, Wu Q. Effect of gonadotropin-releasing hormone analogue treatment in improving final adult height of children with central precocious puberty or early and fast puberty: a Meta analysis. Zhongguo Dang Dai Er Ke Za Zhi. 2021; 23:1161-8.

J Pediatr Res 2024;11(3):142-8
DOI: 10.4274/jpr.galenos.2024.65624

Original Article

Hyponatremia as a Biochemical Marker of Complicated Acute Appendicitis: A Retrospective Cohort Study

Adel Ahmed Alfayez[1], Jamal Al-Hudhaif[1], Abdullah M. Zahi[1], Nawaf Mushabab Al-Hassan[2], Saad Ahmed Aldohaim[2], Mohammed Ali Hejji[2], Osama Khalid Al-Harbi[2], Nawaf Abdullah Alsaadi[2]

[1]Prince Sultan Military Medical City, Department of Pediatric Surgery, Riyadh, Saudi Arabia
[2]King Saud Medical City, College of Medicine, Riyadh, Saudi Arabia

ABSTRACT

Aim: Acute appendicitis is a frequent surgical emergency which affects the lower right quadrant of the abdomen. Failure to diagnose this condition might result in perforation, abscess development, or peritonitis if not tackled. Hyponatremia was the focus of our retrospective cohort investigation because it may serve as a biochemical indicator for spotting serious forms of acute appendicitis in our patient group.

Materials and Methods: All pediatric patients aged up to 14 years who were admitted to the Prince Sultan Military Medical City, under our service between 2020 and 2023 were retrospectively reviewed. Data of interest were retrieved from the medical files of our study subjects and entered into Excel sheets, including medical history, age, sex, type of referral, and associated comorbidities, as well as clinical data such as abdominal pain, nausea/vomiting, anorexia, fever, changes in bowel movement, dysuria, and any recent histories of upper respiratory tract infection.

Results: Thirty-one (19%) patients were found to have a complicated acute appendicitis, confirmed by the presence of gross or micro-perforation and segmental gangrenous segment on histopathological analysis. Statistically significant differences were observed in those patients with the complicated form, compared to others with the non-complicated form of acute appendicitis in terms of preoperative sodium levels, along with intra-operative findings of perforated appendices. Compared to the non-complicated patients, those with complicated acute appendicitis had a much lower mean blood sodium level.

Conclusion: This study suggests the use of hyponatremia as a potential biomarker for complicated cases. Early diagnosis and appropriate response can assist medical and surgical practitioners in providing more focused and effective management plans for complicated cases, which would improve patient outcomes.

Keywords: Acute appendicitis, pediatrics, hyponatremia, biomarkers, and sodium level

Introduction

When blood salt levels drop too low, a condition known as hyponatremia develops. Excessive perspiration, nausea, vomiting, diarrhea, and the side effects of several drugs are among the potential causes of this disease (1). Common surgical emergencies affecting the lower right quadrant of the abdomen include acute appendicitis, characterized by pain, nausea, and vomiting. Standard methods for

Address for Correspondence
Jamal Al-Hudhaif, Prince Sultan Military Medical City, Department of Pediatric Surgery, Riyadh, Saudi Arabia
Phone: +966505440091 **E-mail:** hudhaif@gmail.com **ORCID:** orcid.org/0009-0002-1551-4955
Received: 10.06.2024 **Accepted:** 08.07.2024

diagnosing acute appendicitis include clinical examination, imaging techniques, and the presence of inflammatory markers, such as C-reactive protein, neutrophil shift, and white blood cell (WBC) count. If untreated, complicated acute appendicitis (CAA) may progress to perforation, abscess development, or peritonitis. The fact that the symptoms of this condition might overlap with those of non-CAA (NCAA) and cause unusual presentations makes diagnosis difficult (2). Recent research suggests that hyponatremia may also be a sign of CAA (2).

An important area of study is the development of an accurate and practical molecular marker for early identification of CAA. Adults with complex appendicitis may show signs of hyponatremia, as reported by Sheen et al. (3). Conversely, hyponatremia was investigated in a meta-analysis by Anand et al. (4) for its possible use as a diagnostic indicator of CAA in children. Hyponatremia and CAA were shown to be significantly correlated in a prospective evaluation of diagnostic accuracy (5). Shuaib et al. (6) studied hyperbilirubinemia, hyponatremia, and their combined use in diagnosing CAA prior to surgery. Taken together, these studies suggest that hyponatremia may be a useful diagnostic indicator, particularly in those patients with CAA.

This retrospective cohort study aimed to examine the correlation between CAA and hyponatremia. We aimed to thoroughly examine the medical records of eligible patients in order to determine whether hyponatremia could be a valuable addition to the existing diagnostic criteria for predicting CAA prior to surgery. By incorporating blood sodium levels as dependable indicators, their integration into diagnostic algorithms has the potential to improve accuracy, shorten the time required for surgical intervention, assist clinicians in anticipating surgical complexities, and enhance patient outcomes.

Materials and Methods

The objective of our study was to examine and either corroborate or challenge the findings of previous studies on this subject. One of our primary goals was to determine whether hyponatremia could be used as a biochemical marker to identify complicated forms of acute appendicitis in our group of patients.

Study Design

All pediatric patients aged up to 14 years who were admitted to the Prince Sultan Military Medical City under our service between 2020 and 2023 were retrospectively reviewed. Patients aged <14 years who had a clinical versus radiological picture of acute appendicitis and underwent appendectomy (open or laparoscopic) met the inclusion criteria (n=162). Patients older than 14 years of age, those with chronic metabolic or endocrine problems, and those who underwent incidental appendectomy were excluded (n=0).

Informed consent not applicable in this study as such study is not requiring patients consent, instead The Prince Sultan Military Medical City (Ethical Board Committee) accepted our study (IRB approval no.: E-2130).

Data Collection

The data of interest were retrieved from the medical files of our study subjects and entered into Excel sheets, including their medical history, age, sex, type of referral, and associated comorbidities, as well as clinical data such as abdominal pain, nausea/vomiting, anorexia, fever, changes in bowel movement, dysuria, and any recent history of upper respiratory tract infection (URTI). Laboratory data included WBC count, absolute neutrophil count, creatinine, blood urea nitrogen (BUN), and glucose. The electrolytes used included sodium (Na), potassium (K), and chloride. Radiological investigations included the modality and findings. Intra-operative data covered any findings and/or complications.

Definitions

NCAA is evident on histopathological examination, with features of inflammation alone.

CAA is evident on histopathological examination, with necrotic segments in a completely gangrenous or perforated appendix.

Laboratory Findings

Hyponatremia was defined as blood serum concentration ≤135 mmol/L; leukocytosis as a WBC count >12-16×10^9 (depending on the reference ranges based on the patient's age); neutrophilia as an absolute neutrophil count >7×10^9 and creatinine, BUN, glucose, potassium, and chloride, all of which were within their normal ranges. All laboratory investigations were performed when the patients presented to the emergency department before medical management was initiated.

Statistical Analysis

Microsoft Excel 2010 was used for data collection, storage, and management. We used SPSS® version 21.0 (IBM Inc., Chicago, Illinois, USA) to analyze the data and create the figures. The results of the descriptive analysis

are presented as percentages and figures for the categorical variables. We used the Shapiro-Wilk test and Q-Q plots to check whether the continuous variables were normal. The median (interquartile range) with box-and-whisker plots was used to display the data which were not normally distributed. Therefore, for continuous variables, the Mann-Whitney U test was used to compare the groups with and without perforated appendicitis. Odds ratios (OR) were obtained by comparing the proportions of categorical variables across groups using the chi-square test. The results were considered statistically significant if the p value was <0.05.

Results

A total of n=162 patients were analyzed, along with their socio-demographic data, associated comorbidities (Tables I, II) and with their type of referral (Figure 1). From a total number of 162 patients, 31 (19%) were found to have a CAA confirmed by the presence of gross or micro-perforation and segmental gangrenous segments on histopathological analysis.

Clinical data were analyzed between both groups, CAA versus NCAA, including abdominal pain, nausea/vomiting, anorexia, fever, changes in bowel movement, dysuria, and any recent history of URTI (Table III). A 5% level of significance was observed for nausea, vomiting, and fever (p=0.029 and 0.036 respectively).

Table I. Socio-demographic characteristics

Characteristic	Group I complicated acute appendicitis (n=31)	Group II non-complicated acute appendicitis (n=131)	p value
Age in years, median (IQR)	11 (9-13)	10 (8-12)	0.266
Age group			
2-5, n (%)	4 (12.9)	9 (6.9)	0.271
6-8, n (%)	3 (9.7)	31 (23.7)	0.086
9-14, n (%)	24 (77.4)	91 (69.5)	0.385
Gender, n (%)			
Male	18 (58.1)	73 (55.7)	0.813
Female	13 (41.9)	58 (44.3)	
Length of stay in days, median (IQR)	4 (3-6)	1 (1-2)	<0.001*

*Statistically significant at the 5% level of significance
IQR: Interquartile range

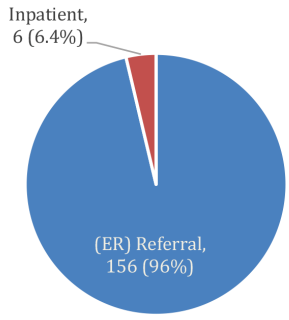


Figure 1. Type of referrals

Table II. Associated comorbidities

Associated comorbidities	ALL	Group I complicated acute appendicitis (n=31)	Group II non-complicated acute appendicitis (n=131)
Asthma	7	2	5
Obesity	2	0	2
Allergic to nuts	2	1	1
Celiac disease	1	0	1
Autism	1	0	1
Esophageal stricture causing GERD*	1	0	1
Gastroenteritis	1	0	1
Cow milk allergy	1	0	1
Iron deficiency anemia	1	0	1
ADHD* not on meds, urethral stenosis	1	0	1
Adrenal insufficiency**	1	0	1
Anxiety disorder	1	0	1
Central precious puberty	1	0	1
Epilepsy, GDD*, chromosome 16p 11 microdeletion syndromes	1	1	0
Known to have chronic constipation	1	0	1
Large PDA* (post catheter closure), not on meds	1	0	1
Sickle cell anemia, nephrocalcinosis, dental caries	1	0	1

*GERD: Gastroesophageal reflux disease
**Patient was compliant to treatment, and had not been admitted to hospital with electrolyte disturbances for long time (therefore this patient was not excluded) ADHD: Attention deficit hyperactivity disorder, GDD: Global developmental delay, PDA: Patent ductus arteriosus

Statistically significant differences were observed in those patients with CAA, compared to the others (NCAA) in terms of their preoperative sodium levels, along with intra-operative findings of perforated appendicitis. A statistically significant difference between CAA, and NCAA was found with regard to the laboratory investigations, namely sodium levels with a p value of 0.011 which is below the 5% level of significance (Table IV). Other laboratory investigations showed differences as well, including: WBC pre-Op 16 10^9/L vs. 13.5 10^9/L, p value of 0.009, and neutrophil absolute count pre-op 14.3 10^9/L vs. 10 10^9/L, p value of 0.009. Interestingly, substantially reduced mean serum sodium levels were observed in CAA, compared to NCAA when comparing the two groups with the presence of hyponatremia (Tables V, VI) (Figure 2**)** with a p value of 0.001, OR 4.60, and 95% confidence interval of 1.83-11.55.

Regarding radiological investigations, ultrasound (US) was diagnostic in 60.5%, and not in 33.3%, while computed tomography (CT) was diagnostic in 17.9%, and ruled out in 27.2%. It is important to mention here that, in our practice, it is unusual to apply CT except in cases of borderline presentation, along with physician suspicion of either ruling in or ruling out the diagnosis of acute appendicitis. Moreover, radiological diagnoses of NCAA were 82%, and of CAA, it was (10.5%). Other cases that did not undergo imaging investigations, either clinically diagnosed or US could not visualize the appendix, which is why they were subtracted from the percentage group (10 cases were not performed, while two cases were not performed, but were not diagnostic) (Table VII). Table VIII demonstrates the intra-operative findings, along with any complications.

Table III. Clinical presentations in both groups (complicated acute appendicitis) versus (non-complicated acute appendicitis)

Symptom	Group I complicated acute appendicitis (n=31) n (%)	Group II non-complicated acute appendicitis (n=131) n (%)	p value
Abdominal pain (n=162)	31 (100)	131 (100)	0.998
Nausea/Vomiting (n=144)	31 (100)	113 (86.3)	0.029*
Anorexia (n=141)	30 (96.8)	111 (84.7)	0.072
Fever (n=62)	17 (54.8)	45 (34.4)	0.036*
Constipation (n=21)	7 (22.6)	14 (10.4)	0.068
Diarrhea (n=29)	6 (19.4)	23 (17.6)	0.815
Dysuria (n=7)	3 (9.7)	4 (3.1)	0.107
History of recent (URTI)** (n=20)	5 (16.1)	15 (11.5)	0.486
Incidental finding (n=1)***	0 (0.0)	1 (0.8)	0.918

*Statistically significant at the 5% level of significance
**Upper Respiratory Tract Infections (URTI)
***The reason for the other diagnostic workup (n=1): Enlarged right kidney with grade 4 hydronephrosis and features of PUJ obstruction. Left grade 1 hydronephrosis

Table IV. Laboratory values

	Group I complicated acute appendicitis (n=31) median (IQR)	Group II non-complicated acute appendicitis (n=131) median (IQR)	p value
Na level pre-op (normal 135-145 mmol/L)	137 (133-138)	137 (136-139)	0.011*
Na level post op (n=3)	135 (135-135)	139.5	0.221
WBC pre-op (normal 4.00-11.00 *10^9/L)	16 (12.8-20)	13.5 (9.3-16.9)	0.009*
WBC post-op (n=3)	8.4 (8.4-8.4)	7.2	0.221
Neutrophils absolute count pre-op (normal 2.8-6.30 10^9/L)	14.3 (9.2-16.9)	10 (6.5-13.5)	0.009*
Neutrophils post-op (n=3)	2.4 (2.4-2.4)	5.6	0.221
Chloride level at presentation (normal 95-110 mmol/L)	98.5 (96.8-102)	101 (100-103)	0.003*
Potassium level at presentation (normal 3.5-5.1 mmol/L)	4 (3.8-4.3)	4 (3.8-4.2)	0.416

Table IV. Continued

	Group I complicated acute appendicitis (n=31) median (IQR)	Group II non-complicated acute appendicitis (n=131) median (IQR)	p value
Creatinine level at presentation (normal 39-60 mcmol/L)	45 (32-50)	40 (35-46)	0.568
BUN level at presentation (normal 1.8-6.4 mmol/L)	3.4 (2.7-3.9)	3.6 (2.9-4.2)	0.267
The glucose level at presentation (3.3-5.6 mmol/L)	6.3 (4.8-7.2)	5.6 (5-6.4)	0.286

*Statistically significant at a 5% level of significance the medians are equal but with different distributions (the means are 135.5 and 137.5)
IQR: Interquartile range, WBC: White blood cell, BUN: Blood urea nitrogen

Table V. Sodium level correlation with the severity of acute appendicitis

	Na level pre-op median (IQR)	p value
Group I complicated acute appendicitis (n=31)	137 (133-138)	0.011*
Group II non-complicated acute appendicitis (n=131)	137 (136-139)	

*Statistically significant at the 5% level of significance
IQR: Interquartile range

Table VI. Hyponatremia correlation with the severity of acute appendicitis

	Hyponatremia				
	Yes (n=25) n (%)	No (n=137) n (%)	p value	OR	[95% CI]
Group I complicated acute appendicitis (n=31)	11 (35.5)	20 (64.5)	0.001*	4.60	[1.83-11.55]
Group II non-complicated acute appendicitis (n=131)	14 (10.7)	117 (89.3)			

*Statistically significant at the 5% level of significance
OR: Odds ratio, CI: Confidence interval

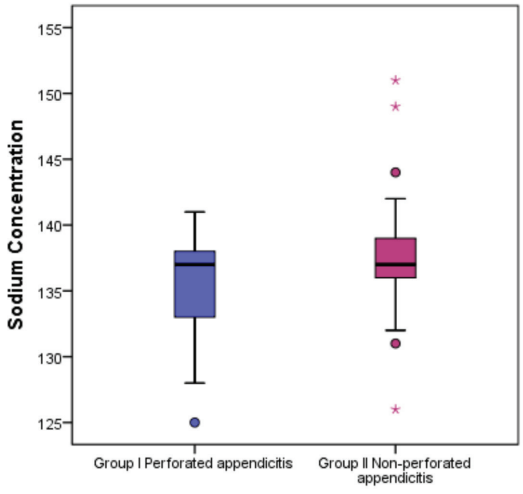


Figure 2. Box and Whisker Plot Diagram, Representing Sodium Concentration by Grouping of Acute Appendicitis

Table VII. Radiological diagnostic modalities

	n (%)
US	
Performed and diagnostic	98 (60.5)
Performed but non-diagnostic	54 (33.3)
Not performed	10 (6.2)
CT	
Performed and diagnostic	29 (17.9)
Performed but non-diagnostic	44 (27.2)
Not performed	89 (54.9)
Non-complicated acute appendicitis (radiologically)*	133 (82.1)
Complicated acute appendicitis (radiologically)*	17 (10.5)

*Diagnostic radiological findings (n=150); other patients were either clinically diagnosed or the US could not visualize the appendix and diagnosis was based on our clinical findings (n=12)
US: Ultrasound, CT: Computed tomography

Table VIII. Intra-operative findings+complications	
n (stand for number)	**n (%)**
Non-perforated	134 (82.7)
Perforated	28 (17.3)
Appendiceal mass	4 (2.5)
Adjacent bowel injury	0 (0.0)
Bleeding	3 (1.9)

Discussion

Patients diagnosed with CAA throughout the study period were the focus of this study. Individuals with low serum sodium levels were the primary focus of this study. Urgent medical attention is required in cases of acute appendicitis, the leading cause of abdominal pain (7). There is a peak occurrence between the ages of 10 and 30, and the lifetime chance of suffering acute appendicitis is 7% according to studies (8,9). Recent studies have shown that complex appendicitis is associated with low blood-salt levels. Nevertheless, it is still not known what causes hyponatremia in people with CAA (3,4,10).

Acute appendicitis is a common surgical emergency associated with several complications if left untreated. According to recent research examining this possibility, hyponatremia may serve as a diagnostic indicator of CAA, according to recent research which has looked at this possibility (11). Patients with preoperative hyponatremia have an increased risk of CAA (12). Additionally, another study showed that individuals with CAA had lower blood sodium levels (13). Therefore, monitoring sodium levels can help determine the probability of complications in those individuals with acute appendicitis. It is vital to remember that hyponatremia can also result from several other illnesses such as primary bacterial peritonitis (14). In order to choose the best course of action, it is necessary to determine the underlying cause of the low serum sodium levels. The diagnosis of acute appendicitis using CT scan was shown to have a sensitivity of 98.6% and a specificity of 3.4%, while US had a sensitivity of 70.5% and a specificity of 36.8% (15).

A review of the literature revealed strong evidence linking blood sodium levels to the development of CAA (1). Hyponatremia may be worsened by additional risk factors in adulthood, such as certain medications and comorbidities, which can increase the effect of complex appendicitis on blood sodium levels (16). Hyponatremia in appendicitis has no recognized etiology; however, interleukin-6 has been suggested to play a role (17). An extensive literature review revealed that most studies examining the link between hyponatremia and intricate appendicitis have concentrated on adults or children, implying that this specific occurrence has not been thoroughly investigated in previous studies (18,19). Our investigation revealed that those individuals with histologically proven CAA were more likely to have hyponatremia, with a cut-off value of 135 meq/L. Another study found a clear link between the two (2).

Our study may help evaluate the risks of delaying surgical intervention, recognizing the burden of CAA, and using hyponatremia as a diagnostic indicator for complex situations in children. Acute appendicitis is a common and challenging condition to manage owing to its complicated nature. Identifying more markers to help in diagnosis would be advantageous because a more complicated condition may significantly harm the patient.

Study Limitations

It is important to acknowledge the limitations of this study, such as its retrospective design, which depended on pre-existing medical information, and its small sample size. Further prospective, well-designed studies are required in order to evaluate and enhance the accuracy of hyponatremia in predicting CAA.

Conclusion

The findings of the current study add to what is already known regarding the identification and treatment of acute appendicitis. According to this study, hyponatremia may be a useful physiological biochemical indicator of CAA. These findings are in line with a recent systematic review which examined the same issue; thus, it seems that this topic deserves further research. In addition, a correlation between hyponatremia and CAA was shown in this study. Medical and surgical professionals may help improve patient outcomes in CAA by identifying hyponatremia early and responding appropriately, leading to more focused and successful treatment approaches.

Ethics

Ethics Committee Approval: Ethical permission was obtained from The Prince Sultan Military Medical City (Ethical Board Committee) accepted our study (IRB approval no.: E-2130).

Informed Consent: Informed consent not applicable in this study as such study is not requiring patients consent.

