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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

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Manuscript Types

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Editorial Comment:

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Letters To The Editor:

Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1.
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word	Limit Reference	Limit Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	100	No abstract	5	1	1

References:

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In-text Citations:

Assign a number to each reference within the text as you cite it. **The citations are identified by Arabic numbers in superscript**. The number must be used even if the author(s) is named in the text.

Example: In his study, Babbott[11] found that….

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Example: Multiple studies have indicated that….[7-10]

Placement of the citation numbers is generally at the end of the sentence, unless there are two individual sets of citations in each sentence. Generally reference numbers should be placed outside of periods and commas, inside of colons and semicolons.

Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tıp Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Invited Review

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Advancing Pediatric Epilepsy Care: Efficacy and Mechanisms of Melatonin Intervention

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Abstract

Seizures and epilepsies pose significant challenges in pediatric populations, necessitating precise classification and effective management. The International League Against Epilepsy updated its classification system in 2017 to standardize epilepsy care. This study investigated melatonin, a neurohormone known for its role in circadian rhythm regulation, and its potential to enhance the diagnosis, management, and quality of life of pediatric epilepsy patients. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic review was conducted to explore the relationship between melatonin and pediatric epilepsies. PubMed searches were performed using specific search terms, with eligibility criteria including studies on melatonin's pathophysiological, biochemical, and therapeutic effects in pediatric epilepsy. Studies involving patients aged 0-18 years were published between 2003 and 2023. Four-teen studies with 898 pediatric patients were included. Melatonin was administered as an adjunct to antiepileptic therapy with the aim of alleviating disorders associated with epileptic encephalopathies or assisting electroencephalogram procedures. Findings were varied: Some studies indicated a reduction in seizure frequency with melatonin, while others provided inconclusive results. Improvements in sleep disorders related to epilepsy were noted with melatonin supplementation, which indirectly enhanced the overall quality of life. Melatonin has potential as an adjunctive therapy for pediatric epilepsy, with positive effects on seizure frequency and sleep quality. However, methodological limitations in some studies and inconclusive data underscore the need for further research to determine the efficacy of melatonin in pediatric epilepsy management. The diverse potential of melatonin in treating neurological disorders highlights the importance of continued, comprehensive research into its therapeutic application.

Keywords: Melatonin, melatonin receptors, pediatric epilepsy, seizure management, sleep disorders, antiepileptic therapy

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Introduction

Seizures and epilepsies are prevalent conditions in childhood, and accurate classification, management, and treatment are essential for effective patient care.[1] In 2017, the International League Against Epilepsy (ILAE) introduced a revised classification system for seizures, epilepsies, and epileptic syndromes. This update aimed to standardize epilepsy management and enhance communication among healthcare professionals for both scientific and diagnostic therapeutic purposes.[2] The updated ILAE classification system adopts a multilevel framework, including the categorization of seizure types[3], epilepsies, and, where applicable, the definition of epileptic syndromes.[4] Epilepsy, a debilitating disorder in pediatric patients, significantly impacts quality of life and requires prolonged treatment, often without complete seizure control and with potential comorbidities.[5,6] Given these challenges, pediatric epilepsy remains a dynamic and evolving field of research. There is a growing need to explore therapeutic agents that could improve the diagnosis, management, and quality of life of pediatric patients with epilepsy while also considering the risk of adverse effects associated with these treatments. Melatonin, a neurohormone produced by the pineal gland and locally in the retina, exhibits a circadian secretion pattern (elevated levels at night and reduced levels during the day).[7] Although melatonin is well known for its role in regulating circadian sleep-wake rhythms, cancer inhibition, free radical detoxification, and protection against oxidative stress, its potential antiepileptic properties have been less extensively studied.[8-10] Emerging scientific evidence suggests that melatonin may improve patients' quality of life by influencing sleep quality, reducing seizure frequency, and modulating oxidative stress.[11] This study aimed to evaluate the role of melatonin in enhancing the management of pediatric epilepsy and its potential benefits in improving overall patient outcomes.

Highlights

- **Epilepsy management::** The 2017 ILAE classification system aimed to standardize epilepsy care, particularly for children.
- **Role of melatonin:** Melatonin, which regulates circadian rhythms, may have potential in pediatric epilepsy treatment.
- **Systematic review:** A Preferred Reporting Items for Systematic Reviews and Meta-Analyses guided review of 14 studies (898 patients) examines melatonin's role in pediatric epilepsy.
- **Study findings:** Melatonin, an adjunct to antiepileptic therapy, may reduce seizures and improve sleep in children with epilepsy.
- **Variability in findings:** While some studies have shown positive effects of melatonin, others have been inconclusive, indicating a need for further research.
- **Quality of life:** Melatonin may indirectly improve quality of life by addressing epilepsy-related sleep difficulties.
- **Therapeutic potential:** Despite its limitations, melatonin demonstrates promise in pediatric epilepsy care, highlighting the need for extensive investigation.

Material and Method

Study Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (**Figure 1**). The search was independently conducted by two authors using PubMed. To ensure a comprehensive search, the following terms were combined: "Epilepsy" or "Epilepsy, Partial, Motor" or "Epilepsy, Partial, Sensory" or "Epilepsy, Benign Neonatal" or "Epilepsy, Reflex" or "Myoclonic Epilepsy, Juvenile" or "Epilepsy, Rolandic" or "Epilepsy, Frontal Lobe" or "Epilepsy, Complex Partial" or "Epilepsy, Post-Traumatic" or "Epilepsy, Temporal Lobe" or "Epilepsy, Absence" or "Epilepsy, Tonic-Clonic" or "Epilepsy, Generalized" or "Drug Resistant Epilepsy" or "Epilepsies, Myoclonic" or "Epilepsies, Partial" and "Melatonin" or "Receptor, Melatonin, MT2" or "Receptor, Melatonin, MT1" or "Receptors, Melatonin" as keywords or Medical Subject Headings terms. Additionally, the reference lists of all included articles and the top hits from PubMed were reviewed to identify further potentially relevant studies. To prevent overlap with ongoing reviews, international prospective register of systematic reviews was also searched for similar reviews.