Authorship Contributions

Surgical and Medical Practices: A.A.A., J.A.-H., A.M.Z., Concept: A.A.A., J.A.-H., Design: A.A.A., J.A.-H., Data

Collection and/or Processing: A.A.A., A.M.Z., N.M.A.-H., S.A.A., M.A.H., O.K.A.-H., N.A.A., Literature Search: A.A.A., J.A.-H., A.M.Z., N.M.A.-H., S.A.A., M.A.H., O.K.A.-H., N.A.A., Writing: A.A.A., J.A.-H., A.M.Z.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Giannis D, Matenoglou E, Moris D. Hyponatremia as a marker of complicated appendicitis: A systematic review. Surgeon. 2020; 18:295-304.
2. Kim DY, Nassiri N, de Virgilio C, et al. Association Between Hyponatremia and Complicated Appendicitis. JAMA Surg. 2015; 150:911-2.
3. Sheen J, Bowen J, Whitmore H, Bowling K. Hyponatremia as a Marker of Complicated Appendicitis: A Retrospective Analysis. Cureus. 2022; 14:e26672.
4. Anand S, Krishnan N, Birley JR, Tintor G, Bajpai M, Pogorelić Z. Hyponatremia-A New Diagnostic Marker for Complicated Acute Appendicitis in Children: A Systematic Review and Meta-Analysis. Children (Basel). 2022; 9:1070.
5. Gosain A, Williams RF, Blakely ML. Distinguishing acute from ruptured appendicitis preoperatively in the pediatric patient. Adv Surg. 2010; 44:73-85.
6. Shuaib A, Alhamdan N, Arian H, Sallam MA, Shuaib A. Hyperbilirubinemia and Hyponatremia as Predictors of Complicated Appendicitis. Med Sci (Basel). 2022; 10:36.
7. Di Saverio S, Podda M, De Simone B, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020; 15:27.
8. Krzyzak M, Mulrooney SM. Acute Appendicitis Review: Background, Epidemiology, Diagnosis, and Treatment. Cureus. 2020; 12:e8562.
9. Liang MK, Andersson RE, Jaffe BM, Berger DH. The Appendix. In: Brunicardi F, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE. eds. Schwartz's Principles of Surgery, 10e. McGraw-Hill Education; 2015.
10. Pogorelić Z, Lukšić B, Ninčević S, Lukšić B, Polašek O. Hyponatremia as a predictor of perforated acute appendicitis in pediatric population: A prospective study. J Pediatr Surg. 2021; 56:1816-21.
11. Symeonidis NG, Pavlidis ET, Psarras KK, et al. Preoperative Hyponatremia Indicates Complicated Acute Appendicitis. Surg Res Pract. 2022; 2022:1836754.
12. Poston LM, Leavitt T, Pope S, et al. Pre-appendectomy hyponatremia is associated with increased rates of complicated appendicitis. Surg Open Sci. 2023; 13:88-93.
13. Ozdemir DB, Karayigit A, Dizen H, et al. Role of hyponatremia in differentiating complicated appendicitis from uncomplicated appendicitis: a comparative study. Eur Rev Med Pharmacol Sci. 2022; 26:8057-63.
14. Ameer MA, Foris LA, Mandiga P, Haseeb M. Spontaneous Bacterial Peritonitis. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
15. Alnuaymah F, Etonyeaku AC, Alsaeed HS, et al. Clinical, Radiological and Pathological Appraisal of Acute Appendicitis in Al Qassim, Saudi Arabia: A Single-Center Retrospective Analysis. Cureus. 2022; 14:e28627.
16. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. Intern Med J. 2010; 40:574-80.
17. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013; 56:519-22.
18. Turhan VB, Ünsal A, Öztürk B, Öztürk D, Buluş H. Predictive value of serum sodium level in determining perforated appendicitis. Ulus Travma Acil Cerrahi Derg. 2022; 28:290-5.
19. Lindestam U, Almström M, Jacks J, et al. Low Plasma Sodium Concentration Predicts Perforated Acute Appendicitis in Children: A Prospective Diagnostic Accuracy Study. Eur J Pediatr Surg. 2020; 30:350-6.

J Pediatr Res 2024;11(3):149-54
DOI: 10.4274/jpr.galenos.2024.83669

Original Article

Germ Cell Neoplasms of Sacrococcygeal Region: Clinical Characteristics, Outcomes and Analysis of Recurrence after Treatment; A Comprehensive 20-Year Single Center Study

Samir Hasan, Ülgen Çeltik, Gözde Şakul, Ahmet Çelik, Mustafa Orkan Ergün

Ege University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Turkey

ABSTRACT

Aim: This study aimed to evaluate the clinical characteristics and outcomes of recurrent sacrococcygeal germ cell tumors (SC-GCTs).

Materials and Methods: This study was conducted with patients diagnosed with SC-GCTs between 2002 and 2022. Epidemiology, diagnostic and treatment methods, anatomic/histopathological classifications and recurrence were evaluated.

Results: This study included 55 patients (Female/Male: 45/10). According to Altman's-classification, 16 patients (29.1%) were Type I, 14 (25.5%) Type II, 12 (21.8%) Type III and 13 (23.6%) Type IV. Histologically, 69.1% of the lesions were mature teratomas, 14.5% were immature teratomas, and 16.4% were malignant teratomas. Eleven patients developed recurrent sacrococcygeal teratoma (recurrence age: 5 months-12 years). According to Altman's classification, 2/11 patients were Type II, 5/11 patients were Type III, and 4/11 patients were Type IV. The pathological results of the original tumors were mature teratoma in 4/11 patients, immature teratoma in 4/11 patients, and malignant teratoma in 3/11 patients. Malignant relapse with yolk sac tumor was detected in 6/11 patients, mature teratoma in 4/11 patients, and immature teratoma in 1/11 patients.

Conclusion: The risk of malignancy increases with age and Altman's Type III and IV. Recurrent tumors may have different histopathological types from the original tumor. The risk of recurrence as a malignant tumor after immature teratomas was higher than mature teratomas.

Keywords: Sacrococcygeal teratoma, recurrence, malignant teratoma

Introduction

Teratomas arise from germ cells or other totipotent cells (1-3). Primordial germ cells (PGCs) appear during the third week of gestation in the yolk sac wall near the allantois. They move along the dorsal mesentery of the hindgut, reaching the genital ridges by about the sixth week of gestation. A disturbed migration of PGCs results in misplacement at different sites in the body's midline. Extragonadal germ cell tumors (EGCT) are believed to develop after the malignant transformation of the residual PGCs (4). In another embryologic theory, sacrococcygeal teratomas (SCTs) develop at the base of the coccyx and are thought to be derived from Hensen's node (primitive knot) (5).

The incidence of SCT is approximately 1:27,000 (5) to 1:40,000 (6,7) live births. SCT is a rare tumor; however, it is still the most common fetal neoplasm and most common germ cell tumor (GCT) in infancy and early childhood (8).

Address for Correspondence
Mustafa Orkan Ergün, Ege University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Turkey
Phone: +90 532 412 53 43 **E-mail:** orkan.ergun@gmail.com **ORCID:** orcid.org/0000-0003-4046-3782
Received: 24.02.2024 **Accepted:** 31.07.2024

The patients can be classified anatomically by Altman's classification into 4 types (Type I: fully external, Type II: mainly external, Type III: mainly internal, Type IV: fully internal) (9), and histologically as mature, immature or malignant teratomas (1).

For decades, the diagnosis and treatment of SCTs have progressed and become standardized, and good prognosis is usually achieved. Nevertheless, increasing recurrent cases with poor survival rates have become a major challenge. Incomplete resection, tumor spillage, and residual coccyx have been identified as the main risk factors for recurrence. Previously published series have reported 2% to 35% recurrence rates (10,11).

This article aims to clarify any special characteristics in the history, clinical presentation, and outcomes of recurrent SC-GCTs.

Materials and Methods

This study was carried out in a pediatric surgery department in concordance with international ethical standards and the World Health Organization's Helsinki Declaration. This study was approved by the Ege University Faculty of Medicine, Medical Research Ethics Committee (approval no.: 20-11T/4) and informed consent was obtained for all subjects.

This study was performed retrospectively and included all SC-GCTs in a single center. The pertinent clinical information and available pathologic data were collected from 55 patients with germ cell neoplasms of the sacrococcygeal area from 2002 to 2022.

The demographics, time of diagnosis, clinical complaints and associated malformations were reviewed. Preoperative alpha-fetoprotein (AFP) levels were evaluated according to reference values according to the patients' ages (12). Radiological images were examined, and the patients were assigned into 4 groups according to Altman's classification (9). Surgical techniques, pathological results, and postoperative follow-up period were also investigated.

Those patients with recurrent diseases were evaluated. Time to recurrence, the predictive value of the level of AFP, and the role of magnetic resonance imaging (MRI) in diagnosing recurrent SC-GCTs and long-term outcomes were included in this study. Possible risk factors for recurrence were also evaluated. Statistical analyses were performed using the SPSS Statistics 26.0 version, including Pearson's chi-square test, ANOVA test, and the post-hoc test. A p value of <0.05 was considered statistically significant.

Results

This study included 55 patients with SC-GCTs treated at our center. There were 10 males and 45 females with a male-to-female ratio of 1 to 4.5.

Routine maternal ultrasonic examination identified the lesions prenatally in 19/55 patients. Fourteen patients were diagnosed at birth, and 10 patients were diagnosed in the infantile period. Twelve of 55 patients presented beyond the neonatal or infantile period. Most of the patients presented with sacrococcygeal mass (61%). The presentation symptoms and associated anomalies are given in Table I according to the patients' ages.

Detailed radiological examinations were made by ultrasonography (USG) (31/55 patients), MRI (44/55 patients), and computed tomography (CT) (4/55 patients). AFP levels ranged from 1- 455.075 ng/mL (mean: 58.560). Seven patients had higher AFP levels relative to nomograms according to their age.

Table I. Demographics and clinical status of the patients

Age at diagnosis	No of patients	Sex (M/F)	Clinical complaint	Associated anomalies
Prenatal	19 (34.5%)	3/16	Incidental sacrococcygeal mass in routine maternal USG No hydrops fetalis was detected	Meningocele 5.2% (1/19) ASD 5.2% (1/19)
0-28 days	14 (23.7%)	2/12	Sacrococcygeal mass	Currarino triad 7.1% (1/14)
29 days-1 year	3 (7.3%)	2/1	Swelling in the Sacrococcygeal area 66.6% (2/3) Constipation 33.3% (1/3)	Currarino triad 33.3% (1/3)
>1 year	19 (34.5%)	3/16	Constipation 42% (8/19) Swelling in the Sacrococcygeal area 15.7% (3/19) Weakness in the lower extremities 10.5% (2/19) Bruising in the genital area 10.5% (2/19) Difficulty in urination 15.7% (3/19) Frequent urination 5.2% (1/19)	Rectal duplication cyst (1/19) Currarino triad 5.2% (1/19) Anal stenosis 10.5% (2/19)

M/F: Male/Female, USG: Ultrasonography, ASD: Atrial septal defect

Sixteen (29.1%) patients were Altman Type I, 14 (25.5%) were Type II, 12 (21.8%) were Type III, and 13 (23.6%) were Type IV. Surgical resection was performed on all patients. The posterior sacrococcygeal approach was performed in 45 patients; 3 patients required an abdominal approach, and 7 patients required both. The surgical margins were free of tumor in the first operation in all patients.

Pathological examinations were reported as mature teratomas in 38 (69.1%), immature teratomas in 8 (14.5%), and malignant teratomas in 9 (16.4%) patients. Yolk sac tumor (YST) was detected in all malignant teratomas. The histopathological results are depicted in Table II and they are also grouped based on their preoperative Altman classifications.

One patient was referred to our clinic after having primary surgery elsewhere (a neurosurgeon had operated on this patient with a pre-diagnosis of meningomyelocele). However, the tissue biopsy performed intraoperatively revealed a yolk sac teratoma, and the patient was referred to our institution.

The patients were evaluated using the ANOVA test based on their Altman classifications and pathology results. A statistically significant relationship was found between the Altman classification and the pathology outcome (p=0.001). The risk of malignancy in Types III and IV according to the Altman classification was higher compared to Type I and II. It was 33.3% in Type III and 38.4 % in Type IV.

A post-hoc test was conducted to determine between which groups significant statistical differences existed. In this test, every Altman's type was compared with the other Altman's types. While no significant deference was found between Types I and II, and similarly between Types III and IV, significant differences were found when comparing Type I with Types III and IV, and also Type II with Types III and IV (Table III).

Adjuvant chemotherapy was given postoperatively in high-grade immature teratomas and malignant teratomas. Combinations of cisplatin, etoposide, and bleomycin (BEP) or carboplatin, etoposide, and bleomycin (JEb) were administered.

In the long-term follow-up period, recurrent disease developed in eleven patients (20%). The diagnosis of original tumor in these 11 patients was made prenatally in 4, at birth in 6 patients, and at the age of 11 in one patient. According to Altman's classification, 2 of these patients were Type II, 5 were Type III, and 4 were Type IV. All of these patients were treated with primary surgery. In 2 patients, chemotherapy was given after the excision of the primary tumor. The pathological results of the original tumors were mature teratoma in 4, immature teratoma in 4, and malignant teratoma in 3 patients (YST). The median follow-up period at recurrence was 29 months (5 months-12 years). Four patients were diagnosed with palpable sacrococcygeal masses by physical examination during routine follow-up. Five cases did not have abnormal signs or symptoms, but serum AFP levels were elevated. In total, the serum levels of AFP were elevated in most of the recurrent patients, but not in all (9/11). Among those with elevated AFP levels, the range was between 5,243 and 58,745. One patient had recurrent urinary infections and the remaining one patient had constipation and weakness in the lower extremity. All of these patients underwent USG and MRI examinations.

Pathological examination revealed malignant relapse with YST in 6 patients (Table III). The recurrence was local in 10 patients, and in one patient, it was combined with distal metastatic lesions in the liver and lungs; all coccyges had been previously removed during the primary surgeries. All 11 recurrent cases received a second operation, and the tumors were removed completely.

The recurrence rate in mature teratomas was 13.1% (5/38) with a 40% malignancy rate while the recurrence rate in immature teratomas was 50% (4/8) with a 75% malignancy rate. The recurrence of mature teratoma after malignant teratoma was detected in one patient (Table IV).

Most of the recurrence occurred in the first 2 years of life (72.7%; 8/11) but the risk of recurrence continues into older ages (12 years in this series) as the recurrence of a mature teratoma at 12 years of age was observed (8).

During this study, one patient with malignant SCT and a recurrence of malignant SCT with distal metastatic lesions died.

We examined the relationship between the clinical characteristics of patients and recurrent tumors in Table V below. Only the pathology of the primary tumor showed a statistically significant relationship (p=0.02).

Table II. Altman's classification of diagnosis and histology after surgery

	Type I	Type II	Type III	Type IV	Total	p value
Mature	15	12	5	6	38 (69.1%)	
Immature	1	2	3	2	8 (14.5%)	0.001
Malignant	0	0	4	5	9 (16.4%)	
Total	16 (29.1%)	14 (25.5%)	12 (21.8%)	13 (23.6%)	55	

Table III. Comparison of Altman's groups

Altman's Type		p value
Type I	Type II	0.742
	Type III	0.001*
	Type IV	0.001*
Type II	Type I	0.742
	Type III	0.005*
	Type IV	0.004*
Type III	Type I	0.001*
	Type II	0.005*
	Type IV	0.981
Type IV	Type I	0.001*
	Type II	0.004*
	Type III	0.981

Table IV. Histology of SCTs at original operation and recurrent operation

Histology before recurrence	Number of patients	Histology after recurrence			Malignant recurrence rate
		Mature	Immature	Malignant	
Mature	38	3	0	2	5% (2/38)
Immature	8	0	1	3	37.5% (3/8)
Malignant	9	1	0	1	11.1% (1/9)
Total	55	4	1	6	10.9% (6/55)

SCTs: Sacrococcygeal teratomas

Table V. The relationships between the malignant recurrence and clinical features

		Number of patients	Number of malignant recurrent patients	p value
Sex	Male	10	2	0.29
	Female	45	4	
Histology before recurrence	Mature	38	2	0.02*
	Immature	8	3	
	Malignant	9	1	
Operation age	0-28 days	33	4	0.72
	28 days-1 year	3	1	
	>1 year	19	1	
Altman's classification	Type I	16	0	0.82
	Type II	14	2	
	Type III	12	3	
	Type IV	13	1	

Discussion

SCT is a rare EGCT mostly diagnosed prenatally, during infancy or in early childhood. Neonatal SCTs are mostly mature but can also contain immature and/or malignant components.

Our study included 55 patients with SC-GCTs treated at our center. The male-to-female ratio was 1 to 4.5, which is lower than rates reported in the literature (1:3-4) (4,13). The predominant occurrence in one gender lacks a definitive explanation.

The prenatal diagnosis detection rates have increased in recent years with the routine use of maternal USG. Fetal MRI can also be used to provide more detailed anatomical information.

In those patients who are not diagnosed prenatally, the most common presenting cause was the finding of a sacral mass, followed by intrapelvic organ compression symptoms such as constipation, frequent urination or difficulty in urination and weakness in the lower extremities causing repetitive falling or an inability to walk in the current series which is compatible with the literature (5).

In our study, 29.1% of the patients were Type I, 25.5% were Type II, 21.8% were Type III and 23.8% were Type IV according to Altman's classification. Type III and Type IV rates were higher in our series than in the literature (14) most probably due to the referral of those complicated cases from other centers.

There are several factors described in the literature which can increase the risk of recurrence after resection: gross or microscopic incomplete resection, failure to respect the coccyx, and tumor rupture or spillage before or during surgery (4). The recurrence rate after mature teratoma was 13.1%, while it was 50% after immature teratoma. Also, the recurrence of malignant teratoma after an immature teratoma was higher (75%; 3/4) compared to mature teratoma. De Backer et al. (15) and Hager et al. (16) showed that incomplete resection is not the only contributing factor accounting for the development of a malignant recurrence. As most SCTs are composed of cells of different origins and differentiation status in a complex histological pattern, overlooking small areas with YST during pathological assessment has been put forward as being a possible explanation for malignant recurrences after teratomas diagnosed initially as mature.

The risk of malignancy increases with age. While most mature and immature teratomas were diagnosed prenatally, at birth, or in the neonatal period, the mean time of diagnosing malignant teratomas was 16 months. This finding supports Biskup et al.'s (17) theory which suggests that mature teratoma cells have the potential to undergo malignant transformation, meaning that a mature SCT which is not resected or not radically resected may eventually present as a somatic type malignancy.

Derikx JP et al. (18) have also suggested the development of YST directly from the teratoma via malignant transformation, while others suggest that microscopic YST foci present in the previous teratoma, if not recognized initially, ultimately predominate in the recurrent tumor (19-21)

The risk of malignancy in Types III and IV according to Altman's classification was higher compared to Types I and II. This finding can be explained by the relatively late diagnosis of those types.

During conventional follow-up, recurrences are detected by physical examination, imaging techniques such as MRI, CT, or US, and the measurement of serum markers. The serum level of AFP (secreted by YST cells) was elevated in most of the recurrent patients, but not in all (9/11). Therefore, serum AFP levels are an important determinant, but alone are not sufficient to diagnose the recurrence of SCTs (in another study, AFP levels had a 75% sensitivity and 96% specificity in diagnosing recurrent patients (22). The history of the patients, the clinical examination findings and the radiologic imaging findings are important in identifying recurrent patients. In our study, MRI was the gold standard diagnostic method.

Recurrent tumors may have a different histopathological type than the original tumor. The risk of recurrence as a malignant tumor after immature teratomas were higher than the mature teratomas (75% vs. 40%); and also, a case of recurrent mature teratoma after malignant teratoma has been reported (4,18).

The most malignant element is the YST. Rarely, these tumors may include another malignant component, usually embryonal carcinoma, or even more rarely a non-germ cell/somatic malignant component such as primitive neuroectodermal tumor (23).

According to our study and the literature (2), most of the recurrent SCTs occur within the first 2 years (in our study 8/11); however, because of the continued risk of recurrence, we recommend following up these patients at least up to the age of 6 years.

In earlier studies of GCTs, the survival of children with SC-GCT was very poor (24,25). This site is no longer considered to be associated with poor survival in more recent reports since the introduction of the platinum-based regimen and progress in surgery (13). In our study, the mortality rate was approximately 1.8% (1/55). In the German review, the only significant prognostic factors in SC-GCT appeared to be the presence of multiorgan distant metastases, but neither stage, extent of metastasis, bone involvement, or serum AFP were identified as prognostic factors (26). Our study is consistent with this finding. During this study, we lost one patient with malignant SCT and a recurrence of malignant SCT with distant metastatic lesions.

Study Limitations

One limitation of the present study was the retrospective nature of the data. Additionally, all procedures were conducted at a single institution, and the number of patients was limited, allowing for descriptive, rather than comparative analyses.

Conclusion

The risk of malignancy increases with age and Altman's Type III and IV. Recurrent tumors may have different histopathological types from the original tumor. The risk of recurrence as a malignant tumor after immature teratomas was higher than for mature teratomas.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine, Medical Research Ethics Committee (approval no.: 20-11T/4).

Informed Consent: Informed consent was obtained for all subjects.

Authorship Contributions

Surgical and Medical Practices: Ü.Ç., A.Ç., M.O.E., Concept: M.O.E., Design: S.H., Ü.Ç., M.O.E., Data Collection and/or Processing: S.H., G.S., Analysis or Interpretation: S.H., Ü.Ç., G.S., A.Ç., M.O.E., Literature Search: S.H., Writing: S.H., Ü.Ç.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Conklin J, Abell MR. Germ cell neoplasms of sacrococcygeal region. Cancer. 1967; 20:2105-17.
2. Chen SH, Du CJ, Lai JY, et al. Malignant sacrococcygeal germ cell tumors in children in Taiwan: A retrospective single-center case series. Medicine (Baltimore). 2021; 100:e24323.
3. De Corti F, Sarnacki S, Patte C, et al. Prognosis of malignant sacrococcygeal germ cell tumours according to their natural history and surgical management. Surg Oncol. 2012; 21:e31-7.
4. Kops AL, Hulsker CC, Fiocco M, et al. Malignant recurrence after mature Sacrococcygeal teratoma: A meta-analysis and review of the literature. Crit Rev Oncol Hematol. 2020; 156:103140.
5. Yoon HM, Byeon SJ, Hwang JY, et al. Sacrococcygeal teratomas in newborns: a comprehensive review for the radiologists. Acta Radiol. 2018; 59:236-46.
6. Yoshida M, Matsuoka K, Nakazawa A, et al. Sacrococcygeal yolk sac tumor developing after teratoma: a clinicopathological study of pediatric sacrococcygeal germ cell tumors and a proposal of the pathogenesis of sacrococcygeal yolk sac tumors. J Pediatr Surg. 2013; 48:776-81.
7. Wang Y, Wu Y, Wang L, Yuan X, Jiang M, Li Y. Analysis of Recurrent Sacrococcygeal Teratoma in Children: Clinical Features, Relapse Risks, and Anorectal Functional Sequelae. Med Sci Monit. 2017; 23:17-23.
8. Yao W, Li K, Zheng S, Dong K, Xiao X. Analysis of recurrence risks for sacrococcygeal teratoma in children. J Pediatr Surg. 2014; 49:1839-42.
9. Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey-1973. J Pediatr Surg. 1974; 9:389-98.
10. De Backer A, Madern GC, Hakvoort-Cammel FG, Haentjens P, Oosterhuis JW, Hazebroek FW. Study of the factors associated with recurrence in children with sacrococcygeal teratoma. J Pediatr Surg. 2006; 41:173-81.
11. Derikx JPM, De Backer A, Van De Schoot L, et al. Factors associated with recurrence and metastasis in sacrococcygeal teratoma. Br J Surg. 2006; 93:1543-8.
12. Blohm ME, Vesterling-Hörner D, Calaminus G, Göbel U. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol. 1998; 15:135-42.
13. De Corti F, Sarnacki S, Patte C, et al. Prognosis of malignant sacrococcygeal germ cell tumours according to their natural history and surgical management. Surg Oncol. 2012; 21:e31-7.
14. Niramis R, Anuntkosol M, Buranakitjaroen V, et al. Long-Term Outcomes of Sacrococcygeal Germ Cell Tumors in Infancy and Childhood. Surg Res Pract. 2015; 2015:398549.
15. De Backer A, Madern GC, Hakvoort-Cammel FG, Haentjens P, Oosterhuis JW, Hazebroek FW. Study of the factors associated with recurrence in children with sacrococcygeal teratoma. J Pediatr Surg. 2006; 41:173-81.
16. Hager T, Sergi C, Hager J. Sacrococcygeal teratoma - A single center study of 43 years (1968-2011) including follow-up data and histopathological reevaluation of specimens. Eur Surg - Acta Chir Austriaca [Internet]. 2012 Aug 10 [cited 2021 May 21];44(4):255–66. Available from: https://link.springer.com/article/10.1007/s10353-012-0098-3
17. Biskup W, Calaminus G, Schneider DT, Leuschner I, Göbel U. Teratoma with malignant transformation: experiences of the cooperative GPOH protocols MAKEI 83/86/89/96. Klin Padiatr. 2006; 218:303-8.
18. Derikx JPM, De Backer A, Van De Schoot L, et al. Factors associated with recurrence and metastasis in sacrococcygeal teratoma. Br J Surg. 2006; 93:1543-8.
19. Rescorla FJ, Sawin RS, Coran AG, Dillon PW, Azizkhan RG. Long-term outcome for infants and children with sacrococcygeal teratoma: a report from the Childrens Cancer Group. J Pediatr Surg. 1998; 33:171-6.
20. Lo Curto M, D'Angelo P, Cecchetto G, et al. Mature and immature teratomas: results of the first paediatric Italian study. Pediatr Surg Int. 2007; 23:315-22.
21. Hawkins E, Issacs H, Cushing B, Rogers P. Occult malignancy in neonatal sacrococcygeal teratomas. A report from a Combined Pediatric Oncology Group and Children's Cancer Group study. Am J Pediatr Hematol Oncol. 1993; 15:406-9.
22. van Heurn LJ, Knipscheer MM, Derikx JPM, van Heurn LWE. Diagnostic accuracy of serum alpha-fetoprotein levels in diagnosing recurrent sacrococcygeal teratoma: A systematic review. J Pediatr Surg. 2020; 55:1732-9.
23. D'Angelo P, De Pasquale MD, Barretta F, et al. Malignant sacrococcygeal germ cell tumors in childhood: The Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) experience. Pediatr Blood Cancer. 2021; 68:e28812.
24. Baranzelli MC, Flamant F, De Lumley L, Le Gall E, Lejars O. Treatment of non-metastatic, non-seminomatous malignant germ-cell tumours in childhood: experience of the "Société Française d'Oncologie Pédiatrique" MGCT 1985-1989 study. Med Pediatr Oncol. 1993; 21:395-401.
25. Malignant germ cell tumors in 57 children and adolescents - Brodeur - 1981 - Cancer - Wiley Online Library [Internet]. [cited 2021 May 21]. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/1097-0142(19811015)48:8%3C1890::AID-CNCR2820480830%3E3.0.CO;2-D
26. Calaminus G, Schneider DT, Bökkerink JPM, et al. Prognostic value of tumor size, metastases, extension into bone, and increased tumor marker in children with malignant sacrococcygeal germ cell tumors: a prospective evaluation of 71 patients treated in the German cooperative protocols Maligne Keimzelltumoren (MAKEI) 83/86 and MAKEI 89. J Clin Oncol. 2003; 21:781-6.

J Pediatr Res 2024;11(3):155-63
DOI: 10.4274/jpr.galenos.2024.65481

Original Article

Evaluation of Permanent Tooth Development in Pediatric Cancer Survivors: A Single Center Experience

Nurşah Eker[1], Orkun Dinç[1], Narmin Asadova[2], Ali Mentes[2], Dilek Gül[3], Beste Atasoy[3], Alican Sarısaltık[4], Gülnur Tokuç[1]

[1]Marmara University Faculty of Medicine, Department of Pediatric Hematology Oncology, İstanbul, Turkey
[2]Marmara University Faculty of Dentistry, Department of Pediatric Dentistry, İstanbul, Turkey
[3]Marmara University Faculty of Medicine, Department of Radiation Oncology, İstanbul, Turkey
[4]Republic of Turkey Ministry of Health, Çayırova District Health Directorate, Kocaeli, Turkey

ABSTRACT

Aim: Childhood cancer survival has improved significantly with advances in multimodal treatment. However, treatment-related long-term side effects, including dental developmental abnormalities, remain a concern. The aim of this study was to investigate permanent tooth development and associated risk factors in childhood cancer survivors who were treated before the age of six years, focusing on non-leukemia cases.

Materials and Methods: This study was conducted on childhood cancer cases treated with chemotherapy and/or radiotherapy at a single center. Patients diagnosed before the age of six and who were twelve or above at the time of assessment were included. Dental examinations, including Decayed, Missing, Filled Teeth index and radiographic assessments, were performed. Statistical analyses were performed in order to identify associations between treatment modalities and dental findings.

Results: Of 914 patients, 90 met the inclusion criteria, with 35 participating in this study. The mean age at diagnosis was four years, with a mean follow-up duration of ten years. Root shortening, hypoplasia, and hypodontia were observed to be common dental anomalies. There was a significant association between alkylating agents, vinca alkaloid plus alkylating agents and root shortening ($p<0.001$, $p<0.001$). No significant differences in dental findings were found based on gender, tumor site, or other treatment modalities ($p<0.05$). As the age at diagnosis increased, the risk of root shortening ($p=0.026$) and the frequency of hypodontia significantly increased with the duration after diagnosis ($p=0.048$).

Conclusion: Childhood cancer survivors treated during early dentition periods are at risk of dental developmental anomalies, with alkylating agents showing the most significant impact. This emphasizes the necessity of providing these patients and their families with information on the importance of maintaining oral and dental health during and after cancer treatment.

Keywords: Childhood, cancer, dental health

Introduction

Survival rates in childhood cancers are increasing due to evolving multimodal treatments, reaching up to 80% in 5-year survival rates. The significance of addressing treatment-related secondary and long-term side effects is increasing due to their impact on the quality of life of these patients. The long-term effects of cancer treatment can vary depending on the specific cancer subtype and the type

Address for Correspondence
Nurşah Eker, Marmara University Faculty of Medicine, Department of Pediatric Hematology Oncology, İstanbul, Turkey
Phone: +90 505 689 14 84 **E-mail:** nursaheker@hotmail.com **ORCID:** orcid.org/0000-0002-7707-3035
Received: 22.04.2024 **Accepted:** 14.08.2024

of treatment received. These effects can include endocrine, cardiac, and neurocognitive impairments, as well as an increased risk of developing secondary malignancies (1). Furthermore, adverse effects on dental development can also occur in the long term in childhood cancer survivors (2). In addition to the adverse effects of both chemotherapy and radiotherapy, nutritional disorders during intensive treatment periods, decreased saliva secretion, recurrent oral mucositis, and gingivitis attacks can negatively impact oral and dental development (3,4). Dental agenesis and caries, enamel hypoplasia, root development anomalies, and microdontia are some of the developmental anomalies which have been observed in this population (5,6). The period of infancy, during which dental stem cell proliferation is most effective, appears to exhibit a more pronounced effect in those children who have undergone cancer treatment (7). A review of the literature reveals that cancer treatment has a negative impact on dental development, with the age at which the treatment is received being identified as the most important factor (8). The majority of studies conducted have focused on cases diagnosed with acute lymphoblastic leukemia, which is the most common cancers in childhood (9-12).

This study differs from the previous literature in that it aimed to eliminate the age factor and include non-leukemia childhood cancer survivors who were treated before the age of six. The objective was to ascertain the impact of cancer treatment on permanent tooth development and identify risk factors affecting dental development in these cases after the age of 12, with a single center approach.

Materials and Methods

A retrospective evaluation was conducted on cases diagnosed with non-leukemia childhood cancer and treated with chemotherapy and/or radiotherapy at our center from January 2010. Cases with a cancer diagnosis at an age of six years or below were selected. This study included cases where the patients were aged 12 or above at the time of the study. Prior to undergoing dental and radiographic examination, all patients and their parents or caregivers provided written informed consent. The oral examination entailed the assessment of the Decayed, Missing, Filled Teeth (DMFT) index, developmental enamel and/or dentin defects including hypoplasia, hypodontia, and dental crowding. The examinations were performed by a single pediatric dentist in a standard dental setting. Panoramic radiographs were taken to investigate the presence of agenesis, supernumerary or impacted teeth, pulp chamber enlargement, calcification, alterations in root morphology alterations (shortening and dilaceration) and disturbances in tooth eruption. The demographic characteristics of the included cases, as well as their cancer diagnosis, chemotherapeutic drugs received, radiotherapy (if received), and radiotherapy site and dose were obtained from the data files. The potential impact of anticancer treatments on dental development was evaluated, with a focus on identifying any associated risk factors. Cases diagnosed at an age of six years or above, aged below 12 years during the study period, diagnosed with leukemia, or those who did not provide consent for participation were excluded from this study.

The study protocol was approved by the Marmara University Faculty of Medicine, Clinical Research Ethics Comittee (date: 03.02.2023, number: 09.2023.333), and before the start of this study, the families of all participants signed an informed consent form.

Statistical Analysis

Data analysis of this study was performed by the IBM SPSS for Windows version 29 program. Associations between categorical independent and dependent variables (hypoplasia, hypodontia, short root anomaly, class, and number of caries >4) were evaluated with the chi-square and Fisher's exact tests. Univariate logistic regression analysis was used to examine the relationships between dental findings and continuous independent variables. Also, the continuous independent variables were categorized based on their median values as the cut-off point, and the Mann-Whitney U test was used to evaluate any relationships between individual and clinical characteristics and DMFT. The statistical significance level was accepted as $p<0.05$.

Results

The records of 914 patients who had received treatment for non-leukemia childhood cancer at our center were retrospectively evaluated. There were 369 (40.3%) cases with a diagnosis age of six years or below. Among these cases, 32 (3.5%) did not attend regular follow-ups, 73 (7.9%) were lost to follow-up, and 32 (3.5%) only underwent surgical treatment without receiving chemotherapy or radiotherapy, so they were not included in this study. From the remaining 232 (25.3%) cases, those aged 12 or above and meeting the study criteria were planned for dental development evaluation, resulting in 90 (9.8%) eligible cases. Of these cases, 35 (3.8%) agreed to participate in this study and attended the appointment for examination.

The mean age at diagnosis was four years, with a mean current age of 13.5 years. The average duration from diagnosis to the present day was calculated as ten years.

Female cases constituted 37.1% of the total. Regarding diagnoses, brain tumors were the most common (31.4%), followed by lymphoma (20%) among the cases (Table I). Approximately half of the cases (51.4%) had involvement in the head and/or neck region. Treatment characteristics are summarized in Table II. Fifteen cases (42.9%) had a history of radiotherapy, and when evaluating the radiotherapy sites, 7 cases (46.6%) had received craniospinal radiotherapy, and 4 cases (26.7%) had received only cranial radiotherapy. The most commonly used chemotherapeutic agents were vinca alkaloids (88.6%), followed by alkylating agents (57.1%). Regarding chemotherapy combinations, approximately one-third of the cases (29.4%) consisted of alkylating agents, vinca alkaloids, and platinum group drugs. The average duration of treatment was six months.

When dental findings were evaluated, at least one dental pathology was present in all cases. Root shortening was detected in those case with the least findings, who had received a combination of alkylating agents. This case constituted the only case with a DMFT index of zero. While the average number of decays was four in all cases, the average DMFT score was found to be five. Hypoplasia was detected in twenty cases (57.1%), root shortening in 11 cases (31.4%) (Figure 1), hypodontia in eight cases (22.9%), and taurodontism was detected in only two cases (5.7%). Hypoplasia was mostly seen in the upper central incisors. Hypodontia was mostly seen in the lower second premolars followed by the upper lateral incisors. Root shortening was mostly in the lower central and lateral incisors. Figure 2 shows examples of normal panoramic radiographs alongside radiographs of dental development pathologies. The presence of hypodontia was observed in five cases along with hypoplasia. Among these cases, two had a diagnosis of brain tumors, two had Wilms' tumors, and one had a diagnosis of abdominal lymphoma.

The relationship between clinical characteristics and dental findings was analyzed. There was no statistically significant difference between gender, head-neck

Table I. Clinical characteristics of the childhood cancer survivors

	n (%)
Gender (Male/Female)	22 (62.9)/13 (37.1)
Diagnosis	
Brain tumor	11 (31.4)
Lymphoma	7 (20.0)
Wilms tumor	5 (14.3)
Langerhans cell histiocytosis	4 (11.4)
Germ cell tumor	3 (8.6)
Neuroblastoma	3 (8.6)
Ewing sarcoma	1 (2.9)
Rhabdomyosarcoma	1 (2.9)
Site of involvement	
Head and neck	18 (51.4)
Other	17 (48.6)
Primary disease status	
Complete remission (CR)	33 (94.3)
Stable disease (SD)	2 (5.7)

Table II. Treatment characteristics of the childhood cancer survivors

Treatment	**n (%)**
Radiotherapy	15 (42.9)
Radiation therapy site	
- Craniospinal	7 (46.6)
- Cranial	4 (26.7)
- Other	4 (26.7)
Chemotherapy	34 (97.1)
- Alkylating agents	20 (57.1)
- Vinca alkaloids	31 (88.6)
- Platinum	17 (48.6)
- Anthracyclines	12 (34.3)
Chemotherapy combination (n=34)	
- Alkylating - Vincas - Anthracyclines - Platinum	3 (8.8)
- Alkylating - Vincas - Anthracyclines	7 (20.6)
- Alkylating - Vincas - Platinum	10 (29.4)
- Vincas - Anthracyclines	2 (5.9)
- Vincas - Platinum	1 (2.9)
- Platinum	3 (8.8)
- Vinca alkaloids	8 (23.5)
- Glucocorticoids	10 (28.6)

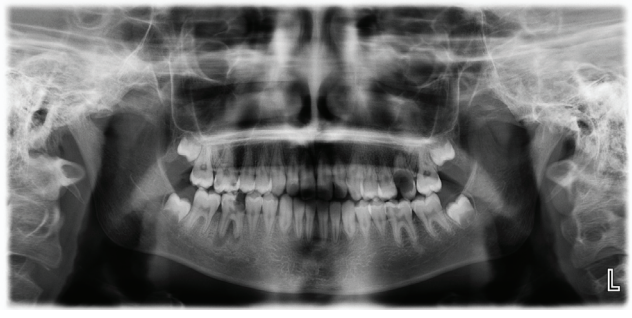


Figure 1. In the panoramic radiograph of a patient who received treatment for Ewing sarcoma, root shortening is present in all teeth

involvement, history of radiotherapy, history of receiving glucocorticoids, and hypoplasia, hypodontia and root shortening (Table III). Regarding chemotherapeutics, a statistically significant higher frequency of root shortening was found in the group who had received alkylating agents along with vinca alkaloids (p<0.001). There was no statistically significant feature identified when comparing the DMFT index with the clinical characteristics, treatment modalities and chemotherapeutic agents (p>0.05). As the age at diagnosis increased, the risk of root shortening (p=0.026) and the frequency of hypodontia significantly increased with the duration after diagnosis (p=0.048) (Table IV). The patients' ages, DMFT scores, and teeth with dental anomalies are shown in Table V.

Table III. Dental findings based on individual and clinical characteristics

Variables		Hypoplasia		Hypodontia		Root shortness	
		n (%)	p value	n (%)	p value	n (%)	p value
Gender							
	Female	8 (61.5)	0.686	3 (23.1)	0.999	3 (23.1)	0.478
	Male	12 (54.5)		5 (22.7)		8 (36.4)	
Head/neck involvement							
	Absent	11 (64.7)	0.380	4 (23.5)	0.999	6 (35.3)	0.632
	Present	9 (50.0)		4 (22.2)		5 (27.8)	
Radiotherapy							
	Absent	12 (60.0)	0.693	4 (20.0)	0.700	5 (25.0)	0.467
	Present	8 (53.3)		4 (26.7)		6 (40.0)	
Alkylating agents							
	Absent	7 (46.7)	0.278	3 (20.0)	0.999	**0 (0.0)**	**<0.001**
	Present	13 (65.0)		5 (25.0)		**11 (35.5)**	
Vinka alkaloids							
	Absent	2 (50.0)	0.999	0 (0.0)	0.553	0 (0.0)	0.285
	Present	18 (58.1)		8 (25.8)		11 (35.5)	
Platinum							
	Absent	10 (55.6)	0.845	5 (27.8)	0.691	8 (27.8)	0.632
	Present	10 (58.8)		3 (17.6)		6 (35.3)	
Anthracycline							
	Absent	11 (47.8)	0.123	5 (21.7)	0.999	6 (26.1)	0.451
	Present	9 (75.0)		3 (25.0)		5 (41.7)	
Alkylating agents and vinca alkaloids							
	Absent	7 (46.7)	0.278	3 (20.0)	0.999	**0 (0.0)**	**<0.001**
	Present	13 (65.0)		5 (25.0)		**11 (35.5)**	
Alkylating agents, vinca alkaloids and anthracycline							
	Absent	13 (52.0)	0.458	6 (24.0)	0.999	6 (24.0)	0.227
	Present	7 (70.0)		2 (20.0)		5 (50.0)	
Steroid							
	Absent	15 (60.0)	0.712	5 (20.0)	0.661	7 (28.0)	0.689
	Present	5 (50.0)		3 (30.0)		4 (40.0)	

Bold font indicates statistical significance

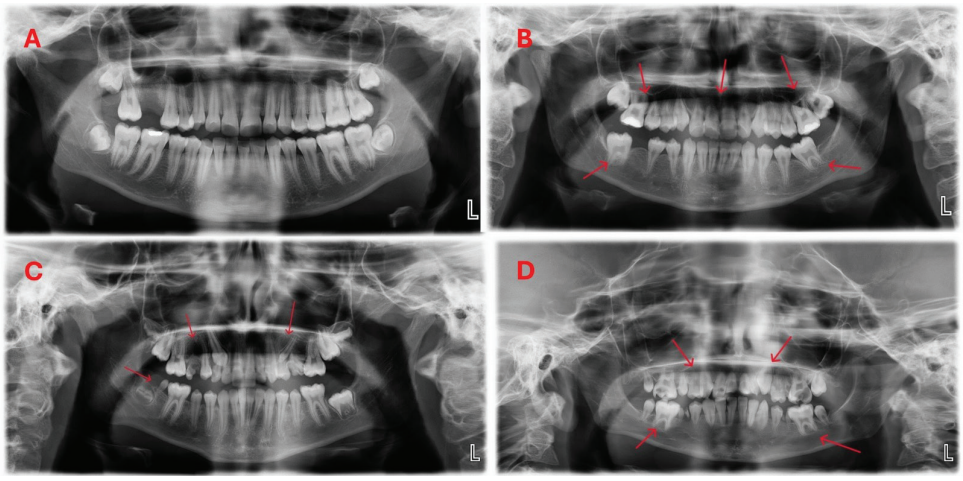


Figure 2. Panoramic radiographs of a normal child and the childhood cancer survivors. **A)** A 13-year-old girl with normal root lengths and tooth morphology. **B)** A 13-year-old girl with short, V-shaped deformed roots. **C)** A 12-year-old girl with undeveloped or hypoplastic teeth. **D)** A 12-year-old boy with short and malformed roots in all teeth