Selection Criteria

Eligible studies included those investigating the pathophysiological, biochemical, and therapeutic actions of melatonin, its metabolic pathways, and its relation to pediatric epilepsies. We included articles examining melatonin's role in electroencephalogram (EEG) procedures, its potential interactions with anti-seizure drugs, and its impact on the overall quality of life of patients with epilepsy. Studies were excluded if they did not focus on pediatric patients (0 to 18 years), did not explicitly address the relationship between melatonin, its receptors, and epilepsy, or did not directly investigate aspects of EEG signal recording or quality in patients with epilepsy were excluded. Additionally, we excluded studies lacking accessible data or full text, articles in languages other than English, duplicates, and studies with inadequate scientific methodology. The search and evaluation were conducted independently by two authors (S.M.C. and D.B.), with any discrepancies resolved by F.F.C., an experienced researcher in systematic reviews. After applying the inclusion and exclusion criteria and reviewing the abstracts, the investigators reached a consensus. Only studies published between 2003 and 2023 that involved pediatric and adolescent patients (birth to 18 years) were included.

Data Extraction and Criteria Assessment

Data extracted included title, year of publication, study design, sample size, population characteristics, intervention, comparator (if applicable), outcomes, and conclusions. The data extraction followed the Population, Intervention, Comparison, Outcome

framework and was organized into structured tables using Excel. One investigator conducted the initial extraction, which was independently verified by another investigator. Two investigators, along with F.F.C., reviewed each article independently and resolved discrepancies through discussion and consensus. The final results were reviewed by the senior investigator (S.M.C.).

Risk of Bias Assessment

Risk of Bias (RoB) was assessed using the ROBINS-I tool for non-randomized studies and the RoB 2 tool for randomized trials. Two authors (F.F.C. and D.B.) performed the assessment independently, achieving a 92% inter-rater agreement. Discrepancies were resolved through discussion. Articles with serious RoB were excluded. The RoB assessment is detailed in tables 1aS and 1bS in the online resource.

Study Quality Assessment

The study quality was assessed using the GRADE approach. The initial grade was determined based on study design, with randomized trials providing high-quality evidence and observational studies providing low-quality evidence. Factors that could lower or increase quality were evaluated, resulting in an overall evidence grade (high, moderate, low, very low). Two authors (S.M.C. and F.C.) conducted this assessment independently, obtaining a 94% inter-rater agreement. Articles rated as very low quality were excluded. The quality assessment is presented in table 2S of the online resource.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population, including demographics, intervention methods, and outcome measures. Quantitative outcomes, such as seizure frequency, sleep parameters, and EEG recordings, were analyzed using meta-analytic techniques when applicable. Random-effects models were used to account for heterogeneity among studies, with effect sizes and 95% confidence intervals estimated to assess the overall treatment effects of melatonin. Subgroup analyses were performed to explore variability based on factors such as age, epilepsy type, and melatonin dosage. Sensitivity analyses were conducted to evaluate the robustness of findings by excluding studies with high RoB or small sample sizes. Publication bias was assessed using funnel plots and Egger's test, with adjustments made if significant bias was detected. Statistical significance was defined as $p<0.05$.

Ethical Considerations

The research did not involve human or animal subjects, so ethical approval from the ethics committee was not required. All procedures adhere to standard ethical guidelines and academic research regulations. No consent form was required due to the study design.

Results

We identified 14 studies that examined the role of melatonin or its receptors in pediatric epilepsy (**Table 1**). The combined cohort of these studies included 898 patients who received melatonin as an adjunct to anti-seizure therapy. The primary aim of this study was to improve conditions associated with the underlying pathology in epileptic encephalopathies or to assist with EEG procedures.

Study Selection and Focus

Among the included studies, only two reviews by Kennaway[12] and Banerjee and Kumar[13] focused on the relationship between exogenous melatonin administration and its effectiveness as an anti-seizure therapy. These reviews also examined how melatonin affects the circadian rhythm of endogenous melatonin in patients with seizure, particularly addressing its role in pediatric patients with sleep-related epilepsy disorders.

Melatonin Levels and Epileptic Activity

Five studies investigated the correlation between melatonin levels and cerebral epileptic activity. These studies assessed variations in melatonin secretion among pediatric epileptic patients by analyzing both baseline secretion and levels during or shortly after seizures. A common finding was a reduction in basal melatonin levels or alterations in circadian rhythm among epileptic patients. Tarcin et al.[14] reported reduced basal melatonin levels in pediatric patients with status epilepticus and electrical status epilepticus during sleep (ESES) compared to controls. Similarly, Ayça et al.[15] observed lower serum melatonin levels at 9 a.m. in patients with ESES in a cohort of 39 pediatric patients.

Manni et al.[16] studied both adults and adolescents with juvenile myoclonic epilepsy using a semi-structured interview (Morningness-Eveningness Questionnaire), Pittsburgh Sleep Quality Index (PSQI), and salivary melatonin measurements. They found an altered circadian rhythm of melatonin levels in patients with epilepsy, potentially influenced by the epileptic condition.

The Pharmacological Therapeutic Role

Three studies explored melatonin's pharmacological role in treating typical childhood epilepsy. Sun et al.[17] and Wan et al.[18] examined melatonin's anticonvulsant activity in infantile spasms, either as an adjunct to or replacement for traditional anti-seizure therapy. Their studies indicated that melatonin, combined with adrenocorticotropic hormone (ACTH) or used alone significantly reduced spasm frequency and prolonged the period without spasms.

Verma et al.[19] conducted a randomized, double-blind, placebo-controlled clinical trial on the effect of melatonin in the treatment of generalized epilepsy with generalized-onset motor seizures in adolescents and adults. This study found that melatonin (3 mg/day) combined with valproate resulted in a significant reduction in seizure frequency, an increased seizure-free rate, and improved sleep quality.

Inconclusive Data

Some studies have provided inconclusive data regarding melatonin's efficacy in pediatric epileptic disorders. For instance, Brigo et al.[20] reviewed melatonin as an add-on therapy in 106 patients aged 18 years. Despite several promising results regarding seizure frequency reduction, the poor quality of some studies prevented definitive conclusions about melatonin's effectiveness as an add-on therapy.

Impact of Sleep Quality

Seven studies emphasized melatonin's effectiveness in improving sleep quality in children with epilepsy. Melatonin supplementation enhances the overall quality of life by improving sleep-related issues associated with epilepsy.

Bonuccelli et al.[21] conducted a double-blind, placebo-controlled study of 100 patients aged 1-6 years. They administered liposomal melatonin and performed sleep EEG. They found reduced sleep latency and improved EEG outcomes, thereby enhancing the efficiency of the procedure and the safety of melatonin use.

Gustafsson et al.[22] compared the EEG results of 129 children administered melatonin and 113 children subjected to sleep deprivation. Their study indicated that melatonin was more effective in inducing sleep in younger children (0-4 years) than in older children (9-12 years), likely due to greater sleep lability in younger patients. Jain et al.[23] observed that prolonged release of melatonin reduced sleep latency, increased rapid eye movement (REM) latency, and decreased REM sleep duration in pediatric patients (aged 6-11 years) over 4 weeks without worsening spike density or seizure frequency.

Additional Observations

Four studies noted improvements in sleep quality among pediatric patients with epilepsy and associated sleep disorders. Verma et al.[19] reported enhanced sleep quality, as measured by the PSQI, in patients with generalized epilepsy receiving melatonin together with anti-seizure medication. Myers et al.[24] conducted randomized controlled trials in patients with Dravet syndrome and revealed increased total sleep and improved quality of life with melatonin use.

Discussion

Melatonin is a hormone synthesized primarily by the pineal gland and is well known for its role in regulating circadian rhythms. In addition to its circadian functions, melatonin acts as a neuroregulatory hormone with notable immunoregulatory, anti-inflammatory, immunosuppressive, and antioxidant properties. These characteristics highlight the potential significance of addressing the pathophysiological mechanisms underlying neurological disorders, including epilepsy.

Extensive research has investigated melatonin's anticonvulsant properties through both *in vivo* and *in vitro* studies. For example, Mosìnska et al.[25] explored the anticonvulsant effects of melatonin receptor agonists in mice, whereas Solmaz et al.[26] demonstrated neuroprotective and anticonvulsant effects in male albino guinea pigs treated with high doses of melatonin (50-160 mg/kg), leading to reduced convulsion severity and mortality.

In the context of pediatric epilepsy, melatonin has shown promise as an adjunctive therapy to anti-seizure medications, positively influencing seizure frequency and overall quality of life. Verma et al.[19] conducted randomized, double-blind, placebo-controlled clinical trials and revealed favorable outcomes with a reduction in seizure frequency when melatonin was added to the treatment regimen for generalized epilepsy.

The potential therapeutic benefits of melatonin extend to infantile spasms. Wan et al.[18] demonstrated significant reductions in seizure latency and frequency in mouse models. Sun et al.[17] conducted a prospective, randomized, double-blind, placebo-controlled trial, confirming melatonin's efficacy and safety as an adjunct to ACTH therapy in patients with infantile spasm syndrome, particularly among those aged 3 months to 2 years.

Melatonin's utility in the pediatric population also includes its application in sleep EEG. Gustafsson et al.[22] compared EEG outcomes between pediatric patients receiving melatonin and those subjected to sleep deprivation. The study found that melatonin effectively addressed sleep difficulties without compromising the quality of brain electrical recordings. The interrelationship between sleep and epilepsy is complex, with many epilepsy types manifesting predominantly, if not exclusively, during sleep. For instance, interictal epileptiform activity is notably activated during N3 sleep, whereas seizures and interictal discharges are less frequent during REM sleep. This intricate relationship underscores the multifaceted impact of melatonin on both sleep and epilepsy.

Jain et al.[23] conducted a randomized, double-blind, placebo-controlled, crossover study involving children aged 6-11 years. Their study revealed a statistically significant reduction in sleep latency and improvements in overall quality of life and disease tolerance among patients with epilepsy.

Further support for melatonin's role in managing sleep disorders associated with epilepsy was reported by Kennaway et al.[12] and Banerjee and Kumar[13] Both studies independently confirmed melatonin's effectiveness in improving sleep disorders and highlighted its protective effects against convulsions. These findings collectively emphasize melatonin's potential as a multifaceted therapeutic agent for managing epilepsy and associated sleep disturbances.

Table 1. *Summary of results*

Authors and years of study	Sample age	The type of study	Epilepsy characteristics	Melatonin findings
Kennaway[12]		Review		Not possible to draw conclusions on the control of the frequency and severity of seizures regarding the use of melatonin as an add-on therapy in epileptic patients, or on the alteration of the circadian rhythm of melatonin, although it appears altered Improvement of sleep disorders in patients with epilepsy and sleep disorders
Banerjee and Kumar[13]		Review		Lower melatonin concentrations in children with seizures; effective in improving children's sleep by reducing the time; reduces the severity of seizures; and improves chronic sleep disorders in subjects with epilepsy
Tarcin et al.[14]	91 children with epileptic seizures	Case study	Generalized tonic-clonic epilepsy, absence epilepsy, juvenile myoclonic epilepsy, status epilepticus in sleep	Lower baseline melatonin levels in children with epileptic seizures and in the ESES group than in the control group
Ayça et al.[15]	39 children	Case control study	Continuous spikes and waves during sleep, and various epilepsy	Significant reduction in blood melatonin levels in patients with ESES
Manni et al.[16]	13 patients with juvenile myoclonic epilepsy	Case control study	Cryptogenic focal epilepsy juvenile myoclonic epilepsy	Onset of low-light melatonin occurs approximately 59 minutes later in generalized epilepsy, and the peak melatonin level in these patients was significantly lower than that of controls
Sun et al.[17]	70 patients aged 3-2 years	Randomized controlled trial	Infantile spasms	Short-term efficacy of melanin on infantile spasm
Wan et al.[18]	60 3-month-old, specific pathogen-free rats	Experimental preclinical study	Infantile spasms	Combined ACTH and melatonin treatment effectively reduced the number of spasms and increased latency in NMDA rats
Verma et al.[19]	104 patients aged 13-60 years. 21 were pediatric and adolescent patients	Randomized controlled trial	Generalized epilepsy with generalized onset motor seizures.	Add-on melatonin and valproate for generalized epilepsy with generalized-onset motor seizures can result in significantly better clinical outcomes Add-on melatonin improved the quality of sleep
Brigo et al.[20]	106 patients aged 18 years	Systematic reviews	Epileptic syndrome	Not possible to draw any conclusions regarding the role of melatonin in reducing seizure frequency or improving quality of life in people with epilepsy
Bonuccelli et al.[21]	100 children aged 1-6 years	Randomized controlled trial	Epileptic syndrome, febrile seizures, suspected seizures for sleep disturbance, behavioral problems/ psychomotor delay	Safety and efficacy of liposomal melatonin as a sleep inducer in pediatric patients with epileptic sleep
Gustafsson et al.[22]	232 patients, aged 1-16 years	Retrospective study	Generalized and focal epilepsy	Melatonin is equally efficient in inducing sleep and does not affect the occurrence of epileptiform discharges in EEG recordings
Jain et al.[23]	11 patients aged 6-11 years	Randomized controlled trial	Benign Rolandic epilepsy, childhood absence epilepsy, focal epilepsy	Statistically significant decreases in sleep Latency and wakefulness after sleep onset No clear effects on seizures
Myers et al.[24]	13 pediatric patients	Randomized controlled trial	Dravet syndrome	No increase in total sleep due to melatonin administration; clinical benefits on sleep disturbance
Yaşgüçlükal et al.[27]	59 children aged 4-15 years	Multicenter study	Epileptic encephalopathy with spike-and-wave activation in sleep	Lower melatonin levels in patients with EE-SWAS than in the control group