Table IV. Age characteristics and dental development findings, univariate logistic regression analysis

	Hypoplasia		**Hypodontia**		**Root shortening**	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Age at initial diagnosis	0.666 (0.421-1.053)	0.082	0.803 (0.494-1.305)	0.375	**1.968 (1.085-3.571)**	0.026
Time since diagnosis (years)	1.158 (0.785-1.708)	0.460	**1.985 (1.008-3.912)**	**0.048**	0.719 (4.469-1.102)	0.130
Current age (years)	0.765 (0.492-1.190)	0.234	1.288 (0.778-2.131)	0.325	1.246 (0.789-1.969)	0.345
Treatment duration (months)	0.927 (0.839-1.023)	0.132	0.982 (0.887-1.086)	0.720	0.925 (0.809-1.058)	0.254

OR: Odds ratio, CI: Confidence interval

Table V. Age, DMFT* scores and numbers of the teeth** with dental anomalies of the patients

Patient	**Age (year)**	**DMFT* score**	**Hypoplasia**	**Hypodontia**	**Root shortening**
1	12	3	11,21	-	31,32,41,42
2	12	2	-	-	-
3	12	2	21	-	-
4	12	4	11,21	-	-
5	12	4	11,21	-	31,32,41,42,35
6	12	6	-	-	-
7	12	9	11,21	35,45	-
8	12	10	-	-	-
9	13	3	13,21	-	-
10	13	4	-	-	-
11	13	4	11,21	-	-
12	13	4	11,12,13,21,22,23	15	-
13	13	5	11,21	-	-
14	13	6	-	-	-
15	13	8	14	12,22	-
16	13	8	11	-	-

Table V. Continued

Patient	Age (year)	DMFT* score	Hypoplasia	Hypodontia	Root shortening
17	13	13	11,21	-	11,12,21,22,31,32,41,42
18	13	15	11,12,21,22	-	-
19	13	18	21	-	31,32,41,42
20	14	3	-	35,45	31,31,41,42,14,24,36,46
21	14	4	-	-	-
22	14	4	-	-	-
23	14	5	-	45	
24	14	6	-	-	-
25	15	0	-	-	32,41,42
26	15	4	34,44	-	31,32,41,42
27	15	4	-	-	-
28	15	9	11	23	31,32,33,34,35,41,42,43,44,45
29	15	11	11,21	-	31,32,33,34,35,41,42,43,44,45
30	16	8	21	-	-
31	16	10		-	-
32	16	13	11,21	26	-
33	16	15	-	-	31,32,41,42,44
34	17	2	-	22	32,42
35	17	6	11	-	-

*DMFT: Decayed, Missing, Filled Teeth
**Dental numbering system is used according to FDI WORLD DENTAL FEDERATION NOTATION (ISO 3950)

Discussion

Of the 90 patients meeting our study criteria, only 35 attended their appointments for oral examination. While oral and dental health is important for every child, it is especially crucial for those children undergoing cancer treatment. However, when facing a life-threatening cancer disease, both families and healthcare providers understandably prioritize preserving the patient's life and ensuring they lead a healthy life without compromising their quality of life. Unfortunately, oral and dental health does not rank high in terms of importance. In a study involving 4,856 childhood survivors, it was found that socioeconomic status and difficulty in accessing dental care, apart from cancer treatment, were significant risk factors in the development of dental anomalies (13). In our study, despite emphasizing the importance of oral and dental health and informing patients that they would be examined promptly by a pediatric dentistry specialist with knowledge of their past treatments, only 38.8% underwent examination. This result underscores the unfortunate reality that dental health still does not receive the attention it deserves from families and patients, highlighting a significant need for education in this regard.

A study including 35 patients with a history of treatment due to solid tumors demonstrated that the number of malformed teeth was higher in those patients treated under the age of six (14). In another more comprehensive study involving 1,273 cases, it was shown that a treatment history at ages 5-6 was the most significant risk factor for dental caries development when combined with radiotherapy (15). Another study reviewed 93 pediatric cases receiving chemotherapy who were divided into two age groups for analysis. The first group consisted of cases treated between 9 months and 4 years of age, while the second group included cases treated between 5 and 7 years of age. A higher frequency of microdontia and hypodontia was observed in the first group (16). In our study, all cases consisted of patients treated under the age of six years, with the average age at diagnosis being four years. As the age at diagnosis increased, the rate of root shortening development significantly increased. If we consider that the highest age among our cases is six years, it is thought

that the reason is based on the continued increase in root development of permanent teeth during this period.

In our cases, while the average number of dental caries was four, the mean DMFT index was determined to be five. In a study involving 62 cases, where all age groups were included and only solid tumors were evaluated, although the average DMFT score was higher in those patients who had received cancer treatment compared to a control group of healthy individuals, this difference was not statistically significant (17). In a multicenter study comparing 50 cancer patients, mostly leukemia cases, with 51 healthy individuals, it was shown that dental caries was more common in cancer patients, but this difference was not statistically significant (18). Similar to the literature, in our study, there was no statistically significant difference between the DMFT scores and the patients' clinical characteristics and treatment modalities. Other studies have also shown, similar to our study results, that chemotherapy alone does not have an impact on the prevalence of dental caries development in the long term (19,20). In a study examining dental development anomalies which may occur due to treatment, it was stated that there was no statistically significant difference between the average DMFT score and the chemotherapeutic agents used (14). Similarly, in our study, there was no statistically significant difference between DMFT and chemotherapeutic agents.

In our study, hypoplasia was found in 57.1% of cases, root shortening was present in approximately one-third, and hypodontia was observed in 22.9%. In another study from the literature, it was reported that microdontia was observed in 19% and hypodontia in 9% of 150 patients who had received cancer treatment (21). A study conducted by the Childhood Cancer Survivors Study group indicated that abnormal dental roots were found in 5% of children who underwent cancer treatment compared to 3% in their siblings, suggesting that their treatment affected the root anomalies (22). In our study, root shortening was present in approximately one-third of cases, and taurodontism was observed in 5.7%. Another study conducted in Sweden also reported that short and V-shaped roots were observed in 94% of patients who had received chemotherapy and radiotherapy (23). In recent study, hypodontia was mostly seen in the lower second premolars followed by the upper lateral incisors. Root shortening was mostly in the lower central and lateral incisors. In another study in the literature, hypodontia, similar to our study, was most commonly observed in the second premolar teeth, whereas root anomalies, unlike in our study, were most frequently found in the first and second premolars as well as the first molars (16).

When evaluating the relationship between treatment and dental findings in our study, no statistically significant difference was found between the history of steroid use and dental findings. Some of the effects of steroid use on dental tissues include a reduction in alveolar bone, osteoporosis due to decreased osteoblast count, and the formation of fibrosis in periodontal spaces (24). In a study examining the effects of steroid dose and treatment duration on dental development anomalies in 31 children with nephrotic syndrome, the negative effects of steroids on dental health were demonstrated, and it was indicated that long-term use was more influential than dosage (25). In our study, ten patients who had received steroids also had a history of receiving a chemotherapeutic agent. However, when comparing the dental findings of those patients who had received steroids with those who had not, no statistically significant difference was found. This lack of difference may be attributed to the generally short duration of steroid use in those patients with solid tumors.

In our study, a history of radiotherapy and the radiation therapy area did not show a statistically significant effect on dental development. In a recent study, the risk of agenesis and root changes was found to be significantly higher in those patients receiving chemotherapy and radiotherapy (26). In the study conducted by Kılınç et al. (16), root malformation was found to be statistically more frequent in those cases receiving both chemotherapy and radiotherapy compared to those cases receiving chemotherapy alone. Furthermore, the frequency of root malformation was observed to increase proportionally with the dosage of radiotherapy (16). In another study conducted by Proc et al. (27), similar to our study, it was found that radiotherapy did not influence the type and severity of dental abnormalities. However, regarding chemotherapy, a statistically significant higher frequency of root shortening was observed in the group receiving alkylating agents and the group receiving alkylating agents in combination with vinca alkaloids. Alkylating agents negatively affect odontoblasts due to their rapid proliferation during odontogenesis, which explains the root shortening observed in our study. Another recent study also showed that alkylating agents significantly influenced the formation of root shortening (26).

Study Limitations

The limitation of our study was that we lacked information regarding the dental status of the patients before undergoing their anticancer treatment.

Conclusion

In conclusion, undergoing cancer treatment during the primary dentition period leads to dental developmental anomalies. This study demonstrates that among the treatment modalities, alkylating agents have the most detrimental effect on dental development. Additionally, it is believed that these patients and their families should be supported with education emphasizing the importance of oral and dental health.

Ethics

Ethics Committee Approval: The study protocol was approved by the Marmara University Faculty of Medicine, Clinical Research Ethics Comittee (date: 03.02.2023, number: 09.2023.333).

Informed Consent: Before the start of this study, the families of all participants signed an informed consent form.

Authorship Contributions

Surgical and Medical Practices: N.E., N.A., O.D., Concept: N.E., A.M., Design: N.E., B.A., D.G., Data Collection and/or Processing: N.E., A.M., N.A., O.D., Analysis and/or Interpretation: N.E., A.S., Literature Search: N.E., A.M., G.T., Writing: N.E., A.M.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Zubowska M, Wyka K, Fendler W, Młynarski W, Zalewska-Szewczyk B. Interleukin 18 as a marker of chronic nephropathy in children after anticancer treatment. Dis Markers. 2013; 35:811-8.
2. Valéra MC, Noirrit-Esclassan E, Pasquet M, Vaysse F. Oral complications and dental care in children with acute lymphoblastic leukaemia. J Oral Pathol Med. 2015; 44:483-9.
3. Maguire A, Craft A, Evans RG, et al. The long-term effects of treatment on the dental condition of children surviving malignant disease. Cancer. 1987; 60:2570-5.
4. Dens F, Boute P, Otten J, Vinckier F, Declerck D. Dental caries, gingival health, and oral hygiene of long term survivors of paediatric malignant diseases. Arch Dis Child. 1995; 72:129-32.
5. Lauritano D, Petruzzi M. Decayed, missing and filled teeth index and dental anomalies in long-term survivors leukaemic children: a prospective controlled study. Med Oral Patol Oral Cir Bucal. 2012; 17:e977-80.
6. Nemeth O, Hermann P, Kivovics P, Garami M. Long-term effects of chemotherapy on dental status of children cancer survivors. Pediatr Hematol Oncol. 2013; 30:208-15.
7. Bagattoni S, D'Alessandro G, Prete A, Piana G, Pession A. Oral health and dental late adverse effects in children in remission from malignant disease. A pilot case-control study in Italian children. Eur J Paediatr Dent. 2014; 15:45-50.
8. Stolze J, Vlaanderen KCE, Holtbach FCED, et al. Long-Term Effects of Childhood Cancer Treatment on Dentition and Oral Health: A Dentist Survey Study from the DCCSS LATER 2 Study. Cancers (Basel). 2021; 13:5264.
9. Pajari U, Lanning M. Developmental defects of teeth in survivors of childhood ALL are related to the therapy and age at diagnosis. Med Pediatr Oncol. 1995; 24:310-4.
10. Rosenberg SW, Kolodney H, Wong GY, Murphy ML. Altered dental root development in long-term survivors of pediatric acute lymphoblastic leukemia. A review of 17 cases. Cancer. 1987; 59:1640-8.
11. Heimdahl A, Johnson G, Danielsson KH, Lönqvist B, Sundelin P, Ringden O. Oral condition of patients with leukemia and severe aplastic anemia. Follow-up 1 year after bone marrow transplantation. Oral Surg Oral Med Oral Pathol. 1985; 60:498-504.
12. Minicucci EM, Lopes LF, Crocci AJ. Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. Leuk Res. 2003; 27:45-50.
13. Patni T, Lee CT, Li Y, et al. Factors for poor oral health in long-term childhood cancer survivors. BMC Oral Health. 2023; 23:73.
14. Halperson E, Matalon V, Goldstein G, et al. The prevalence of dental developmental anomalies among childhood cancer survivors according to types of anticancer treatment. Sci Rep. 2022; 12:4485.
15. Wogelius P, Dahllöf G, Gorst-Rasmussen A, Sørensen HT, Rosthøj S, Poulsen S. A population-based observational study of dental caries among survivors of childhood cancer. Pediatr Blood Cancer. 2008; 50:1221-6.
16. Kılınç G, Bulut G, Ertuğrul F, et al. Long-term Dental Anomalies after Pediatric Cancer Treatment in Children. Turk J Haematol. 2019; 36:155-61.
17. Cubukçu CE, Sevinir B. Dental health indices of long-term childhood cancer survivors who had oral supervision during treatment: a case-control study. Pediatr Hematol Oncol. 2008; 25:638-46.
18. Kerbaqe C, Macari AT, Kerbaqe A, Chedid N. Comparison of oral health characteristics in pediatric cancer and cancer free patients: a multicenter study. Pediatric Dental Journal. 2023; 33:139-46.
19. Uderzo C, Fraschini D, Balduzzi A, et al. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. Bone Marrow Transplant. 1997; 20:865-9.
20. Dahllöf G, Heimdahl A, Bolme P, Lönnqvist B, Ringdén O. Oral condition in children treated with bone marrow transplantation. Bone Marrow Transplant. 1988; 3:43-51.
21. Pedersen LB, Clausen N, Schrøder H, Schmidt M, Poulsen S. Microdontia and hypodontia of premolars and permanent molars in childhood cancer survivors after chemotherapy. Int J Paediatr Dent. 2012; 22:239-43.
22. Kaste SC, Goodman P, Leisenring W, et al. Impact of radiation and chemotherapy on risk of dental abnormalities: a report

from the Childhood Cancer Survivor Study. Cancer. 2009; 115:5817-27.

23. Näsman M, Forsberg CM, Dahllöf G. Long-term dental development in children after treatment for malignant disease. Eur J Orthod. 1997; 19:151-9.

24. Glickmann I, Stone IC, Chawla TN. Effect of cortisone acetate on the periodontal tissues of white mice. J Dent Res. 1951; 30:461.

25. Piekoszewska-Ziętek P, Olczak-Kowalczyk D, Pańczyk-Tomaszewska M, Gozdowski D. Developmental Abnormalities of Teeth in Children With Nephrotic Syndrome. Int Dent J. 2022; 72:572-7.

26. Rabassa-Blanco J, Brunet-Llobet L, Marcote-Sinclair P, Balsells-Mejía S, Correa-Llano MG, Miranda-Rius J. Prevalence of, and risk factors for, dental sequelae in adolescents who underwent cancer therapy during childhood. Oral Dis. 2024; 30:604-14.

27. Proc P, Szczepańska J, Skiba A, Zubowska M, Fendler W, Młynarski W. Dental Anomalies as Late Adverse Effect among Young Children Treated for Cancer. Cancer Res Treat. 2016; 48:658-67.

J Pediatr Res 2024;11(3):164-8
DOI: 10.4274/jpr.galenos.2024.73558

Original Article

Clinical Value of Systemic Immune Inflammation and Pan-Immune Inflammation in Adenoid Hypertrophy

Tuğba Yemiş[1], Mehmet Birinci[1], Metin Çeliker[1], Gökçe Aydın Balaban[2], Erdal Eren Askeroğlu[1], Özlem Çelebi Erdivanlı[1]

[1]Recep Tayyip Erdoğan University Faculty of Medicine, Department of Otorhinolaryngology, Rize, Turkey
[2]Rize State Hospital, Clinic of Otorhinolaryngology, Rize, Turkey

ABSTRACT

Aim: This study aimed to investigate the relationship between adenoid hypertrophy, the most common cause of obstructive sleep apnea (OSA) in children, with the systemic immune inflammation index (SII) and the pan-immune inflammation value (PIV), and to evaluate the clinical utility of SII and PIV in prognostic and predictive aspects.

Materials and Methods: The retrospective data from 29 patients presenting to the otorhinolaryngology clinic with dyspnea and undergoing adenoidectomy for OSA between June, 2022 and June, 2023 were reviewed. Thirty age- and sex-matched healthy subjects were included as the control group. The preoperative and postoperative 6-month SII and PIV values of both groups were compared.

Results: There was no significant difference between the groups in terms of age and gender ($p>0.05$). Platelet SII and PIV were statistically significantly higher in patients in the preoperative period compared to the control group ($p<0.05$). No significant differences were found in the preoperative neutrophil, lymphocyte, and monocyte counts between the patients and the control subjects ($p>0.05$). Postoperative neutrophil, platelet, and monocyte counts, as well as the SII and PIV values of the patients, were significantly higher than of those in the control group ($p<0.05$).

Conclusion: Our study highlights the potential utility of SII and PIV in assessing systemic inflammation in adenoid hypertrophy-related OSA. However, the unexpected increase in postoperative SII and PIV values underscores the need for further research into their clinical implications.

Keywords: Pan-immune inflammation value, systemic immune inflammation index, adenoid hypertrophy, obstructive sleep apnea

Introduction

Adenoid tissue situated in the nasopharynx can undergo hypertrophy, leading to the obstruction of the air passage from the nasal cavity to the nasopharynx (1). If left untreated, adenoid hypertrophy can contribute to conditions such as nocturnal hypoxia and obstructive sleep apnea (OSA). Risk factors for snoring, including adenotonsillar hypertrophy, chronic tonsillitis, obesity, and male gender, have been identified (2). Untreated adenoid hypertrophy in children may result in chronic upper airway obstruction, potentially leading to secondary enuresis, severe morning headaches, loss of appetite, behavioral disorders, impaired school performance, and growth-development retardation. Progressive cases can lead to various cardiopulmonary complications such as pulmonary ventilation deficiency, chronic hypoxia, hypercapnia, right heart hypertrophy, cor pulmonale and pulmonary edema (3). In these instances, systemic inflammatory markers and proinflammatory

Address for Correspondence
Tuğba Yemiş, Recep Tayyip Erdoğan University Faculty of Medicine, Department of Otorhinolaryngology, Rize, Turkey
Phone: +90 506 967 09 32 **E-mail:** tugba.yemis@erdogan.edu.tr **ORCID:** orcid.org/0000-0001-8713-0251
Received: 24.01.2024 **Accepted:** 31.07.2024

cytokines increase, promoting lymphoid tissue proliferation (4).

The systemic immune inflammation index (SII) and pan-immune inflammation value (PIV) are derived from complete blood count elements using specific formulas. While studies have extensively explored SII and PIV in diseases such as colorectal cancer, breast cancer, and rheumatoid diseases, their utility extends to assessing severity and prognosis in other diseases (5,6).

In this study, our aim was to investigate the associations between SII and PIV in relation to adenoid hypertrophy-induced OSA in children. Additionally, we sought to evaluate the potential of SII and PIV as clinical indicators supporting surgical interventions for patients with adenoid hypertrophy.

Materials and Methods

Upon receiving approval from the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (approval no.: 2024/26, date: 18.01.2024), the records of patients visiting the otorhinolaryngology clinic between June, 2022 and June, 2023 were meticulously examined. Informed consent was obtained from the parents of all patients, with acknowledgement of the study objectives and possible publication of the medical data. Inclusion criteria encompassed those individuals with an active complaint of dyspnea and a history of adenoidectomy due to OSA. Exclusions were made for patients over 18 years of age, those categorized as overweight or obese, individuals with genetic syndromes, congenital malformations, nasal septum deviation, sinonasal infections, otitis media, as well as those with chronic or hematological diseases. A cohort of 29 patients meeting the specified criteria was identified and enrolled into this study. Additionally, data from 30 healthy subjects matched in terms of age and sex were utilized as the control group for comparative analysis.

Adenoidectomy Procedure

All patients underwent a comprehensive preoperative assessment, including endoscopic nasal examination, nasopharynx examination, otoscopic and endoscopic ear examination, as well as tympanometry. Preoperative tympanograms consistently displayed type A patterns in all patients. Adenoidectomy was conducted under general anesthesia with patients in a supine position employing an adenoidectomy curette. Hemostasis was meticulously ensured through tamponade post-procedure. Notably, none of the pediatric patients exhibited clinical signs of infection during the adenoidectomy procedure.

Laboratory Analyses

Preoperative routine blood samples were collected from the antecubital vein into tubes containing ethylenediaminetetracetic acid. Hemogram analysis was performed on a Mindray BC-600 Hematology Analyzer. The following formulas were used to calculate PIV and SII (5,7):

$$PIV = \frac{\text{neutrophil\#} * \text{platelet\#} * \text{monocyte\#}}{\text{lymphocyte\#}}$$

$$SII = \frac{\text{neutrophil\#} * \text{monocyte\#}}{\text{lymphocyte\#}}$$

The patients were scheduled for follow-up appointments at the 1st week, 3rd month, and 6th month following surgery. At the 6-month follow-up, transnasal flexible endoscopy revealed the absence of adenoid tissue in all patients. Additionally, those patients who underwent blood tests for any other medical reason during the 6th postoperative month or thereafter were retrospectively included in this study.

Statistical Analysis

Data analysis was conducted using the SPSS 25.0 statistical package program. The normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Descriptive statistics are presented according to normality as mean±standard deviation or median (minimum-maximum). The Mann-Whitney U test was used to compare independent groups, specifically the "control group" and the "patient group" in the preoperative and postoperative periods. Additionally, the Wilcoxon signed-rank test was used to compare dependent groups, specifically the preoperative and postoperative measurements within the patient group. A p value <0.05 was considered statistically significant.