ESES; Electrical status epilepticus in sleep, ACTH; Adrenocorticotropic hormone, NMDA; N-methyl-D-aspartic acid, EEG; Electroencephalogram, EE; Epileptic encephalopathy, SWAS;Spike and wave activation in sleep

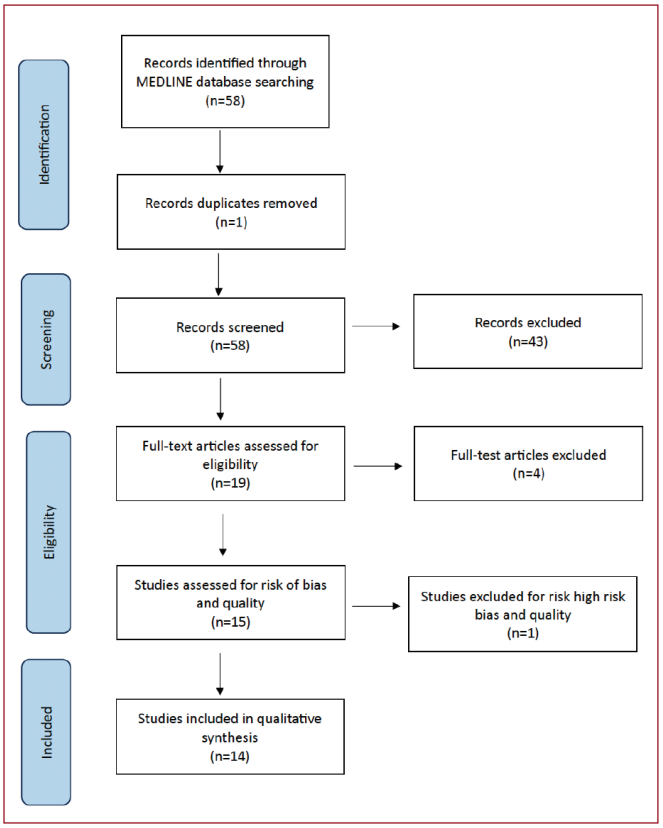

Figure 1. PRISMA flowchart of systematic search strategy. Data were added to the PRISMA template under the terms of the Creative Commons Attribution Licesence[28]

Conclusion

This review highlights the potential significance of exogenous melatonin in managing pediatric epileptic disorders. The findings suggest that melatonin may play a role in the pathophysiology of cerebral electrical disturbances, as indicated by fluctuations in blood melatonin levels during epileptic seizures. Notably, melatonin has shown promise in certain pediatric epilepsies, particularly when used as an adjunct to anti-seizure medications. Administration of this drug has demonstrated potential to reduce seizure frequency and improve overall treatment outcomes.

Additionally, melatonin is a safe and effective option for enhancing sleep quality during EEG procedures. By decreasing sleep latency, melatonin facilitates the optimal recording of cerebral electrical activity without compromising the accuracy of the EEG results. This benefit is particularly relevant for addressing sleep disorders that are frequently associated with pediatric epilepsy and epileptic encephalopathies.

Overall, the integration of exogenous melatonin into therapeutic strategies for pediatric epilepsy has promise as a multifaceted intervention. The potential to improve sleep quality and reduce seizure frequency underscores its value in enhancing the overall quality of life of pediatric patients. Further research is needed to fully elucidate its efficacy and establish standardized guidelines for its clinical use.

Informed Consent: The consent form was not needed due to the study design.

Author Contributions: Salvatore Michele Carnazzo: Surgical and Medical Practies, Concept, Design, Literature Search, Writing.; Desirèe Balconara: Data Collection or Processing, Literature Search, Writing.; Francesco Fabrizio Comisi: Concept, Analysis or Interpretation.; Martino Ruggieri: Analysis or Interpretation.

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Vitamin D Levels in Growth-Paining Children

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Abstract

The most common cause of non-inflammatory recurrent musculoskeletal pain in children is growing pains. History and physical examination are often sufficient to diagnose these patients. Since the exact etiology is not known, different treatments can be applied. The effect of vitamin D levels on children with growing pains was investigated. Clinical and laboratory findings of 138 pediatric patients with growing pain and 30 healthy control subjects were examined and then the changes in pain scores of children and their families with follow-up and treatment were evaluated. The pain was most commonly seen in the form of lower extremity pain at night and in girls. Although growing pains can be treated with nonpharmacological methods, there were also patients who required pharmacological treatment. Vitamin D deficiency was observed in children with growing pain. Vitamin D treatment was given to 46 patients with vitamin D deficiency. Pain scores made by both themselves and their families decreased in 91.4% of the patients who came for control. After the use of vitamin D in children with growing pains, the mean pain score reported by the children decreased from 7.26±1.757 to 2.46±2.38. The mean pain score reported by families about their children decreased from 7.56±1.97 to 2.51±2.53 after vitamin D supplementation. Although most of the time growing pain is a self-limiting clinical picture, vitamin D supplementation may be necessary after a differential diagnosis was made because of the high level of anxiety in the families of children who do not respond to non-pharmacological approaches.

Keywords: Growing pain, vitamin D, children

Introduction

Growing pain is the most common cause of intermittent musculoskeletal pain in children.[1] Although there is no definite consensus on the definition of growing pains, they are defined as pains of unknown cause that usually occur in the evening and night in children in the developmental age without any musculoskeletal disease, sometimes awakening them from sleep at night and lasting from a few minutes to several hours.[2,3] Anatomical/mechanical factors, fatigue, psychological, pain threshold, and vitamin D deficiency theories have been proposed to explain the etiology of growing pains. Vitamin D levels are normal in very few children with growing pains.[4,5] The relationship

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between growing pain, vitamin D level and perception of pain was evaluated in this study.

Material and Method

A total of 138 children who presented to the pediatric rheumatology outpatient clinic with the complaint of limb pain and were diagnosed with growing pain and 30 healthy age-matched children who were referred to the general pediatric outpatient clinic without any joint-muscle complaint and included in the follow-up protocol of healthy children were enrolled in the study after Fırat University Non-Interventional Research Ethics Committee approval (date: 23/02/2017, decision no: 04/04). The families of the patients were asked to sign an informed consent form. Diagnosis of growing pain was made with detailed medical history and physical examination according to the specified criteria.[6,7]

Highlights

- The effect of vitamin D supplementation in children with growing pains was demonstrated in a case-controlled prospective study.
- Pain scores were reduced by administering vitamin D to children with growing pains and vitamin D deficiency.
- Our study is important because it is a case-controlled prospective study.

Information on personal and family medical history was obtained from all patients included in the study. Age at the time of presentation, gender, postal and e-mail addresses, kinship between parents (if any), number and ages of siblings, indication for previous hospitalization, previous surgery and presence of other individuals with growing pain in the family were questioned. Detailed physical examination, body weight, and height measurements were performed in all patients.

Complete blood count, creatine kinase, calcium, alkaline phosphatase (ALP), phosphorus, magnesium, parathormone (PTH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and 25(OH)-VitD3 were assessed.

Pain scoring was performed in patients aged 6 years who were evaluated as having growing pains using the Wong-Baker FACES Pain Rating scale.[8] According to this scoring system, patients aged below 6 years selected the intensity of pain they felt from their faces on the pain scale chart.

Pain was scored using the Visual Analog scale (VAS) in patients aged 6 years who were assessed as having growing pain. For the parents, the VAS was used to measure pain intensity as described by their children.[8] Among the patients who were evaluated as having growing pain, those with 25(OH)-VitD3 levels below 12 ng/mL (vitamin D deficiency)[9] were prescribed single oral doses of 150,000 IU cholecalciferol (DEVIT-3 oral drops DEVA Holding Co, İstanbul, Türkiye) if the child was under 6 years of age and 300,000 IU if the child was 6 years of age or older. These children were called for follow-up appointments two months later. At the follow-up visit, 25(OH)-VitD3, PTH, calcium and phosphorus levels were measured and pain scoring was performed.

A data evaluation form was prepared for each patient to record demographic data, clinical conditions, laboratory values, and treatment regimen information.

Statistical Analysis

For data analysis in this study, computerized version 22.0 of the statistical program Statistical Package for Social Science for Windows was used. Normally distributed data were expressed as mean ± standard deviation and non-normally distributed continuous variables were expressed as median (minimum-maximum). The Wilcoxon test was used to compare dependent groups, Mann-Whitney U test was used to compare different groups and the chi-square test was used to compare percentage values. Results were considered statistically significant at $p<0.05$.

Results

The patients in the growing pain group comprised 138 patients, including 62 (44.9%) men and 76 (55.1%) women. In the control group, 11 (36.7%) of 30 patients were male, and 19 (63.3%) were female. The median ages of patients in the growing pain group and healthy controls were 7.8 (3.8-14.8) and 9.4 years (4.3-14.8) respectively. No statistically significant differences were found between the study and control groups in terms of age and gender ($p>0.05$).

Six (4.3%) patients in the growing pain group and four (13.3%) control subjects had a family history of growing pain.

Patients in the growing pain group were evaluated according to the time of presentation to the hospital, location and frequency of pain, whether the pain woke them up from sleep or was relieved by massage, the need for a painkiller, and any other symptoms accompanying the pain. The clinical characteristics of the group with increasing pain are presented in **Table 1**.

Table 1. *Clinical characteristics of growing pain in patients*

Time of pain onset	**N**	**%**
At night	87	63
In the afternoon	19	13.8
In the afternoon and at night	32	23.2
Pain location	**N**	**%**
Calf	45	32.4
Thigh	16	11.6
Thigh/calf	61	44.2
Other	16	11.6
Frequency of pain	**N**	**%**
Every day	33	23.9
2-4 days a week	63	45.6
Once a week	29	21
Less than once a week	13	9.4
Pain waking up children from sleep	**N**	**%**
Yes	89	64.5
Pain relieved by massage	**N**	**%**
Yes	110	79.7
Not massaged	11	7.9
Need for a painkiller	**N**	**%**
Yes	81	58.7

The patients in the growing pain group (total n=138) experienced only abdominal pain (n=23, 16.6%), headache (n=17, 12.3%), both abdominal pain and headache (n=8, 5.8%), or any other accompanying pain (n=4, 2.9%), whereas 86 (62.3%) patients had not any accompanying pain.

The median body weights of the patients in the growing pain group and the healthy controls were 25 kg (13.8-73.5) and 29 kg (16-70) respectively. The median heights of the patients in the growing pain group and the healthy controls were 128 cm (98.5-185) and 134.5 cm (105-178). When the anthropometric measurements were evaluated, no statistically significant difference was found between the study and control groups in terms of height or body weight (p>0.05).

Laboratory parameters of the growing pain and control groups were evaluated. The hemoglobin and hematocrit values were lower in the growing pain group than in the control group, with a statistically significant intergroup difference (p<0.05). In patients with anemia, the lowest hemoglobin value was 10.2, and microcytic anemia was detected. Nutritional anemia was also considered. Malignancy was not considered based on laboratory and physical examination findings. The 25(OH)-VitD3 levels were lower in the growing pain group than in the control group, with a statistically significant intergroup difference (p<0.05). When acute-phase reactants (ESR, CRP) of patients in the growing pain and control groups were evaluated, no statistically significant difference was not found between the groups (p>0.05) (**Table 2**).