Results

The mean age of the patient group (n=29; 16 males, 13 females) was 5.2±2 years, while the control group had a mean age of 6.3±3.8 years (n=30; 17 males, 13 females). Age and gender distributions were similar between both groups (p>0.05).

The hematological parameters and inflammatory indices of both the control and patient groups before and after surgery are presented in Table I. Statistical analysis revealed that platelet count, SII, and PIV were significantly higher in the preoperative patient group compared to the control group (p=0.002, p=0.027, and p=0.006 respectively), as

Table I. Comparison of hematological parameters and inflammatory indices between control and patient groups before and after surgery for adenoid hypertrophy-induced OSA

Parameters	Control group (n=30)	Patient group (n=29)	
		Preoperative values	Postoperative values at the 6th month
Neutrophil (10^3/mm^3)	3.4±0.9	4.1±1.8	5.5±2.3$^{+,++}$
Platelet (10^3/mm^3)	320.8±43.4	372.4±69.3*	382.7±74.4^{++}
Lymphocyte (10^3/mm^3)	3.7±1.2	3.7±1.3	3.3±1.5
Monocyte (10^3/mm^3)	0.5±0.2	0.6±0.2	0.7±0.3^{++}
SII	324.9±156.1	471±277*	783.8±806.5$^{+,++}$
PIV	173.4±104.6	296.2±211.5*	544.5±585.3$^{+,++}$

*Significantly high compared to control values (Mann-Whitney U test)
$^{+}$Significantly high compared to preoperative values (Signed-rank test)
$^{++}$Significantly high compared to control values (Mann-Whitney U test)
OSA: Obstructive sleep apnea, SII: Systemic immune inflammation index, PIV: Pan immune inflammation value

determined by the Mann-Whitney U test. Conversely, there were no significant differences in the preoperative values of neutrophils, lymphocytes, and monocytes between the patient group and the control group ($p>0.05$).

Comparing preoperative and postoperative values within the patient group, significantly higher values for neutrophils, SII, and PIV were observed postoperatively compared to the preoperative values ($p=0.012$, $p=0.008$, and $p=0.020$ respectively), as determined by the Wilcoxon signed-rank test. However, there were no significant differences between preoperative and postoperative platelet, lymphocyte, and monocyte levels ($p>0.05$).

In the comparison of measurement values between the postoperative patient group and the control group, significantly higher levels of neutrophils, platelets, monocytes, SII, and PIV were observed in the postoperative patient group ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.011$, $p<0.001$, and $p<0.001$ respectively), as determined by the Mann-Whitney U test. Conversely, there were no significant differences in lymphocyte levels between the postoperative patient group and the control group ($p>0.05$).

Discussion

The SII and PIV were significantly higher in the preoperative patient group compared to the control group. In comparing preoperative and postoperative values within the patient group, significantly higher levels of neutrophils, SII, and PIV were observed postoperatively compared to preoperative levels. In the comparison of measurement values between the postoperative patient group and the control group, significantly higher values for SII and PIV were observed in the postoperative patient group.

In our study, we investigated the association between SII and PIV values and chronic systemic inflammation in patients undergoing adenoidectomy for OSA induced by adenoid hypertrophy. This study represents the first evaluation of SII and PIV in the context of adenoid hypertrophy. Adenoidectomy is one of the most common procedures in otorhinolaryngology practice, primarily due to adenoid hypertrophy being a leading cause of OSA in children, potentially resulting in nocturnal hypoxia if left untreated (8). In cases of hypoxia, systemic inflammatory markers and proinflammatory cytokines increase, triggering lymphoid tissue proliferation (4). Additionally, obstructive sleep disorders are associated with elevated inflammatory markers. While the precise mechanisms underlying various diseases, such as cardiovascular and cerebrovascular diseases, infections, and malignancies, remain unclear, chronic inflammation is believed to play a significant role in their pathogenesis (9). Therefore, analyzing the relationship between the inflammatory status of a disease or cancer and its prognosis can be achieved by evaluating systemic inflammation (10).

Previous studies have indicated that easily obtainable ratios, such as the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), are useful tools in assessing systemic inflammation. Subsequent research has shown that the SII value is related to disease severity and prognosis (6,11). Moreover, studies have investigated the prognostic and predictive value of PIV, a newer inflammatory marker. Fucà et al. (5) found PIV to be more significant than other known inflammation markers in metastatic colorectal cancer patients, while Şahin et al. (12) demonstrated its importance in breast cancer patients. However, Truffi et

al. (13) found no correlation between PIV and prognosis in breast cancer. The prognostic and predictive roles of SII and PIV in patients with adenoid hypertrophy remain unknown.

Considering this information, we anticipated a decrease in the inflammatory process after adenoidectomy, leading to a reduction in parameters indicating systemic inflammation. A study by Uygur et al. (14) demonstrated the severity of OSA with NLR, indicating a correlation between PLR and the apnea-hypopnea index. Another notable finding in this study is that NLR can also serve as a marker for cardiac and vascular diseases (14,15). However, Korkmaz et al. (16), in their study, found no correlation between the severity of OSA and the NLR value.

In our findings, platelet count, SII, and PIV values in the preoperative patient group were statistically significantly higher than those in the control group. This disparity between the preoperative group and the control group supports the hypothesis that hypoxia-induced systemic inflammation is triggered in adenoid hypertrophy causing OSA, and that inflammatory factors decrease after adenoidectomy. However, contrary to our expectations, significantly higher levels of neutrophils, SII, and PIV were observed in the postoperative Patient Group compared to preoperative values. This unexpected difference in preoperative and postoperative SII and PIV values could be attributed to the marked increase in the neutrophil count, which typically reflects ongoing inflammation (8). However, neither these patients nor the control group exhibited signs of active infection. Therefore, the notable rise in postoperative SII and PIV values may be attributed to unknown effects of surgery, anesthesia, or the healing phase. Additionally, it is plausible that six months post-surgery is not a sufficient time period to observe a decrease in inflammatory markers.

In the comparison of measurement values between the postoperative patient group and the control group, significantly higher levels of neutrophils, platelets, monocytes, SII, and PIV were observed in the postoperative patient group. Conversely, no significant correlation was found between lymphocyte levels in the postoperative patient group and those in the control group.

Study Limitations

The retrospective nature of our study limited the use of biochemical markers to further elucidate the underlying mechanisms of systemic inflammation. Additionally, while the differences in SII and PIV values between the control group and preoperative patient group indicate potential utility in assessing systemic inflammation, the unexpected increase in postoperative SII and PIV values presents a challenge in the interpretation. The numerous unknowns surrounding these indices, coupled with the potential effects of the postoperative period on inflammatory markers, warrant further investigation.

Conclusion

Our study highlights the potential utility of SII and PIV in assessing systemic inflammation in patients with adenoid hypertrophy-related OSA. However, the unexpected increase in postoperative SII and PIV values underscores the need for additional research to better understand the underlying mechanisms and clinical implications of these inflammatory indices in the context of adenoidectomy and OSA.

Ethics

Ethics Committee Approval: This study was approved by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (approval no.: 2024/26, date: 18.01.2024).

Informed Consent: Informed consent was obtained from the parents of all patients, with acknowledgement of the study objectives and possible publication of the medical data.

Authorship Contributions

Surgical and Medical Practices: T.Y., M.B., M.Ç., Ö.Ç.E., Concept: T.Y., Design: T.Y., Ö.Ç.E., Data Collection and/or Processing: G.A.B., E.E.A., Analysis and/or Interpretation: T.Y., M.B., Literature Search: T.Y., M.Ç., Ö.Ç.E., Writing: T.Y.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Arambula A, Brown JR, Neff L. Anatomy and physiology of the palatine tonsils, adenoids, and lingual tonsils. World J Otorhinolaryngol Head Neck Surg. 2021; 7:155-60.
2. Wang J, Zhao Y, Yang W, et al. Correlations between obstructive sleep apnea and adenotonsillar hypertrophy in children of different weight status. Sci Rep. 2019; 9:11455.
3. Öner T, Tekin Ş, Yıldırmak ZY, Coşkun BU. Evaluation of Cardiac Function in Pediatric Patients with Upper Airway Obstruction. Med Bull Haseki. 2019; 57:175-9.
4. Kim J, Bhattacharjee R, Dayyat E, et al. Increased cellular proliferation and inflammatory cytokines in tonsils derived

from children with obstructive sleep apnea. Pediatr Res. 2009; 66:423-8.

5. Fucà G, Guarini V, Antoniotti C, et al. The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. Br J Cancer. 2020; 123:403-9.
6. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. J Cancer. 2018; 9:3295-302.
7. Hu B, Yang X-R, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014; 20:6212-22.
8. Baran H, Evman MD, Avcı H. The Effect of Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Mean Platelet Volume in Surgical Decision and Follow-up of Adenotonsillectomy. South Clin Ist Euras. 2021; 32:181-6.
9. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000; 283:1829-36.
10. Wu J, Yan L, Chai K. Systemic immune-inflammation index is associated with disease activity in patients with ankylosing spondylitis. J Clin Lab Anal. 2021; 35:e23964.
11. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017; 8:75381-8.
12. Şahin AB, Cubukcu E, Ocak B, et al. Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy. Sci Rep. 2021; 11:14662.
13. Truffi M, Sottotetti F, Gafni N, et al. Prognostic Potential of Immune Inflammatory Biomarkers in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy. Cancers (Basel). 2022; 14:5287.
14. Uygur F, Tanriverdi H, Aktop Z, et al. The neutrophil-to-lymphocyte ratio in patients with obstructive sleep apnoea syndrome and its relationship with cardiovascular disease. Heart Lung. 2016; 45:121-5.
15. Huang J, Zhang Q, Wang R, et al. Systemic Immune-Inflammatory Index Predicts Clinical Outcomes for Elderly Patients with Acute Myocardial Infarction Receiving Percutaneous Coronary Intervention. Med Sci Monit. 2019; 25:9690-701.
16. Korkmaz M, Korkmaz H, Küçüker F, Ayyıldız SN, Çankaya S. Evaluation of the association of sleep apnea-related systemic inflammation with CRP, ESR, and neutrophil-to-lymphocyte ratio. Med Sci Monit. 2015; 21:477-81.

J Pediatr Res 2024;11(3):169-75
DOI: 10.4274/jpr.galenos.2024.86244

Original Article

Investigating the Use of Therapeutic Hypothermia in Partially Eligible Infants: A Single-centre Experience

Begüm Cezayir[1], Sezgin Güneş[2]

[1]İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Pediatrics, İzmir, Turkey
[2]İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Pediatrics, Division of Neonatology, İzmir, Turkey

ABSTRACT

Aim: Neonatal encephalopathy remains one of the most significant causes of neonatal morbidity and mortality. The present study compared the risk factors, demographic data, laboratory and imaging findings, and short-term outcomes of two groups of patients.

Materials and Methods: A retrospective analysis was conducted on 45 patients who had undergone therapeutic hypothermia (TH) between January 1st, 2021, and August 31st, 2023. According to blood gas parameters; Group 1 (32 patients) met the criteria (pH ≤7.0 and/or base excess BE ≤-16) for TH, while Group 2 (13 patients) did not (pH >7.0, BE >-16, and with an absence of clinical findings).

Results: A comparison of the demographic data revealed higher incidences of birth trauma (p=0.046) and neonatal risk (p=0.026) in Group 1 than in Group 2, with no other significant differences. Severe amplitude electroencephalogram (aEEG) abnormalities were more common in Group 1 but one patient of Group 2 displayed moderate abnormality during follow-up. A comparison of all imaging findings [aEEG, transfontanelle ultrasonography (USG), abdominal USG, cranial magnetic resonance imaging, echocardiography] revealed no significant differences (p=0.45). At the end of the follow-up period, 35 patients (77.7%) were discharged, while two (4.4%) patients did not survive (both in Group 1). Upon discharge, all patients in Group 2 exhibited normal neurological examination findings.

Conclusion: Re-evaluating the existing criteria for the identification of those infants who may benefit from TH, but who are often deemed ineligible due to incomplete adherence to the treatment criteria, could significantly reduce the mortality and morbidity associated with birth asphyxia.

Keywords: Neonatal encephalopathy, asphyxia, blood gases, therapeutic hypothermia

Introduction

Neonatal encephalopathy (NE) is the third leading cause of death among neonates (1-3). Therapeutic hypothermia (TH) administered to patients diagnosed with moderate (stage 2) and severe (stage 3) encephalopathy according to the modified Sarnat & Sarnat grading scale remains the sole proven therapeutic approach to this condition, requiring initiation within 6 hours following birth. When administered within this recommended timeframe, TH exhibits a greater success rate than in cases where the treatment is started after this critical window (4).

While the initiation criteria of treatment is are determined by the Turkish Society of Neonatology (TSN) guidelines, many centres opt for TH even in cases where the patients do not fully meet these established criteria based on a risk-benefit analysis of such therapy (5). The present study evaluated short-term treatment outcomes through a comparison of two patient groups (Group 1 and Group 2), in order to provide clinicians with insights into the risks and benefits associated with the administration of TH to patients whose eligibility falls within a grey area.

Address for Correspondence
Begüm Cezayir, İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Pediatrics, İzmir, Turkey
Phone: +90 554 814 74 54 **E-mail:** bgmkyn@hotmail.com **ORCID:** orcid.org/0000-0002-7874-0215
Received: 28.05.2024 **Accepted:** 21.08.2024

Materials and Methods

We present here a retrospective analysis of 45 patients diagnosed with stage 2 and stage 3 NE who were treated with TH in the neonatal intensive care unit of our hospital between January 1st, 2021 and August 31st, 2023. Prior to starting, approval for this study was obtained from the Non-Interventional Research Ethics Committee of İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital (decision no.: 2023/6-150, date: June 21st, 2023). The diagnoses of NE and adherence to TH indications were confirmed using the Neonatal Encephalopathy Diagnosis and Treatment Guidelines 2018, as published by the TSN and the clinical severity of NE was assessed using the modified Sarnat & Sarnat grading scale (5,6). The treatment criteria for TH included gestational age equal to or greater than 36 weeks and a postnatal age under 6 hours, with umbilical cord artery or arterial blood gases analysis indicating a pH of 7.0 or lower and/or a BE of -16 mmol/L or lower within the first hour following birth, a 10-minute Apgar score below 5 or the continuous need for resuscitation, or the presence of moderate to severe encephalopathy, as assessed clinically (5).

The patients included in this study were divided into two groups. Those patients meeting the specified criteria for TH, including a pH of 7.0 or lower and/or a BE of -16 mmol/L or lower in blood gas analyses, were assigned to Group 1, while those treated with TH without entirely meeting the established blood gas criteria (having a pH >7.0 and a BE >-16 mmol/L), yet displaying neurological examination findings consistent with stage 2 or 3 encephalopathy, were assigned to Group 2. The patients in Group 2 had at least three of the pathological neurologic findings (lethargy, obtunded, stupor, decreased activity, no activity, hypotonia, flaccidity, distal flexion posture, decerebrate state, weak sucking, biting, incomplete Moro reflex; constricted, deviated, dilated or nonreactive pupils etc.) which was evaluated as stage 2 or 3 encephalopathy according to the Sarnat & Sarnat classification. Those patients with missing data in their medical records, patients born before 36 weeks gestation, those with a birth weight below 1,800 grams, as well as those with major congenital malformations, chromosomal anomalies, and/or severe intracranial haemorrhage were excluded from this study. In all patients, hypothermia was started during the first 6 hours and was finished within 72 hours. A comparison was made of the prenatal, natal and postnatal risk factors, demographic data, laboratory and imaging findings, as well as the short-term outcomes of those patients who met the treatment criteria and those who did not completely fulfil these criteria.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.). Categorical variables were expressed as numbers and percentages. A Kolmogorov-Smirnov test was used to assess the normality of the data distribution, and a simple correlation test was used to evaluate the relationship between two variables. A chi-square test was used to evaluate any differences between categorical variables, and Student's t-test and analysis of variance (ANOVA) were used for comparisons of normally distributed quantitative variables. The Mann-Whitney U test and Kruskal-Wallis test were applied to assess those parameters which did not follow a normal distribution. A p value of less than 0.05 was considered statistically significant in all analyses.

Results

In the study period, 45 patients were diagnosed with NE, of whom 32 (71.1%) were assigned to Group 1 and 13 (28.8%) to Group 2. The one significant difference was the number of natal risk factors being higher in Group 1 (p=0.026). A comparison of the two groups' modified Sarnat & Sarnat grading scale scores revealed the rate of stage 3 encephalopathy to be higher in Group 1, while the rate of stage 2 encephalopathy was higher in Group 2 (p=0.02) (Table I).

In the comparison of groups categorized according to the difference in blood gas parameters, aspartate transaminase, alanine transaminase and Troponin-I values were higher in Group 1 than in Group 2, although the difference was not statistically significant (Table II).

An evaluation of the two groups in terms of their need for respiratory support revealed a significantly higher mean intubation time in Group 1 (5.13±12.5 days) than in Group 2 (0.42±0.6 days) (p=0.045) (Table III). The need for invasive respiratory support upon admission was higher in Group 1 than in Group 2 (p=0.008) (Table IV). When comparing the groups in terms of enteral feeding, no significant difference was observed in the median time for transition to enteral feeding, while the time for transition to total enteral feeding was longer in Group 1 than in Group 2 (p=0.008) (Table V). Of the 45 patients, eight (17.7%) underwent inotropic therapy, with a significantly greater number in Group 1 than in Group 2 (p=0.049).

No birth trauma was noted in 40 of the 45 patients (88.8%), while cephalohematoma was observed in three (6.6%) and clavicular fracture in two (4.4%) patients. The rate of birth trauma was significantly higher in Group 1 than in Group 2 (p=0.046) (Table IV).

Table I. Demographic data and first neurological examination findings

Demographic data	Group 1†	Group 2†	Total†	p value
Maternal age (Mean)	26.5±5.4	29.3±6.2	39.2±1.2	0.32
Gestational week (Mean)	38±1.7	38.9±1.3	27.3±8.6	0.89
The mode of delivery (n)				
NSD C/S	13 19	8 5	21 (46.6%) 24 (53.4%)	0.17
Birth weight (Mean, gr)	3,056±527	3,348±439	3,140±355	0.068
Gender (n)				
Female Male	14 18	8 5	22 (49%) 23 (51%)	0.22
Delivery hospital (n)				
Yes No	13 19	8 5	21 (46.6%) 24 (53.4%)	0.17
Prenatal risk (n)				
No risk	25	9	34 (75.5%)	0.593
Abnormal placental location	3	2	5 (11.1%)	
Maternal hypothyroidism	1	2	3 (6.6%)	
IUGR	1	0	1 (2.2%)	
Enoxaparin sodium use	1	1	1 (2.2%)	
Diabetes mellitus	0	1	1 (2.2%)	
Natal risk (n)				
No risk	11	10	21 (46.6%)	**0.026**
Foetal distress	15	3	18 (40%)	
Placental abruption	6	0	6 (13.3%)	
APGAR 1st min (n) <5	14	3	17 (37.7%)	0.553
APGAR 5th min (n) <5	9	1	10 (22.2%)	0.749
APGAR 10th min (n) <5	7	0	7 (15.5%)	0.09
Sarnat & Sarnat score (n)				
Stage 2 Stage 3	22 10	13 0	35 (77.7%) 10 (22.2%)	**0.02**

†Data presented as mean ± SD, median (IQR) or count (percentages)
NSD: Normal spontaneous delivery, C/S: Caesarean section, IUGR: Intrauterine growth restriction, SD: Standard deviation, IQR: Interquartile range

All patients receiving TH underwent aEEG monitoring, and of these patients, 38 (84.4%) exhibited normal findings, while one (2.2%) displayed mild abnormality, two (4.4%) moderate abnormality and four (8.8%) severe abnormality. Follow-up aEEG to one patient of Group 2 displayed moderate abnormality (Table V).