Among patients in the growing pain group, pre-treatment pain scoring was applied to 46 children with deficient 25(OH)-VitD3 levels, and in addition, the families of these children were requested to score the growing pains of their children before treatment.

Forty-six children with 25(OH)-VitD3 level below 12 ng/mL were prescribed single oral doses of cholecalciferol (DEVIT-3 ampoule, DEVA Holding, İstanbul, Türkiye) and were called for control visits 2 months later. There were seven children under the age of six and 39 children over the age of six.

Mean pain scores of children in the growing pain group were evaluated after vitamin D supplementation. The mean self-reported pain score was 7.26±1.757 points. After the use of vitamin D, the mean pain score reported by the children themselves was 2.46±2.38 points. The mean pain score reported by the families for their children was 7.56±1.97 points at baseline. After vitamin D supplementation, the mean pain score recorded by the families for their children was 2.51±2.53 points (**Figure 1**). The change in pain scores of 35 children who used vitamin D due to growing pains and came for control was evaluated. There was a statistically significant difference between vitamin D use and the pain scores reported by both the children themselves and their families regarding their children (p<0.001) (**Table 3**). We also evaluated whether there were differences in PTH, calcium, and phosphorus levels among children with growing pain and vitamin D deficiency after vitamin D supplementation.

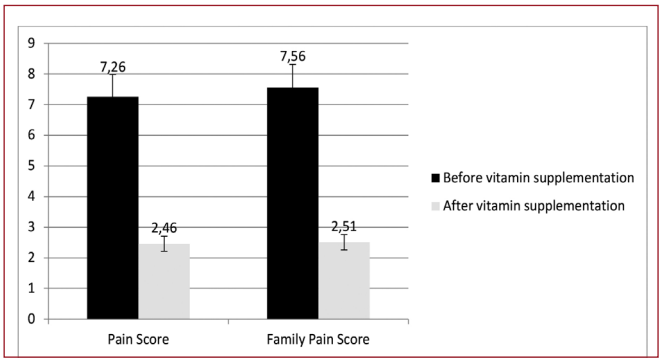

Figure 1. Changes in pain scores with vitamin D supplementation among children with growing pains

Table 2. *Laboratory values of the patients in each group*

	Growing pain group	Control group	P value
25(OH)-VitD3 (ng/mL)*	14.1 (1.5-70.0)	22.50 (5.80-56.60)	**p<0.05**
Hematocrit (%)*	39.6 (32.3-50.6)	42.00 (35.10-47.90)	**p<0.05**
Hemoglobin (g/dL)*	13.2 (10.2-16.5)	13.45 (11.40-15.40)	**p<0.05**
Parathormone (pg/mL)*	46.4 (17.9-449.0)	31.20 (23.20-111.30)	**p<0.05**
Platelets (10e3/µL)*	322500 (139000-764000)	318000 (212000-538000)	p>0.05
Phosphorus (mg/dL)*	5.0 (3.6-15.0)	4.80 (3.50-6.10)	p>0.05
WBC (10e3/µL)*	6900 (2790-16520)	7065 (4120-11910)	p>0.05
Alkaline phosphatase (u/L)*	195.0 (19.4-506.0)	191.50 (2.64-320.00)	p>0.05
Calcium (mg/dL)*	9.7 (8.7-10.6)	9.48 (8.80-10.25)	p>0.05
Sedimentation (mL/sa)*	11.0 (1.0-71.0)	9.00 (1.00-41.00)	p>0.05
Magnesium (mg/dL)*	2.2 (1.3-3.7)	2.11 (1.83-3.10)	p>0.05
Creatine kinase (u/L)*	95.0 (8.0-505.0)	87.00 (18.00-268.00)	p>0.05
C-reactive protein level (mg/L)*	3.1 (3.0-67.9)	3.23 (3.13-38.30)	p>0.05

(*) Results are presented as median (minimum-maximum) values, WBC; White blood cell

Table 3. *Changes in pain scores with vitamin D supplementation in children with growing pains*

	Decreased	Increased	No change	P value
Pain score	32	1	2	**<0.001**
Family pain score	32	0	3	**<0.001**

Table 4. *Changes in PTH, calcium, and phosphorus levels with vitamin D supplementation*

	Pre-treatment	Post-treatment	P value
25(OH)-VitD3 (ng/mL)*	8.3 (6.1-10.4)	23.9 (17.2-38.5)	**<0.001**
Parathormone (pg/mL)*	66.95 (45.25-92.32)	39.4 (33.33-60.9)	**<0.001**
Calcium (mg/dL)*	9.74 (9.24-9.97)	9.72 (9.48-10)	>0.05
Phosphorus (mg/dL)*	4.8 (4.58-5.2)	4.95 (4.65-5.4)	>0.05

(*) Results are presented as median (minimum-maximum) values, PTH; Parathormone

The PTH level was significantly lower after vitamin D supplementation than after pre-treatment values ($p<0.001$). There was no statistically significant difference in calcium and phosphorus levels with vitamin D use relative to pre-treatment values ($p>0.05$) (**Table 4**).

Discussion

In our study, hemoglobin and hematocrit values were found to be significantly lower in children in the growing pain group than in the control group. In a case-control study conducted by Evans et al.[10] with 77 children, vitamin D hypovitaminosis and anemia were found in 85.7% and 10.7% of the children with growing pains, respectively. The mean vitamin D level in children with growing pain was found to be low, consistent with other studies.[5,11-13] In a study conducted by Park et al.[4], the mean vitamin D level was found to be higher in children with pain compared with that in our study. However, none of these studies included a control group. Although vitamin D levels have been reported at different rates, vitamin D deficiency is generally observed in children with pain, as observed in our study. Acute phase reactants (ESR, CRP) were evaluated in children in the growing pain and control groups, and parameters indicating inflammation were found to be at normal levels in our study, similar to other studies.[11]

In a recent study on diagnosing growing pains in children using machine learning, it was observed that more than half of the patients woke up at night due to pain, similar to our study.[14] In another recent study, ALP levels were considered a biomarker of pain. In our study, no significant difference was found in ALP levels between the growing pain and control groups.[15] Mean pain scores were evaluated in children with increasing pain after vitamin D supplementation. We observed that the pain scores of the children themselves and the families of their children decreased after vitamin D supplementation. It was found that there was regression in pain in children after vitamin D supplementation.[11-13] However, none of these studies have employed a different pain scoring system to inform families about the growing pains of their children has not been performed so far.