Of the 45 patients in this study, 35 (77.7%) were discharged at the end of the follow-up period, while two (4.4%) did not survive. Both of those who did not survive had stage 3 NE based on the modified Sarnat & Sarnat grading scale, and were in Group 1. In an assessment of the patients based on their final neurological examination findings, all of the patients in Group 2 had normal findings upon discharge. Taking into account the two non-survivors,

Table II. Laboratory features of the patients

Laboratory tests	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
Blood gas			
pH HCO_3 BE	6.8±0.16 10.3±3.8 -17.5±4.2	7.03±0.3 12.4±2.2 -12.7±2.5	**0.000** **0.028** **0.000**
Urine (mg/dL)	22.5±10.6	26.7±13.3	0.320
Creatinine (mg/dL)	0.83±0.27	0.69±0.3	0.177
AST (U/L)	142±365	81±79	0.379
ALT (U/L)	50±112	27±23	0.293
Troponin (pg/mL)	88±116	51±49	0.140
CRP (mg/L)	3.4±7.2	8.7±21.6	0.400
PT (sec)	18.4±5.4	18.6±5.2	0.893
INR (%)	1.6±0.48	1.5±0.49	0.579
TSH (uIU/mL)	6.5±5	8.9±8.7	0.352
fT4 (ng/dL)	1.67±0.38	1.85±0.36	0.168

AST: Aspartate transaminase, ALT: Alanine transaminase, CRP: C-reactive protein, PT: Prothrombin time, INR: International normalized ratio, TSH: Thyroid-stimulating hormone, fT4: Free T4, SD: Standard deviation

Table III. Duration of intubation, initiation of and reaching full enteral feeding, and length of hospital stay

Data	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
Total intubation days	5.13±12.5	0.42±0.6	**0.045**
First enteral feeding day	3.44±1.9	2.85±1.4	0.365
Days to full enteral feeding	6.59±4.6	4.85±2.4	**0.008**
Duration of hospitalization	16.4±16.4	9±4.5	0.511

SD: Standard deviation

Table IV. Delivery room resuscitation needs and development of birth trauma

Data	Group 1 (n)	Group 2 (n)	p value
Birth trauma			
No trauma Cephalohematoma Clavicular fracture	29 3 0	11 0 2	**0.046**
Respiratory support			
Non-invasive respiratory support Invasive respiratory support	16 16	12 1	**0.008**
Resuscitation			
No need PPV CPR	4 22 6	4 9 0	0.124

PPV: Positive-pressure ventilation, CPR: Cardiopulmonary resuscitation

Table V. Imaging findings

Imaging	Group 1 (n)	Group 2 (n)	p value
aEEG			
Normal Mild abnormality Moderate abnormality Severe abnormality	26 1 1 4	12 0 1 0	0.45
Transfontanelle USG			
Normal Periventricular echogenicity Choroid plexus cyst Unspecified bleeding	24 5 1 2	12 1 0 0	0.57
Abdominal USG			
Normal Unilateral renal agenesis Pelviectasis	25 0 7	9 1 3	0.27
Cranial MRI			
Not available Normal Ischemia Encephalomalacia	16 13 2 1	7 6 0 0	0.72
Echocardiography			
PFO PDA TVR (trace) PDA and TVR (trace) Left ventricular hypertrophy Decreased EF Pulmonary hypertension	14 3 2 2 4 2 5	10 3 0 0 0 0 0	0.15

aEEG: Amplitude electroencephalogram, USG: Ultrasonography, MRI: Magnetic resonance imaging, PFO: Patent foramen ovale, PDA: Patent ductus arteriosus, TVR: Tricuspid valve regurgitation, EF: Ejection fraction

Table VI. Final neurological examination findings at discharge

Final neurological examination findings	Group 1 (n)	Group 2 (n)	p value
Normal neurological examination	18	13	0.24
Exitus or poor neurological examination	6	0	
Discharged with poor neurological examination	4	0	
Unavailable data due to being referred to other facilities	8	0	

and adding the patients with poor neurological examination results, there were a total of six patients in Group 1 who displayed neurological examination findings indicating sequel changes (death, hypoactivity, poor oral feeding and spasticity) (Table VI).

Discussion

Our sample was 51% male, while in a study conducted by Odd et al.'s (7) in 2017, 69% of the 130 NE patients were male, with this ratio not being consistent with our study. The C/S rate was reported as 25.8% in the study of Peebles et al. (8) and 62% in the study by Azak et al. (9). The present study features a high rate of Caesarean births at 53.4%, which can be attributed to the increased preference for C/S over NSD in recent years, and the trend of advising patients with antenatal complications to opt for C/S.

Our study reported a rate of prenatal risk factors for NE of 24.5%, and a rate of natal risk factors of 53.3%, which is consistent with the study conducted by Nelson et al. (10) in 2012 (56%). In a prospective study, a higher rate of maternal hypothyroidism was observed, which is considered a potential risk factor for NE, although its specific pathogenesis remains unidentified (10). The rate of maternal hypothyroidism in the present study was 6.6%.

In another study, infants with a 10-minute Apgar score below 3 exhibited higher rates of mortality and permanent sequelae (11). In the present study, no patient in Group 2 had a 10-minute Apgar score below 5, and in this group, patients were started on TH based on their neurological status rather than their Apgar scores. No significant differences were found in the 5-minute Apgar scores of the two groups. This finding suggests that while the Apgar score can be considered when assessing patients for eligibility for TH, those with unexpectedly higher Apgar scores and those not meeting the blood gas criteria may be overlooked. While the Apgar scoring system follows clear rating steps,

its subjective nature can lead to potential overrating, even in the most experienced centres, due to the assessment's dependence on individual interpretations.

A comparison of the need for respiratory support in the present study in the groups revealed that the Group 1 patients with poorer blood gas parameters had a significantly greater need (p=0.008) for invasive respiratory support, and their intubation times were also longer (p=0.045). In the study by Volpe (12), no neurological deficits were reported during the follow-up of patients with hospital stays of less than one week. In our study, the hospital stays of all patients identified with neurological deficits were longer than two weeks, with a median duration of 36.1 days.

In a study published by Gumus et al. (13) in 2020 comparing the C-reactive protein (CRP) levels of healthy infants with those of infants diagnosed with NE, the authors reported elevated CRP levels in those with NE. The present study did not identify any significant differences in the laboratory features (including CRP) of Group 1 and Group 2.

In our study, 31 cases underwent resuscitation, with PPV being the most frequently administered form (68.8%). In a study conducted by Azak et al. (9) in 2021, 33 patients (66%) underwent resuscitation, PPV being the most frequently administered form (60%) (9). Also in the present study, six patients who underwent CPR were assigned to Group 1. As expected, the patients in Group 1, who exhibited poorer blood gas parameters, required resuscitation more frequently.

In a study conducted by ter Horst et al. (14), approximately 40% of patients with NE exhibited normal aEEG findings, in contrast to the present study, in which 84.6% of patients had normal aEEG findings. In our study, four patients, all of whom were in Group 1, displayed burst suppression under aEEG monitoring. During follow-up, one patient in Group 2 displayed moderate abnormality under aEEG monitoring. Although this patient had moderate abnormality under aEEG monitoring, the final neurological examination findings of this patient were normal at discharge, which underlines the potential neuroprotective effects of TH administered to Group 2 patients who may typically be considered ineligible for TH in many centres. It is plausible that the therapy prevented the onset of neurological deficits, resulting in a higher number of patients showing normal aEEG recordings.

In general, cranial MRI scans are normal in approximately 15-30% of cases. In the present study, among the 22 patients with available MRI scan records, the findings were normal in 19 patients (86%). In a study published by Coşkun et al. (15) in 2021, among the 63 patients with MRI scan records, 33 (52.4%) infants had totally normal MRI findings. Twenty-one of 33 (63.6%) infants had mild, while 12 (36.4%) infants had severe NE. On the other hand, 30 (47.6%) infants had at least one pathology in their MRIs (15). Our study might have shown an overrepresentation of normal MRI findings due to circumstances in which patients with severe NE may not have survived long enough to undergo cranial MRI scans. Furthermore, patients with severe and unstable clinical conditions, and with neurological deficits, might remain intubated for extended periods.

Patients diagnosed initially with mild NE may later progress to moderate-to-severe NE during the follow-up period, and such a progression could potentially result in missed opportunities for TH within the critical 6-hour window. One study documented neurological sequelae in 16% of those patients diagnosed with mild NE, while another study indicated that perinatal asphyxia could induce brain damage, particularly in the basal ganglia and thalamus, affecting 11-40% of those patients diagnosed with mild NE (16-19). Animal-based studies have demonstrated the effectiveness of TH in reducing neuronal loss, particularly in cases with mild selective hippocampal damage (20). In a meta-analysis of 11 randomized and controlled studies, TH resulted in a decrease in mortality and neurological sequelae in those infants with moderate-to-severe NE (21). In hospitals similar to our centre, where the primary focus is on labour, it is common to encounter intermediate cases which do not strictly adhere to the recommendations outlined in standard guidelines or individuals with mild NE. A meta-analysis published by Conway et al. (22) in 2018 examined patients with mild NE who had undergone TH and those who had not, and reported a rate of patients experiencing either mortality, cerebral palsy or low neurodevelopmental test scores at 29% in the TH group, compared to 37% in the non-TH group (22). In a meta-analysis, the rate of poor prognosis was 19.6% among those patients diagnosed with mild NE who underwent TH, compared to 19.7% in those with mild NE who did not receive TH (23). A survey conducted in the United Kingdom in 2018 revealed that 75% of the respondent centres used TH to treat patients with mild NE (24,25). The findings of the present study revealed no differences in the neurological examination findings upon discharge of Groups 1 and 2, and only one patient in Group 2 exhibited abnormal aEEG findings during follow-up. While no direct comparison was possible due to the lack of a group with Group 2 characteristics who did not undergo TH, the authors advocate for an extension of the indications for TH in order to improve neonatal prognosis, considering the

absence of severe complications during TH and the similar discharge assessments observed in both groups.

Study Limitations

This study had several limitations. First of all, it was a retrospective study with a small sample size which decreased the power of our analysis. The cranial MRI device was not located in our clinic, as it was in the main building and at a certain distance. Due to difficulties in transportation, the cranial MRI scan rates of those infants with NE were not enough, leading to the small sample for our study. Secondly, our study was conducted at a single centre, which may not be representative of other hospitals or regions. Last but not the least, short-term outcomes were primarily assessed, which may not fully capture the long-term effects of TH or the full range of potential neurological sequelae. Long-term follow-up would provide more comprehensive insights into the effectiveness of TH. Addressing these limitations in future studies could help validate our findings and provide more robust evidence for the use of TH in partially eligible infants.

Conclusion

The present study investigated the rationale behind the administration of TH to patients who do not entirely meet the established criteria, revealing a need for further studies to reassess and potentially revise the existing indications for TH. The authors emphasize the importance of increasing the availability of the required equipment for TH, as well as the number of centres capable of administering this therapy, which could aid physicians in decision-making when encountering clinically uncertain cases. Most importantly, expanding the eligibility criteria for potentially affected infants with obscure acute period who do not completely meet the criteria, but who may benefit from TH, and allowing their access to such therapy will only be possible through a revision of the existing criteria to include a broader spectrum of cases.

Ethics

Ethics Committee Approval: Prior to starting, approval for this study was obtained from the Non-Interventional Research Ethics Committee of İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital (decision no.: 2023/6-150, date: June 21st, 2023).

Informed Consent: Retrospective analysis.

Authorship Contributions

Surgical and Medical Practices: B.C., S.G., Concept: B.C., Design: B.C., S.G., Data Collection and/or Processing: B.C., Analysis and/or Interpretation: B.C., S.G., Literature Search: B.C., S.G., Writing: B.C.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. World Health Organization. Word Health Statistics: Part I Global Health Indicators 2015. Available from: (http://Wwwwhoint/Whosis/Whostat/En_Whs2011fullpdf) Accessed:20 Nov 2016.
2. Wayessa Z, Belachew T, Joseph J. Birth Asphyxia and Associated Factors Among Newborns Delivered in Jimma Zone Public Hospitals. Southwest Ethiopia: A Cross-Sectional Study. J Midwifery Reprod Health. 2018; 6:1289-95.
3. World Health Organization. Global Health Observatory Data Repository 2015. Available from: Http://Appswhoint/Ghodata/ Accessed:24 Nov 2016.
4. Thoresen M, Tooley J, Liu X, et al. Time is brain: starting therapeutic hypothermia within three hours after birth improves motor outcome in asphyxiated newborns. Neonatology. 2013; 104:228-33.
5. Akisu M, Kumral A, Canpolat FE. Turkish Neonatal Society Guideline on neonatal encephalopathy. Turk Pediatri Ars. 2018; 53(Suppl 1):32-44.
6. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. Arch Neurol. 1976; 33:696-705.
7. Odd D, Heep A, Luyt K, et al. Hypoxic-ischemic brain injury: Planned delivery before intrapartum events. J Neonatal Perinatal Med. 2017; 10:347-53.
8. Peebles PJ, Duello TM, Eickhoff JC, McAdams RM. Antenatal and intrapartum risk factors for neonatal hypoxic ischemic encephalopathy. J Perinatol. 2020; 40:63-9.
9. Azak E, Ceran B, Bagrul D, et al. Evaluation of Cardiac Manifestations in Neonates With Hypoxic İschemic Encephalopathy Received Therapeutic Hypothermia. Turkish Journal of Pediatric Disease. 2021; 15:400-7.
10. Nelson KB, Bingham P, Edwards EM, et al. Antecedents of neonatal encephalopathy in the vermont oxford network encephalopathy registry. Pediatrics. 2012; 130:878-86.
11. Natarajan G, Shankaran S, Laptook AR, et al. Apgar scores at 10 min and outcomes at 6-7 years following hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 2013; 98473-9.
12. Volpe JJ. Neonatal encephalopathy: an inadequate term for hypoxic - ischemic encephalopathy. Ann Neurol. 2012; 72:156-66.
13. Gumus H, Kazanasmaz H, Solmaz A, Aslan H. An investigation of the relationship between base deficit and CRP in asphytic infants. Ann Med Res. 2020; 27:92-6.

14. ter Horst HJ, Sommer C, Bergman KA, Fock JM, van Weerden TW, Bos AF. Prognostic significance of amplitude-integrated EEG during the first 72 hours after birth in severely asphyxiated neonates. Pediatr Res. 2004; 55:1026-33.

15. Coşkun M, Kalkanlı OH, Çolak R, et al. Cranial MRI findings in predicting the severity of hypoxicischemic encephalopathy in term neonates. J Behcet Uz Child Hosp. 2021; 11:15-22.

16. Chalak LF, Nguyen KA, Prempunpong C, et al. Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18-22 months. Pediatr Res. 2018; 84: 861-8.

17. Chawla S, Bates SV, Shankaran S. Is It Time for a Randomized Controlled Trial of Hypothermia for Mild Hypoxic-Ischemic Encephalopathy? J Pediatr. 2020; 220:241-4.

18. Gagne-Loranger M, Sheppard M, Ali N, Saint-Martin C, Wintermark P. Newborns Referred for Therapeutic Hypothermia: Association between Initial Degree of Encephalopathy and Severity of Brain Injury (What About the Newborns with Mild Encephalopathy on Admission?). Am J Perinatol. 2016; 33:195-202.

19. Walsh BH, Inder TE. MRI as a biomarker for mild neonatal encephalopathy. Early Hum Dev. 2018; 120:75-9.

20. Wassink G, Gunn ER, Drury PP, Bennet L, Gunn AJ. The mechanisms and treatment of asphyxial encephalopathy. Front Neurosci. 2014; 8:40.

21. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013; 2013:CD3311.

22. Conway JM, Walsh BH, Boylan GB, Murray DM. Mild hypoxic ischaemic encephalopathy and long term neurodevelopmental outcome - A systematic review. Early Hum Dev. 2018; 120: 80-7.

23. Kariholu U, Montaldo P, Markati T, et al. Therapeutic hypothermia for mild neonatal encephalopathy: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2020; 105:225-8.

24. Lodygensky GA, Battin MR, Gunn AJ. Mild Neonatal Encephalopathy-How, When, and How Much to Treat? JAMA Pediatr. 2018; 172:3-4.

25. Oliveira V, Singhvi DP, Montaldo P, et al. Therapeutic hypothermia in mild neonatal encephalopathy: a national survey of practice in the UK. Arch Dis Child Fetal Neonatal Ed. 2018; 103:388-90.

J Pediatr Res 2024;11(3):176-80
DOI: 10.4274/jpr.galenos.2024.62144

Original Article

Platelets: A Neglected Cell in Cystic Fibrosis Lung Inflammation

Ali Özdemir[1], Murat Ersoy[2]

[1]Mersin City Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Pulmonary, Mersin, Turkey
[2]Mersin City Training and Research Hospital, Clinic of Pediatrics, Mersin, Turkey

ABSTRACT

Aim: There is growing recognition of the critical role of platelets in inflammation and immune responses. However, the role of platelets in lung inflammation in patients with cystic fibrosis (CF) is unclear. Therefore, we aimed to investigate platelet count (PC) and mean platelet volume (MPV) in various clinical conditions in CF patients.

Materials and Methods: A total of 53 pediatric patients with CF were enrolled in this study. Data was retrospectively obtained from the patients' medical records for PC and MPV, and then categorized into 6 groups according to their pulmonary exacerbation and non-pulmonary exacerbation status in chronically colonized or non-colonized patients with CF. The groups were then compared statistically.

Results: The mean age of the patients was 8.01±5.34 years with a male to female ratio of 30:23. In the acute pulmonary exacerbation period, all patients with CF had higher PC than those in a non-pulmonary exacerbation period independent of their chronic colonization status ($p<0.05$). However, PC was not different in non-colonized patients whether they were in acute pulmonary exacerbation or non-pulmonary exacerbation periods ($p>0.05$). Importantly, MPV did not show any statistical significance in any compared settings among these CF patients.

Conclusion: Platelets may play an important role along with other inflammatory cells and mediators in CF lung inflammation during pulmonary exacerbations.

Keywords: Cystic fibrosis, thrombocyte, mean platelet volume

Introduction

Cystic fibrosis (CF) is the most common genetic lung disease affecting mainly the Caucasian population worldwide. It is inherited in an autosomal recessive fashion and affects approximately 100,000 people throughout the world. CF is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR), located on the long arm of chromosome 7. To date, more than 2,000 mutations on the CFTR have been reported. Approximately 70% of CF patients in the Caucasian population are homozygous for the F508del genotype. At the lung level, mutations in the CFTR cause reduced chloride in airway secretion, which favors the reabsorption of sodium and results in dried secretions, poor mucociliary clearance and airway obstruction. This results in recurrent airway bacterial infections *[Pseudomonas aeruginosa (P. aeruginosa)* and *Staphylococcus aureus (S. aureus)* being the most common pathogens]. This is associated with inflammatory cell accumulation and the release of proteolytic and other cell contents with resulting damage to the bronchial walls, leading to a loss of bronchial cartilaginous support and muscle tone, and eventually bronchiectasis (1,2).

Airway inflammation in CF is predominantly neutrophilic in nature with increased concentrations of pro-inflammatory mediators including TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-33, GM-CSF and G-CSF. In addition, other cell types including macrophages and T-lymphocytes express CFTR and contribute to the CF inflammatory response due to a lack of CFTR modulation of the inflammation (3).

Address for Correspondence
Ali Özdemir, Mersin City Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Pulmonary, Mersin, Turkey
Phone: +90 532 325 73 57 **E-mail:** aliozdemir@hotmail.com **ORCID:** orcid.org/0000-0001-7340-0409
Received: 25.06.2024 **Accepted:** 22.08.2024

The researchers suggested that platelets may also be an important contributor to pulmonary inflammation (4,5). Platelet depletion or antiplatelet therapies attenuate injury and mortality in animal models of acute lung injury (6). More importantly, CFTR expression has been shown on human platelets (7). Recent data suggests that CF patients show an increase in circulating activated platelets and platelet reactivity (8). The soluble form of circulating proinflammatory mediator CD40L, which is mainly derived from platelets, was observed to be increased in those patients with CF and *P. aeruginosa* infection (9).

Taken together, these observations support the hypothesis that platelets play a potentially important role in regulating lung inflammation in CF. However, there are few studies examining platelet and lung inflammation interactions in patients with CF (10,11). Therefore, we aimed to investigate platelet count (PC) and mean platelet volume (MPV) in various conditions in our CF patient population.

Materials and Methods

This was a single-center, retrospective study of patients ≤18 years of age with CF, diagnosed by sweat test (>60 mmol/L) and/or positive genotype. The study period occurred between February 2015 and June 2022 at the Mersin City Training and Research Hospital. The medical records of all of the patients with CF were reviewed mainly for patient demographics, complete blood count analysis via an Auto Hematology Analyzer (Advia2120i, Siemens, IRL) and throat/sputum culture results performed on the same day. Those patients with insufficient data or who were lost to follow-up were not included in this study. The patient demographics included age, sex, current body mass index (BMI), CF mutation analysis, age at diagnosis, chronic colonization for *P. aeruginosa* and *S. aureus* defined by the Leeds criteria (12), inhaled antibiotic treatment, latest year best spirometry (if available), and frequency of hospitalization.

Pulmonary exacerbation was defined by a combination of patient-reported symptomatology (increased cough, change in sputum volume, decreased appetite or decreased weight), a clinician-based evaluation and laboratory data (particularly spirometry) in patients with CF (13).

The CF patients were divided into six groups according to their number of obtained respiratory cultures in various clinical status described below;

Group 1. The number of respiratory culture in CF patients with pulmonary exacerbation; n=175.

Group 2. The number of respiratory culture in CF patients with no pulmonary exacerbation, n=127.

Group 3. The number of respiratory culture in chronically colonized CF patients with no pulmonary exacerbation; n=136.

Group 4. The number of respiratory culture in non-colonized CF patients with no pulmonary exacerbation; n=38.

Group 5. The number of respiratory culture in chronically colonized CF patients with pulmonary exacerbation; n=82.

Group 6. The number of respiratory culture in non-colonized CF patients with pulmonary exacerbation; n=47.

Same day PC and MPV from complete blood analysis and throat/sputum cultures obtained from the patient records were categorized into the 6 groups above. It is important to highlight that the same patient's result could be used in different groups for data analysis as per the study design.

This study was approved by the Mersin University Clinical Research Ethics Committee (approval no.: 138, date: 23.02.2022).

Statistical Analysis

Number and percentage values are given as descriptive statistics for categorical variables. Median and quartile values are given as descriptive statistics since the distribution was not suitable for the normal distribution for the continuous variables. The Mann-Whitney U test was used to identify a statistical differences between the mean PC and MPV values among the groups. Statistical significance was considered when p value was <0.05.

Results

During the study period, 53 of the 56 patients with CF met the inclusion criteria with a male to female ratio of 30:23 and a mean age of 8.01±5.34 years. The latest mean BMI (kg/m^2) of the patients was 15.91±2.79. Genetic analysis demonstrated that 9 (17.0%) patients were homozygous for the F508del/F508del mutation, 14 (26.4%) were heterozygous for delF508del/other, and 30 (56.6%) patients had various other mutations. The additional general characteristics of the CF patients, and the number of complete blood analysis and respiratory culture samples obtained among the groups are given in Table I.

When the data was compared among groups, the PC was significantly higher in all CF patients with pulmonary exacerbation in comparison to all patients without pulmonary exacerbation (Group 1 versus Group 2; p=0.001). When the subset groups were compared, the chronically colonized CF patients with pulmonary exacerbation had significantly higher PC than the chronically colonized CF patients with no pulmonary exacerbation (Group 5 versus

Table I. Demographic characteristics of the patients with CF	
Total patients	53
Age* (years)	8.01±5.34
Male	56.6%
Current BMI*	15.91±2.79
Mutation	
Homozygote F508del	9
Heterozygote F508del	14
Other	30
Age at diagnosis* (months)	15±37.83
Pancreatic insufficiency	39 (73.6%)
Chronic colonization	
P. aeruginosa	14 (26.4%)
S. aureus	1 (1.9%)
None	38 (71.7%)
Inhaled tobramycin/colistin	14 (26.4%)
Spirometry* [if available (n=35), predicted %]	
FVC	73.34±20.80
FEV_1	71.34±22.84
Number of matched results of PC & MPV and respiratory culture samples in groups	
Group 1	175
Group 2	127
Group 3	136
Group 4	38
Group 5	82
Group 6	47
Hospitalization* (times during study period)	2.08±2.74

*Results are given as mean ± SD
CF: Cystic fibrosis, BMI: Body mass index, *P. aeruginosa: Pseudomonas aeruginosa, S. aureus: Staphylococcus aureus*, PC: Platelet count, MPV: Mean platelet volume, SD: Standard deviation

Group 3; p=0.048) and the non-colonized CF patients with no pulmonary exacerbation (Group 5 versus Group 4; p=0.0005). In contrast, the PC was not different in the chronically colonized CF patients with no pulmonary exacerbation and the non-colonized CF patients with no pulmonary exacerbation (Group 3 versus Group 4; p=0.3254), and the non-colonized CF patients with pulmonary exacerbation and the non-colonized CF patients with no pulmonary exacerbation (Group 6 versus Group 4; p=0.382). On the other hand, there were no statistically significant differences in terms of MPV in any comparisons among the groups (Table II).

Table II. Comparison of platelet counts and mean platelet volumes among the groups

	Platelet count ($\times10^3$/μL)	**Mean platelet volume (fL)**
Group 1 vs Group 2 p value	419 (358-485) vs 382 (315-451) **0.001**	8 (7.5-8.6) vs 8.2 (7.6-8.8) 0.267
Group 3 vs Group 4 p value	378 (304-472) vs 390.5 (344.7-466.5) **0.3254**	8.2 (7.6-8.9) vs 8.25 (7.7-8.92) 0.5071
Group 5 vs Group 3 p value	431 (386-482) vs 390.5 (344.7-466.5) **0.048**	7.9 (7.5-8.5) vs 8.25 (7.7-8.92) 0.081
Group 5 vs Group 4 p value	431 (386-482) vs 378 (304-472) **0.0005**	7.9 (7.5-8.5) vs 8.2 (7.6-8.9) 0.1292
Group 6 vs Group 4 p value	393 (302-540) vs 378 (303-472.5) **0.382**	8.1 (7.5-8.9) vs 8.2 (7.6-8.9) 0.966

Results are expressed as median and interquartile range

Discussion

CF is characterized by chronic non-resolving lung inflammation, driven by the continuous recruitment of immune cells into the airways which starts at a very early age. This persistent inflammatory state leads to permanent structural damage of the airways in CF patients. Several defective inflammatory mechanisms have been linked to CFTR deficiency including dysregulation of innate and acquired immunity, cell membrane lipid abnormalities, various transcription factor signaling defects, as well as altered kinase and toll-like receptor responses. The inflammation of the CF lung is mainly dominated by neutrophils which release oxidants and proteases, particularly elastase (14,15).

In addition to their well-known role in hemostasis and thrombosis, many studies have identified platelets as playing a key regulatory role in inflammatory reactions (16,17). During neutrophil recruitment to the inflammation site, platelets bind to endothelial cells and interact with leukocytes. The interaction between neutrophil and platelets is mostly mediated by platelet P-selectin binding to P-selectin glycoprotein ligand on leukocytes. Furthermore, firm adhesion of leukocytes to platelets is supported by CD11b/CD18 and CD11a/CD18. In addition to interacting with neutrophils, platelets interact with other leukocyte subpopulations by releasing chemokines thereby activating monocytes. Interestingly, in an experimental mouse model with dysfunctional CFTR, exaggerated acute lung inflammation and platelet activation following

intratracheal lipopolysaccharide or *P. aeruginosa* challenge was seen. This was attributed to the production of aberrant transient receptor potential cation channel 6 (TRPC6)-dependent platelet activation. TRPC6 is thought to be a major driver of lung inflammation and impaired bacterial clearance in CF (18). Autoantibodies to bactericidal/permeability-increasing (BPI) protein, BPI-antineutrophil cytoplasmic autoantibodies (ANCA), are often present in the serum as well as the airways of patients with CF, and have been found to be correlated with airway colonization of *P. aeruginosa*. A study by Hovold et al. (19) found that BPI-ANCA expressed in the airways of CF patients was correlated with *P. aeruginosa* load and PCs. All these studies suggest that the role of platelets in CF lung inflammation is quite complex.

A change in shape also occurs from a disc-shaped cell into an intermediate spherical shaped cell during inflammation (20). It is proposed that platelet volume is correlated with its function (21). Small platelets show lower function than larger sized ones. Previous studies reported conflicting results in MPV values in acute and chronic inflammatory diseases with increased MPV in neonatal sepsis, bronchopulmonary dysplasia, and chronic obstructive lung disease, but decreased MPV in acute appendicitis, Familial Mediterranean Fever, and no change in asthmatic children or chronic inflammatory arthritis (22-26).

A few studies have investigated the values of PC and MPV in limited numbers of children with CF or bronchiectasis (10,27). Nacaroglu et al. (27) examined PC and MPV values in patients with non-CF bronchiectasis. They found that PC in the acute exacerbation and non-exacerbation periods were significantly higher than for those in the control group. Additionally, the average MPV values of the non-exacerbation periods were significantly higher than in the control group. In contrast, the MPV values of the acute exacerbation group were not statistically different when compared to non-exacerbation periods or the control group. A study by Uysal et al. (10) evaluated the relationship between acute exacerbations and the MPV trend in children with CF as a means to predict exacerbations. They reported lower MPV values and higher PC both in the acute exacerbation and the non-exacerbation periods when compared to healthy subjects.

To the best of our knowledge, no studies to date have examined platelet levels and MPV values in different clinical situations in CF patients. The current study suggests a role for platelets in CF lung inflammation by showing that PC was elevated during acute pulmonary exacerbation in patients with CF. This observation is prominent in the chronically bacterial colonized CF population. Interestingly, we did not observe any significant change in PC during acute pulmonary exacerbation in non-colonized CF patients nor in colonized patients in the absence of exacerbation. One speculation in this regard could be that the low grade of lung inflammation present in the absence of exacerbation might not cause prominent changes in PC levels. Notably, our study findings showed no change in platelet size (determined by MPV) in any given scenario. A limited number of studies have reported conflicting results for MPV in CF patients (lower) and in non-CF bronchiectasis patients (higher/non-different) compared to healthy subjects (10,27). The conflicting MPV values in these studies may have been influenced by their different methodological techniques. Based on the current limited data, it can be speculated that MPV values may not be an appropriate marker/predictor for CF lung inflammation.

Study Limitations

The current study has some limitations. First, our clinic is a small center. Therefore, the relatively small sample size of patients with CF might have affected our study results. Second, this study focused only on the correlation of PC and MPV with pulmonary exacerbation, without including other indicators of infection (e.g. white blood cell count, erythrocyte sedimentation rate, C-reactive protein) due to its retrospective nature and incomplete chart data in that regard.

Conclusion

The current study supports the role of platelets in CF lung inflammation during exacerbations with an increase in PC. Further studies with larger CF populations are warranted in order to investigate such a relationship.

Ethics

Ethics Committee Approval: This study was approved by the Mersin University Clinical Research Ethics Committee (approval no.: 138, date: 23.02.2022).

Informed Consent: Not applicable.

Authorship Contributions

Concept: A.Ö., M.E., Design: A.Ö., M.E.,Data Collection and/or Processing: A.Ö., M.E., Analysis and/or Interpretation: A.Ö., M.E., Literature Search: A.Ö., M.E., Writing: A.Ö., M.E.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Ratjen F, Döring G. Cystic fibrosis. Lancet. 2003; 361:681-9.
2. Shteinberg M, Haq IJ, Polineni D, Davies JC. Cystic fibrosis. Lancet. 2021; 397:2195-211.
3. Roesch EA, Nichols DP, Chmiel JF. Inflammation in cystic fibrosis: An update. Pediatr Pulmonol. 2018; 53(Suppl 53):30-50.
4. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost. 2015; 114:449-58.
5. Kim SJ, Davis RP, Jenne CN. Platelets as Modulators of Inflammation. Semin Thromb Hemost. 2018; 44:91-101.
6. Zhao C, Su EM, Yang X, et al. Important Role of Platelets in Modulating Endotoxin-Induced Lung Inflammation in CFTR-Deficient Mice. PLoS One. 2013; 8:e82683.
7. Mattoscio D, Evangelista V, De Cristofaro R, et al. Cystic fibrosis transmembrane conductance regulator (CFTR) expression in human platelets: impact on mediators and mechanisms of the inflammatory response. FASEB J. 2010; 24:3970-80.
8. O'Sullivan BP, Linden MD, Frelinger AL 3rd, et al. Platelet activation in cystic fibrosis. Blood. 2005; 105:4635-61.
9. Bustamante AE, Jaime-Pérez JC, Cordero-Pérez P, et al. A High Level of Soluble CD40L Is Associated with P. aeruginosa Infection in Patients with Cystic Fibrosis. PLoS One. 2016; 11:e0168819.
10. Uysal P, Tuncel T, Olmez D, Babayigit A, Karaman O, Uzuner N. The role of mean platelet volume predicting acute exacerbations of cystic fibrosis in children. Ann Thorac Med. 2011; 6:227-30.
11. Lindberg U, Svensson L, Hellmark T, Segelmark M, Shannon O. Increased platelet activation occurs in cystic fibrosis patients and correlates to clinical status. Thromb Res. 2018; 162:32-7.
12. Lee TW, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. J Cyst Fibros. 2003; 2:29-34.
13. Goss CH. Acute Pulmonary Exacerbations in Cystic Fibrosis. Semin Respir Crit Care Med. 2019; 40:792-803.
14. Cantin AM, Hartl D, Konstan MW, Chmiel JF. Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy. J Cyst Fibros. 2015; 14:419-30.
15. Nichols DP, Chmiel JF. Inflammation and its genesis in cystic fibrosis. Pediatr Pulmonol. 2015; 40(Suppl 40): 39-56.
16. Assinger A, Schrottmaier WC, Salzmann M, Rayes J. Platelets in Sepsis: An Update on Experimental Models and Clinical Data. Front Immunol. 2019; 10:1687.
17. Jenne CN, Kubes P. Platelets in inflammation and infection. Platelets. 2015; 26:286-92.
18. Ortiz-Muñoz G, Yu MA, Lefrançais E, et al. Cystic fibrosis transmembrane conductance regulator dysfunction in platelets drives lung hyperinflammation. J Clin Invest. 2020; 130:2041-53.
19. Hovold G, Lindberg U, Ljungberg JK, Shannon O, Påhlman LI. BPI-ANCA is expressed in the airways of cystic fibrosis patients and correlates to platelet numbers and Pseudomonas aeruginosa colonization. Respir Med. 2020; 170:105994.
20. Zarbock A, Polanowska-Grabowska RK, Ley K. Platelet-neutrophil-interactions: linking hemostasis and inflammation. Blood Rev. 2007; 21:99-111.
21. Thompson CB, Eaton KA, Princiotta SM, Rushin CA, Valeri CR. Size dependent platelet subpopulations: relationship of platelet volume to ultrastructure, enzymatic activity, and function. Br J Haematol. 1982; 50:509-19.
22. Wang J, Wang Z, Zhang M, Lou Z, Deng J, Li Q. Diagnostic value of mean platelet volume for neonatal sepsis: A systematic review and meta-analysis. Medicine (Baltimore). 2020; 99:e21649.
23. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011; 17:47-58.
24. Shen G, Li S, Shao Z, et al. Platelet indices in patients with acute appendicitis: a systematic review with meta-analysis. Updates Surg. 2021; 73:1327-41.
25. Zinellu A, Paliogiannis P, Sotgiu E, et al. Platelet Count and Platelet Indices in Patients with Stable and Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. COPD. 2021; 18:231-45.
26. Tuncel T, Uysal P, Hocaoglu AB, Erge DO, Karaman O, Uzuner N. Change of mean platelet volume values in asthmatic children as an inflammatory marker. Allergol Immunopathol (Madr). 2012; 40:104-7.
27. Nacaroglu HT, Erdem SB, Karaman S, Yazici S, Can D. Can mean platelet volume and neutrophil-to-lymphocyte ratio be biomarkers of acute exacerbation of bronchiectasis in children? Cent Eur J Immunol. 2017; 42:358-62.

J Pediatr Res 2024;11(3):181-4
DOI: 10.4274/jpr.galenos.2024.67944

Case Report

Purulent Pericarditis in an Immunocompetent Young Child

Şeyma Şebnem Ön[1], Ahmet Bozkurt[2], Fırat Ergin[1], Burcugül Karasulu Beci[1], Kübra Cebeci[3], Pınar Yazıcı Özkaya[3], Bülent Karapınar[3], Eser Doğan[1], Osman Nuri Tuncer[4], Zülal Ülger[1]

[1]Ege University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey
[2]Ege University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey
[3]Ege University Faculty of Medicine, Department of Pediatric Intensive Care, İzmir, Turkey
[4]Ege University Faculty of Medicine, Department of Cardiovascular Surgery, İzmir, Turkey

ABSTRACT

Purulent pericarditis in children is a life-threatening condition causing cardiac tamponade and disrupting the hemodynamic status of the patient. It has been associated with high mortality if treatment is delayed. Furthermore, purulent pericarditis may lead to constrictive pericarditis in the long term if not fully treated. Acute purulent pericarditis should be seriously considered in every septic child presenting with signs of right heart decompensation. Echocardiography is important for diagnosis. Diagnostic pericardiocentesis should be performed. Recent experience shows that excellent results can be obtained when adequate surgical drainage and antibiotic therapy are combined. We report a case of purulent bacterial pericarditis caused by methicillin-resistant *Staphylococcus aureus* in an immunocompetent young child presenting with sepsis. The patient was successfully treated with a combined medical and early surgical approach.

Keywords: Purulent pericarditis, *staphylococcus aureus* sepsis, pericarditis, pericardial tamponade

Introduction

Purulent pericarditis is rare and accounts for less than 1% of all cases of pericarditis. Purulent pericarditis usually presents with sepsis clinic accompanied by refractory fever. Suspicion of purulent pericarditis is an indication for emergency pericardiocentesis. Purulent pericarditis should be treated aggressively because death is inevitable if left untreated.

In this case report, we present a 2-year-old immunocompetent girl with purulent bacterial pericarditis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) who presented with sepsis and pericardial tamponade.

Case Report

A 20-month-old female patient was admitted to another center with complaints of vomiting and diarrhea two weeks before presentation to our center. She was diagnosed with gastroenteritis and hospitalized with oral intake disorder and persistent fever (39 °C). Intravenous hydration support was given at this center. Acute phase responses were previously negative [C-reactive protein (CRP) 2 mg/L, white blood cell (WBC): 9,710/mm^3 and 82% neutrophil predominance]. Rotavirus antigen 3+ was detected in stool examination and oral probiotic support was given. On the 3rd day of hospitalization in the other center, the patient developed tachycardia, high fever,

Address for Correspondence
Şeyma Şebnem Ön, Ege University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey
Phone: +90 545 324 26 80 **E-mail:** dr.sebnem.on@gmail.com **ORCID:** orcid.org/0000-0002-1352-7958
Received: 26.09.2023 **Accepted:** 01.07.2024

decreased oxygen saturation and tachypnea. Investigations revealed leukocytosis and increased acute phase response (CRP: 146 mg/L; normal upper limit is 5 mg/L, WBC: 9,920/mm^3, 74% pnl) and increased cardiothoracic index on chest radiography. Pediatric cardiology consultation was requested. During the evaluation of the patient by the cardiologist, diffuse pericardial effusion was observed on echocardiography. The patient was referred to the intensive care unit of another university hospital with the diagnosis of pericardial effusion and sepsis. The patient was hospitalized; ampicillin sulbactam and amikacin combination was started as antibiotic therapy for sepsis. The patient's respiratory virus panel was negative. The Pro-BNP value was 3,264 ng/L (normal value <125 ng/L for reference laboratory) in the tests performed during intensive care unit hospitalization and ibuprofen, aldactazide and colchicine treatments were started due to diffuse pericardial effusion.

Echocardiography performed at this center revealed a 10 mm diffuse pericardial effusion without evidence of tamponade. Pericarditis was considered. The ventricular ejection fraction was normal. Antibiotic treatment was revised to a meropenem+vancomycin combination on the 5th day of hospitalization. There was no growth in the peripheral blood culture and urine culture obtained from the tests performed for the etiology of pericarditis during intensive care unit hospitalization, and the anti-strephtolyzine-O value sent was within the normal limits at 20 IU/mL (normal value <150 IU/mL for reference laboratory). C3 and C4 values were normal; anti-neutrophil cytoplasmic antibody and anti-nuclear antibody values were negative. Viral serology, quantiFERON test, and purified protein derivative of tuberculin were negative.

Pericardial fluid and acute phase reactants of the patient, who did not show clinical improvement during follow-up, increased and an 18 mm thick effusion between the pericardial leaves was detected on thorax computed tomography examination. The patient, who was referred to the pediatric intensive care unit of our hospital on the 7th day of hospitalization, had tachypnea and tachycardia at the first evaluation in our hospital. Her respiratory sounds were deep and her fever was persistently high. Milrinone and dobutamine were started as inotropic treatment because the patient's blood pressure value was at the lower limit of normal (mean arterial pressure MAP 50-55 mmHg). During follow-up, we also observed that the pulse pressure of our patient was narrowed to 25 mmHg. Bilevel positive airway pressure (BiPAP) support was given to the patient due to accompanying respiratory distress. Echocardiographic evaluation performed on admission to our intensive care unit revealed an 18 mm fibrinous pericardial effusion, thickened pericardium, normal left ventricular systolic function and no evidence of cardiac tamponade (Figure 1). After obtaining parental consent, pericardiocentesis was performed and 70 cc of effusion was drained. A pigtail catheter was placed due to the presence of purulent effusion. Bacteriologic, mycotic cultures and ARB were obtained from pericardial fluid samples. The patient's antibiotic therapy was revised as vancomycin+piperacillin tazobactam and fluconazole until the culture results were received. Ibuprofen as an anti-inflammatory agent and pantoprazole as a gastroprotective agent were also initiated. Blood tests obtained from the patient after pericardiocentesis showed a significant decrease in acute phase reactant values. Clinically, fever was controlled, tachycardia and tachypnea regressed, and nasal oxygen support was started since BiPAP was no longer needed. Hemodynamically, the patient was normotensive. After pericardiocentesis, the patient was followed up with daily echocardiography. The next day, it was observed that the amount of fluid coming from the 24-hour drain was 100 cc and 9 mm pericardial effusion continued on the echo and cardiovascular surgery was requested. Surgical drainage and subtotal pericardiectomy were performed (Figure 2) and a pericardial drainage catheter was placed. The removed pericardial tissue was very thick and fibrous. Pathologic evaluation of the surgically removed pericardial tissue was reported as chronic fibrinopurulent pericarditis.