In addition, the relationship between pain and vitamin D levels has been investigated in adult studies in recent years, and it was found that vitamin D levels were deficient or severely deficient in 89.3% of patients with non-specific muscle pain.[16] In adult studies, a significant decrease in the back pain score was found with vitamin D supplementation in patients with back pain whose 25(OH)-VitD3 level was below 30 nmol/L, and vitamin D replacement in women with chronic diffuse pain relieved pain and improved the quality of their lives, while it did not seem to affect spinal inhibitory pathways.[17,18]

Conclusion

In conclusion, although growing pain is a self-limiting clinical feature, the benefits of supportive treatment should be explained to families after a differential diagnosis is made because families have a high level of anxiety. In addition, as understood, vitamin D levels should be evaluated in patients with persistent complaints despite supportive treatment. In children with increasing pain and vitamin D deficiency, the clinical picture may improve earlier with vitamin D supplementation.

Ethical Approval: Ethical approval was obtained from the Fırat University Non-Interventional Research Ethics Committee (date: 23/02/2017, decision no: 04/04).

Informed Consent: The families of the patients were asked to sign an informed consent form.

Author Contributions: Günbey Ö: Surgical and Medical Practices, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Gürgöze MK: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation.; Günbey FB: Surgical and Medical Practices, Data Collection or Processing, Literature Search.

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Effects of Treatment Model on Bone Metabolism in Patients with Severe Hemophilia A

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Abstract

Improving bone health and preventing osteoporosis is an essential approach for hemophilia patients. Regarding precautions, the treatment model may affect bone health. To detect the effect of a treatment model (prophylaxis/on-demand treatment) on bone metabolism in patients with severe hemophilia A was the primary aim of this study. The biochemical markers of bone metabolism and bone mineral density were obtained from the patients enrolled in the study. No statistically significant differences were found between the groups due to the limitations of the prophylaxis group, such as adaptation problems, personal differences, and type of prophylaxis.

Keywords: Hemophilia, bone health, osteoporosis in hemophilia

Introduction

Hemophilia A (HA) is a rare coagulation disorder caused by factor VIII (FVIII) deficiency owing to an X-linked recessive inheritance in the genes encoding FVIII. Approximately, 85% of hemophilia patients are diagnosed with HA, while the remaining is hemophilia B, which is caused by factor IX deficiency. Hemophilias can be categorized into three groups according to factor levels: Mild for factor levels >5-40 IU/dL, moderate for 1-5 IU/dL; and severe for factor levels <1 IU/dL.[1-3]

Regarding the developed treatment options, the estimated lifespan is similar to that of the normal population. Therefore, comorbidities and prevention are increasing challenges in the management of hemophilia. Ensuring normal bone metabolism and bone mineral density (BMD) is the most pivotal of all. Low BMD can culminate in impaired bone strength and an increased risk of fracture due to fragility. In the literature, 27% of patients with hemophilia were reported to have osteoporosis, whereas 43% had osteopenia.[4]

This study aimed to evaluate the effect of prophylactic treatment on bone metabolism and osteoporosis by

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comparing biochemical bone markers and BMD in patients with severe HA who were on prophylaxis and on-demand treatment.

Material and Method

A total of 36 hemophilia patients who were being followed-up by the department of pediatric hematology in Ege University Faculty of Medicine, were enrolled in this study. Ethical approval was obtained from the Clinical Research Ethics Committee of Ege University Faculty of Medicine (decision no: 15-7/20 date: 27.07.2015). In addition, the family and/or patients signed an informed consent form. Of these patients, 24 were on prophylaxis and 12 were on on-demand treatment. Age, height, and body weight of the patients were recorded, and body mass index (BMI) was calculated using these data. Biochemical parameters related to bone metabolism [calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), calcitonin, and 25(OH) vitamin D3] were evaluated in blood samples, and BMD was measured using the dual-energy X-ray absorptiometry method. The biochemical values of the patients were evaluated based on the normal values established in the literature according to their ages.[5]

Statistical Analysis

Statistical Package for Social Sciences v.20 was used to evaluate the laboratory results. Descriptive methods were used to calculate demographic data. The results are presented as mean ± standard deviation within 95% confidence interval. The lower and upper limits of the data in the study groups were calculated using the Student t-test for a single group. Pearson and Spearman correlation analysis were used to examine the relationship between variables, while p values <0.05 were considered statistically significant.

Highlights

- Patients with hemophilia are at increased risk of impaired bone metabolism and the development of osteopenia and/or osteoporosis.
- The reasons beyond impaired bone health and precautions are still highly studied. Regarding precautions, the treatment model may affect bone health. Patients receiving prophylaxis are expected to have higher bone mineral density and better bone health.

Results

Of the 36 male patients enrolled in the current study, 24 were on prophylaxis and 12 were on-demand treatment. The mean age of whole study group was 16.5±7.1 years, whereas the mean age of the prophylaxis group was 17.46±6.1 years (8-30 years), and that of the on-demand therapy group was 16±8.6 years (9-30 years).

The mean body weight of the prophylaxis group was 63.2±18.7 kg (29-100 kg) whilst of the on-demand group was 48±19.2 kg (22-72 kg). The difference between the groups was statistically significant (p=0.047). Likewise, the mean BMIs was 22.4±4.1 kg/m^2 (14.8-29.2) and 18.4±2.6 (14.7-23.1) for prophylaxis and on-demand groups, respectively. BMI was significantly higher in the prophylaxis group (p=0.004). A comparison of the laboratory results between the two groups is presented in **Table 1**. No statistically significant differences were observed between groups in terms of laboratory results.