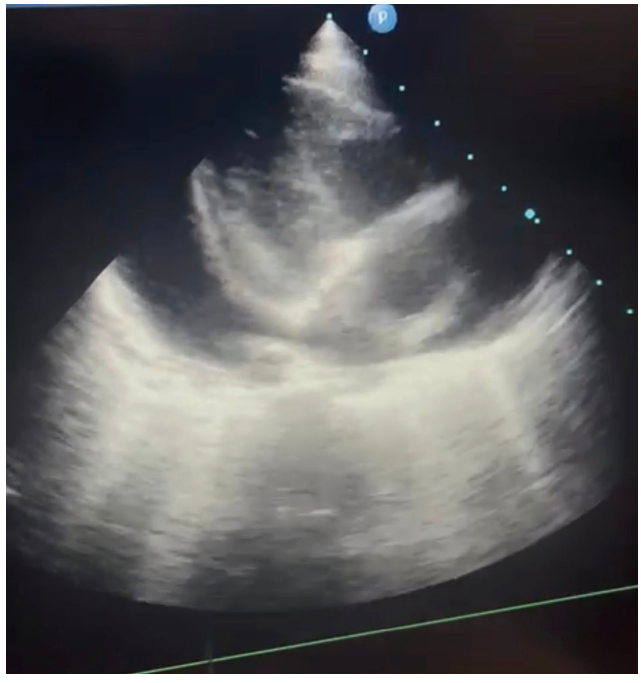


Figure 1. Echocardiographic image of patient (pericardial effusion)

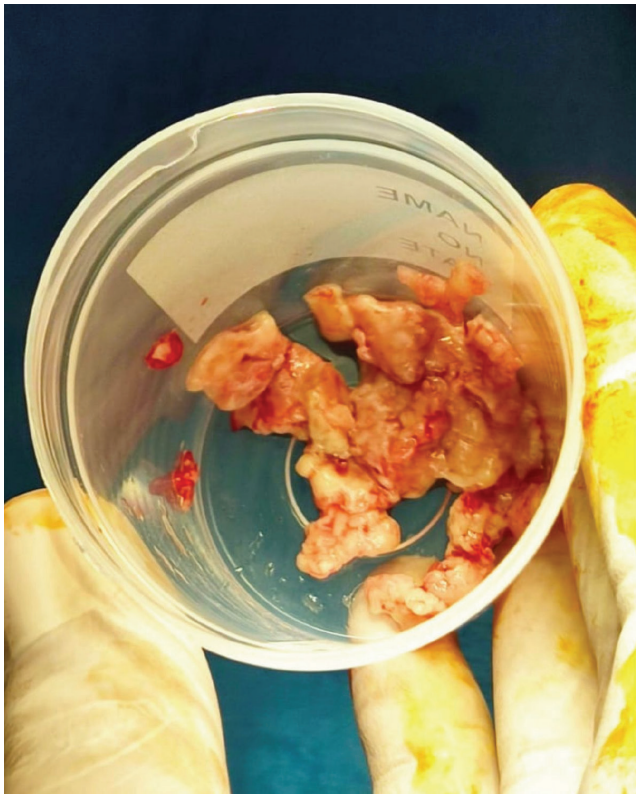


Figure 2. Removed pericardial tissue

MRSA growth was detected in the sample sent from the first pericardiocentesis material. Blood cultures were negative.

In the 2nd week of intensive care unit follow-up, the patient, who no longer needed nasal oxygen and was stabilized, was transferred to our pediatric cardiology service for further treatment. We completed and discontinued 14-day fluconazole and piperacillin-tazobactam treatment in our patient whose vitals were stable in room air in the ward follow-up.

The 6-week antibiotic therapy was completed and the patient was discharged from the hospital with planned outpatient follow-up.

Discussion

Purulent bacterial pericarditis is a rare condition in children (1). It presents as acute pericarditis with symptoms of systemic inflammation, fever, chest pain and dyspnea (2-6). Physical examination findings of purulent pericarditis include increased jugular venous pressure, tachycardia, tachypnea, fever and hepatomegaly. An enlarged heart shadow on chest radiography is one of the most important findings suggesting the diagnosis (5). Pericardial friction sound is not a common finding in purulent pericarditis (7,8). ST segment elevation due to epicardial damage, which is the classical electrocardiographic feature of pericarditis, has also been reported to be rare in purulent pericarditis (9,10). In our patient, there was no pathologic finding on electrocardiogram except for diffuse low voltage. In cases of purulent pericarditis in pediatric patients reported in the literature (2-10), pericardial drainage (temporary pericardial drainage was left in place in some cases) was required in all cases for both diagnostic and therapeutic purposes. Furthermore, all cases were medically treated with antibiotics of different durations (range: 2-8 weeks) and routes [oral/intravenous (IV)/combination].

An older study showed that early intervention with pericardiectomy is indicated in purulent pericarditis if tamponade occurs after initial pericardiocentesis or if the fever persists despite appropriate antibiotic therapy (9,10). It is known that patients with bacterial pericarditis have a higher risk of constrictive pericarditis after pericarditis. Surgical intervention should be considered in purulent bacterial pericarditis in order to reduce the risk of constrictive pericarditis and to decrease morbidity and mortality. The mortality rate in purulent pericarditis is reduced to 20% or less when medical and surgical treatments are combined (9,10).

The spectrum of microorganisms causing purulent pericarditis varies in different parts of the world. In reports in the Western literature, *Streptococcus pneumonia* was the most common cause in the pre-antibiotic era, but *Staphylococcus aureus* has become the most important agent during the antibiotic era (9,10). When a specific focus of infection occurs, the pericardium may become infected by direct spread from septic emboli or pulmonary infection.

In our patient, purulent pericarditis was due to *Staphylococcus aureus* sepsis as a secondary bacterial infection due to rotavirus gastroenteritis.

There are two major complications of purulent pericarditis: cardiac tamponade and septicemia. Cardiac tamponade may develop early due to a rapid accumulation of purulent effusion fluid and it requires early treatment. Sepsis is still a serious complication despite effective antibiotic regimens (10). Antibiotic agent selection should be based on culture antibiograms; however, it is not always possible to culture the agent. Initial empirical antibiotic therapy initiated by the referring clinician sometimes prevents the microorganism from being produced.

Conclusion

Purulent pericarditis in children is a life-threatening condition causing cardiac tamponade. Early diagnosis and early treatment are very important. Emergency pericardiocentesis is life-saving and has diagnostic value. Complete surgical drainage and appropriate parenteral antibiotic therapy are crucial in order to prevent constrictive pericarditis in the long term.

Ethics

Informed Consent: Parental consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Ş.Ş.Ö., F.E., K.C., O.N.T., P.Y.Ö., B.K., Concept: Ş.Ş.Ö., E.D., Z.Ü., Design: Ş.Ş.Ö., E.D., Z.Ü., Data Collection and/or Processing: Ş.Ş.Ö., A.B., B.K.B., Analysis and/or Interpretation: Ş.Ş.Ö., Z.Ü., Literature Search: Ş.Ş.Ö., B.K.B., K.C., O.N.T., Writing: Ş.Ş.Ö., A.B.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Pankuweit S, Ristić AD, Seferović PM, Maisch B. Bacterial pericarditis: diagnosis and management. Am J Cardiovasc Drugs. 2005; 5:103-12.
2. Imazio M, Gaita F. Diagnosis and treatment of pericarditis. Heart. 2015; 101:1159-68.
3. Imazio M, Spodick DH, Brucato A, Trinchero R, Adler Y. Controversial issues in the management of pericardial diseases. Circulation. 2010; 121:916-28.
4. Cakir O, Gurkan F, Balci AE, Eren N, Dikici B. Purulent pericarditis in childhood: ten years of experience. J Pediatr Surg. 2002; 37:1404-8.
5. Megged O, Argaman Z, Kleid D. Purulent pericarditis in children: is pericardiotomy needed? Pediatr Emerg Care. 2011; 27:1185-7.
6. Majid AA, Omar A. Diagnosis and management of purulent pericarditis. Experience with pericardiectomy. J Thorac Cardiovasc Surg. 1991; 102:413-7.
7. Little WC, Freeman GL. Pericardial disease. Circulation. 2006; 113:1622-32. Erratum in: Circulation. 2007; 115:e406.
8. Maisch B, Seferović PM, Ristić AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; The Task force on the diagnosis and management of pericardial diseases of the European society of cardiology. Eur Heart J. 2004; 25:587-610.
9. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015; 36:2921-64.
10. Imazio M, Brucato A, Maestroni S, et al. Risk of constrictive pericarditis after acute pericarditis. Circulation. 2011; 124:1270-5.

J Pediatr Res 2024;11(3):185-8
DOI: 10.4274/jpr.galenos.2024.47786

Case Report

A Rare Complication in a Patient with Acute Promyelocytic Leukemia; ATRA and Posaconazole Associated Hypercalcemia

Yeşim Yiğit[1], Meliha Demiral[2], Ayşen Türedi Yıldırım[3], Hüseyin Gülen[3]

[1]Atatürk City Hospital, Clinic of Pediatric Hematology and Oncology, Balıkesir, Turkey
[2]Atatürk City Hospital, Clinic of Pediatric Endocrinology, Balıkesir, Turkey
[3]Manisa Celal Bayar University Hospital, Clinic of Pediatric Hematology, Manisa, Turkey

ABSTRACT

All-trans retinoic acid (ATRA), a derivative of vitamin A, has dramatically altered the treatment landscape for acute promyelocytic leukemia (APL). APL is characterized by the abnormal maturation of myeloid cells, which become arrested at the promyelocyte stage. ATRA effectively induces these cells to differentiate and undergo apoptosis. While generally well-tolerated, ATRA has been associated with rare adverse effects, including hypercalcemia. This case report underscores the importance of vigilant monitoring for ATRA-related side effects, especially when combined with medications which inhibit cytochrome P450 enzymes. Antifungal prophylaxis is common during leukemia treatment. Here, we present a rare instance of hypercalcemia in a pediatric patient attributed to the concurrent use of posaconazole and ATRA. A 15-year-old girl presented with widespread bruising, abnormal uterine bleeding, and pancytopenia. Subsequent investigations led to an APL diagnosis. Classified as standard-risk APL, she received chemotherapy according to the acute myelogenous leukemia-Berlin-Frankfurt-Münster 2004 protocol. After an ATRA course was started in the third month of maintenance treatment, she applied to the hospital with constitutional symptoms of weakness and fatigue on the third day of treatment. In the biochemical tests of the patient, serum Ca concentration was determined to be 16.5 mg/dL. Parathormone was 64.3 pg/mL and the 25-OH D vitamin level was 22 ng/mL and so were within the normal limits. Complete blood count was within the normal range. Although hypercalcemia is a side effect seen in the combined use of ATRA and azole antifungals, to the best of our knowledge, this is the first report in the literature that it was observed in the pediatric age group due to the simultaneous use of posaconazole and ATRA.

Keywords: All-trans retinoic acid (ATRA), posaconazole, hypercalcemia

Introduction

All-trans retinoic acid (ATRA), a derivative of vitamin A, has dramatically altered the treatment landscape for acute promyelocytic leukemia (APL) (1). APL is characterized by the abnormal maturation of myeloid cells, which become arrested at the promyelocyte stage. ATRA effectively induces these cells to differentiate and undergo apoptosis (2). While generally well-tolerated, ATRA has been associated with rare adverse effects, including hypercalcemia (3). The widespread use of antifungal agents in leukemia treatment often leads to a higher incidence of antifungal-related side effects in this patient population.

Address for Correspondence
Yeşim Yiğit, Atatürk City Hospital, Clinic of Pediatric Hematology and Oncology, Balıkesir, Turkey
Phone: +90 507 943 86 93 **E-mail:** yesimdr@hotmail.com **ORCID:** orcid.org/0000-0002-0255-1266
Received: 18.03.2024 **Accepted:** 04.06.2024

Case Presentation

A 15-year-old girl was diagnosed with APL following investigations which revealed pancytopenia after she presented with symptoms of widespread bruising and abnormal uterine bleeding. Her laboratory tests revealed the following; hemoglobin was 5.5 gr/dL, leukocyte was 1,140/mm^3, thrombocyte was 8,000/mm^3, whereas the bone marrow aspirate showed increased numbers of leukemic promyelocytes (90%) and coagulation tests were consistent with pre-DIC condition. Serum calcium (Ca) concentrations were 9 mg/dL and phosphorus was 3.2 mg/dL. Serum electrolytes and renal function tests were within the normal limits. The bone marrow was hypercellular with 90% leukemic promyelocytes. A chromosome analysis showed 46 XX with translocation (15q+; 17q-) karyotype.

Our patient was considered as being in a standard risk group for APL and she was given acute myelogenous leukemia-Berlin-Frankfurt-Münster 2004 protocol chemotherapy. In this protocol, induction, consolidation, intensification and maintenance chemotherapy courses were applied to the patient sequentially. This protocol includes five types of antineoplastic and antimetabolic drugs (cytarabine, idarubicin, etoposide phosphate, mitoxantrone and thioguanine). ATRA is administered concurrently with cycles of 25 mg/m^2/day in 2 divided doses for 15 days with each 4-week cycle of chemotherapy. ATRA courses were started for the patient, as per the protocol recommendation.

Posaconazole treatment was arranged as 300 milligrams/day prophylaxis, as recommended by the department of pediatric infectious diseases.

Maintenance chemotherapy was planned to be given as 6-thioguanine 40 mg/m^2/day PO and cytarabine 40 mg/m^2 subcutaneously every four weeks for four consecutive days for one year. During maintenance treatment, ATRA was planned to be given 25 mg/m^2/day for fourteen days every three months, starting from the third month.

After the ATRA course was started in the third month of maintenance treatment, she was admitted to the hospital with constitutional symptoms of weakness and fatigue on the third day of treatment. In the biochemical tests of the patient, the serum Ca concentration was 16.5 mg/dL, albumin was 5.1 g/dL, creatinine was 0.9 mg/dL and uric acid was 7.1 mg/dL. Parathormone was found to be 64.3 pg/mL and the 25-OH D vitamin level was found to be 22 ng/mL and so they were within the normal limits. The complete blood count was within the normal range. She was also not using any other medications.

Intravenous hydration and furosemide were started simultaneously. Posaconazole treatment was stopped. After 8 hours, the serum Ca level was measured as 16.2 mg/dL, and corticosteroid was added to the treatment at two doses of 10 mg/m^2/day. After steroid treatment was given in 2 doses with an interval of 12 hours, the serum Ca level was measured as 15 mg/dL. Since the patient's complaints of weakness and fatigue persisted and a significant decrease in her Ca level could not be achieved, 1 mg/kg bisphosphonate (pamidronate) treatment was started. After the first dose of pamidronate treatment, the second dose of pamidronate treatment was given the next day as the control Ca was high at 14 mg/dL. After the second dose, control Ca was measured as being 8 mg/dL. 48 hours after hypercalcemia was detected, both laboratory parameters and the patient's complaints completely resolved. ATRA treatment for 2 weeks was given as planned. Posaconazole was discontinued during subsequent ATRA treatments and hypercalcemia did not recur. Consent was obtained from the patient for publication.

Discussion

ATRA is a cornerstone of APL treatment. Its metabolism, primarily mediated by the cytochrome P450 enzymes CYP2C9 and CYP3A4, can be significantly impacted by azole antifungals. Given their potent inhibitory effects on the cytochrome P450 system, triazole antifungals are commonly used prophylactically in APL patients in order to prevent fungal infections (4).

Invasive aspergillosis is the most common invasive fungal infection among patients with low white blood cell counts. Despite routine antifungal prevention for high-risk hematological cancer patients, breakthrough fungal infections can still occur. Posaconazole has emerged as a valuable option for preventing fungal infections in these vulnerable individuals (5). Prophylaxis with posaconazole was started for our patient, who was at risk for IFI during the period of severe and long-lasting neutropenia.

Although hypercalcemia is a side effect seen in the combined use of ATRA and azole antifungals, to the best of our knowledge, this is the first report in the literature in which it was observed in the pediatric age group due to the simultaneous use of posaconazole and ATRA.

This case highlights the importance of monitoring ATRA's side effects when it is used in combination with drugs inhibiting the cytochrome P450 enzymes.

The exact cause of ATRA-induced hypercalcemia remains uncertain; it is unclear if the parent drug or a metabolite is responsible. Consequently, monitoring ATRA levels might not be helpful in preventing this complication. The proposed mechanisms for ATRA-related hypercalcemia include enhanced bone breakdown by osteoclasts, elevated interleukin-6 stimulating bone resorption, and increased parathyroid hormone-related protein (6-9). Nagasawa and Okawa (3) suggested that ATRA might cause hypercalcemia by increasing PTH-related protein levels.

Sakamoto et al. (10) observed hypercalcemia not only in leukemia patients during initial ATRA treatment, but also in those who had achieved complete remission and were continuing ATRA therapy. This suggests that a genetic predisposition affecting retinoic acid metabolism or its hormone-like actions might be prevalent in the Japanese population (10).

The first treatment of hypercalcemia is to increase the urinary excretion of calcium hydration, via loop diuretics such as furosemide. If there is hypercalcemia due to excess vitamin D, glucocorticoid is effective. Calcitonin reduces osteoclastic resorption in bones, but this effect is short term and transient. Nitrogen-containing bisphosphonates, pamidronate and zoledronic acid, induce osteoclast apoptosis. These are potent inhibitors of bone resorption. Bisphosphonates can rapidly lower serum calcium levels in patients with hypercalcemia from various causes. Its effects last for weeks (11).

Here, a pediatric APL patient with hypercalcemia secondary to ATRA treatment was successfully treated with bisphosphonate. Cordoba et al. (9) found that bisphosphonates such as zoledronic acid can effectively treat hypercalcemia and may be used preventively during subsequent ATRA treatments in order to avoid this complication. Sakamoto et al. (10) reported the successful use of bisphosphonate (pamidronate) in the treatment of hypercalcemia due to ATRA use in an 11-year-old patient diagnosed with APL.

In our patient, we first discontinued posaconazole and then added bisphosphonate (pamidronate) when she had no benefit from the supportive treatment (hydration, forced diuresis) and corticosteroid. We continued ATRA treatment in our patient. No definitive approach has been found in the literature for this side effect, which is not common in the pediatric age group.

Although it is clear that the patients' use of azole group antifungals with ATRA treatment triggers hypercalcemia, there are cases where only ATRA use also causes hypercalcemia (10).

Since there was no clear approach on this issue, we did not discontinue ATRA treatment. During our patient's ATRA cycles, we discontinued azole antifungal prophylaxis and performed close biochemical monitoring. No recurrence of hypercalcemia was observed.

We present this case because it is rare in the pediatric age group, has a variety of approaches, and, to the best of our knowledge, is the first report of hypercalcemia secondary to posaconazole and ATRA treatment in a pediatric APL patient.

Ethics

Informed Consent: Consent was obtained from the patient for publication.

Authorship Contributions

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

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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

References

1. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood. 1988; 72:567-72.
2. Sato A, Imaizumi M, Saito T, et al. Detection of apoptosis in acute promyelocytic leukemia cells in vivo during differentiation-induction with all-trans retinoic acid in combination with chemotherapy. Leuk Res. 1999; 23:827-32.
3. Nagasawa M, Okawa H. All-trans retinoic acid induced hypercalcemia in a patient with acute promyelocytic leukemia: its relation to increased PTH-rP. Int J Hematol. 1994; 59:143-4.
4. Marill J, Cresteil T, Lanotte M, Chabot GG. Identification of human cytochrome P450s involved in the formation of all-trans-retinoic acid principal metabolites. Mol Pharmacol. 2000; 58:1341-8.
5. Mattiuzzi G, Yilmaz M, Kantarjian H, et al. Pharmacokinetics of posaconazole prophylaxis of patients with acute myeloid leukemia. J Infect Chemother. 2015; 21:663-7.
6. Afacan Ozturk HB, Albayrak M, Maral S, et al. Hypercalcemia associated with the interaction between all trans retinoic acid and posaconazole in an acute promyelocytic leukemia case. J Oncol Pharm Pract. 2021; 27:2027-9.
7. Sakakibara M, Ichikawa M, Amano Y, et al. Hypercalcemia associated with all-trans-retinoic acid in the treatment of acute promyelocytic leukemia. Leuk Res. 1993; 17:441-3.

8. Niesvizky R, Siegel DS, Busquets X, et al. Hypercalcaemia and increased serum interleukin-6 levels induced by all-trans retinoic acid in patients with multiple myeloma. Br J Haematol. 1995; 89:217-8.

9. Cordoba R, Ramirez E, Lei SH, et al. Hypercalcemia due to an interaction of all-trans retinoic acid (ATRA) and itraconazole therapy for acute promyelocytic leukemia successfully treated with zoledronic acid. Eur J Clin Pharmacol. 2008; 64:1031-2.

10. Sakamoto O, Yoshinari M, Rikiishi T, et al. Hypercalcemia due to all-trans retinoic acid therapy for acute promyelocytic leukemia: a case report of effective treatment with bisphosphonate. Pediatr Int. 2001; 43:688-90.

11. Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. Curr Opin Pediatr. 2010; 22:508-15.

J Pediatr Res 2024;11(3):189
DOI: 10.4274/jpr.galenos.2024.e001

Erratum

Bağcı U, Tekin A, Tiryaki Birol S, Ulman İ. Evaluation of Factors Affecting Surgical Success in Megameatus Intact Prepuce Cases. J Pediatr Res. 2024;11:123-8.

The mistake has been made inadvertently by the author.

The name of Sibel Tiryaki Birol, one of the authors on the first page of the article, has been corrected by the author as follows:

Incorrect name is highlighted in bold:

Uygar Bağcı, Ali Tekin, Sibel **Tiryaki Birol**, İbrahim Ulman

Corrected name is highlighted in bold:

Uygar Bağcı, Ali Tekin, Sibel **Tiryaki**, İbrahim Ulman

In the Authorship Contributions section on page 127, the incorrect name is highlighted in bold:

Surgical and Medical Practices: U.B., A.T., **S.T.B.**, İ.U., Concept: U.B., İ.U., Design: U.B., A.T., **S.T.B.**, İ.U., Data Collection and/or Processing: U.B., A.T., Analysis and/ or Interpretation: U.B., A.T., İ.U., Literature Search: U.B., Writing: U.B., A.T., **S.T.B.**

In the Authorship Contributions section on page 127, the corrected name is indicated in bold:

Surgical and Medical Practices: U.B., A.T., **S.T.**, İ.U., Concept: U.B., İ.U., Design: U.B., A.T., **S.T.**, İ.U., Data Collection and/or Processing: U.B., A.T., Analysis and/ or Interpretation: U.B., A.T., İ.U., Literature Search: U.B., Writing: U.B., A.T., **S.T.**