Regarding the L1-L4 Z-scores in the prophylaxis group; osteoporosis was detected in 5 cases (20.8%), osteopenia in 6 cases (25%), and 13 cases (54.2%) patients had normal L1-L4 BMD values. Considering the femoral neck Z-scores, osteoporosis was detected in 4 cases (16.7%) patients, osteopenia in 11 cases (45.8%) patients, and normal BMD values in 9 (37.5%) patients. In the on-demand treatment group, assessing the L1-L4 Z-scores, osteoporosis was detected in 3 cases (25%), osteopenia in 3 cases (25%), and normal BMD was observed in 6 cases (50%). By evaluating the femoral neck BMD Z-scores, osteoporosis was detected in 1 case (8.3%) patient, osteopenia was detected in 3 cases (25%), and 8 cases (66.7%) patients had normal BMD values. Vitamin D levels were found to be “deficient or insufficient” in ≥50% of patients in both groups; only 8 (33.3%) patients in the prophylaxis group and 6 cases

Table 1. *Comparison of laboratory findings between groups receiving prophylaxis and on-demand treatment*

	Prophylaxis group (n=24)			On-demand group (n=12)			P value
	N	D	I	N	D	I	
Ca	N=21 (87.5%)	N=2 (8.3%)	N=1 (4.2%)	N=12 (100%)	0	0	0.67
P	N=21 (87.5%)	N=2 (8.3%)	N=1 (4.2%)	N=12 (100%)	0	0	0.53
ALP	N=20 (83.3%)	N=2 (8.3%)	N=2 (8.3%)	N=12 (100%)	0	0	0.42
PTH	N=20 (83.3%)	0	N=4 (16.7%)	N=12 (100%)	0	0	0.14
Calcitonin	N=22 (91.7%)	0	N=2 (8.3%)	N=9 (75%)	0	N=3 (25%)	0.21
	Prophylaxis group (n=24)			**On-demand group (n=12)**			
	Deficient	**Insufficient**	**Normal**	**Deficient**	**Insufficient**	**Normal**	
25 (OH) Vit. D3	N=7 (29.2%)	N=9 (37.5%)	N=8 (33.3%)	N=2 (16.7%)	N=4 (33.3%)	N=6 (50%)	0.09

Ca; Calcium, P; Phosphorus, ALP; Alkaline phosphatase, PTH; Parathormone, 25(OH) Vit. D3; Vitamin D, N; Normal, D; Decreased, I; Increased

(50%) in the on-demand group had normal vitamin D levels according to age. In the remaining cases, vitamin D levels were found to be "deficient or insufficient" in 16 cases (66.7%) patients in the prophylaxis and 6 cases (50%) patients in the on-demand group. In **Table 2**, data on BMD measurements is presented comparatively between the two groups.

Discussion

Survival has increased significantly in patients with hemophilia due to advanced treatment modalities, such as the initiation of primary prophylaxis at an early age and accessibility to factor preparations. In addition to survival, improvements in lifestyle and quality have been achieved. Consequently, preventing comorbidities and improving quality of life are hot research topics. Protecting bone health is the most essential task.

Soft tissue synthesis, epiphyseal bone growth, and bone remodeling occur simultaneously in childhood. BMD increases throughout childhood and adolescence, reaching a plateau on average in the twenties and reaching peak bone mass.[6] Low BMD is related to increased resorption and decreased formation of bone, resulting in impaired bone mass. The worldwide prevalence of osteoporosis among men is 11.7%; thus, research is needed on this issue.[7]

Osteopenia and osteoporosis are reported to be detected in patients with hemophilia at early ages before adolescence, at 12 years of age.[6] In a recently published meta-analysis, regardless of age, region, or economic status, hemophilia patients have been demonstrated to have low BMD, about four times higher than healthy controls.[7] Many factors have an impact on peak bone mineral mass, including normal body weight and weight-related physical activity as the strongest predictors found in studies conducted in healthy children and adolescents.[6-8] Certain predictors of low BMD should be determined, and precautions should be taken.

In this study, body weight and BMI in the prophylaxis group were significantly higher than the on-demand group. However, no significant difference was detected between the two groups in terms of BMD, vitamin D level, and other laboratory markers. The mean BMI of the on-demand group was 18.4 kg/m^2, which is classified as underweight. An increased risk of fracture has been reported in previous studies.[9,10] Nevertheless, the mean BMI of the prophylaxis group was normal. Based on this finding, the estimated low BMD and related fracture risk can be considered to be decreased in the prophylaxis group.

Regarding the laboratory markers evaluated in this study; Ca, P, ALP, and PTH levels were within normal ranges according to age in the on-demand group. Comparing the two groups, no statistically significant difference was detected in terms of laboratory results. Elevated ALP levels were detected in 2 cases (8.3%) in the prophylaxis group. One of these cases presented with osteoporosis at L1-L4 BMD and osteopenia at the femoral neck, whereas he had normal laboratory results except for ALP level. Similarly, another patient had osteopenia in the femoral neck, despite normal laboratory results. Elevated PTH levels were detected in 4 cases (%16.7) in the prophylaxis group. Regarding PTH acting as a stimulator of osteoclast differentiation via osteoblasts and causing bone destruction, elevated PTH levels suggest that the balance between bone formation and resorption is disturbed in favor of bone destruction. Osteoporosis was detected in one of these patients, osteopenia in 2 cases, and normal BMD in one patient. Cases with normal BMD results can be detected early by PTH elevation.

The primary function of vitamin D is not only to ensure Ca absorption from the intestines but also to stimulate osteoclastogenesis and increase osteocalcin production by osteoblasts *in vivo*. In our study, no statistically significant difference was observed between the two groups regarding 25(OH) vitamin D3 levels. Nonetheless, recent studies showed that patients with hemophilia tend to have significantly lower vitamin D and BMD levels compared with healthy controls.[11,12] Low vitamin D levels can be associated with sustained immobilization and reduced sun exposure due to recurrent and frequent joint bleeding. Supporting this notion, Gamal Andrawes et al.[11] demonstrated a significant negative correlation between the vitamin D levels of children with severe HA and the Hemophilia Joint Health score. Although no significant difference was observed between the two groups, 61% (n=22) of our patients were found to have vitamin D deficiency and/or insufficiency, which is consistent with the literature. In the current study, no scale that assesses physical activity and joint health was used, which would be helpful in understanding the mechanism. Because vitamin D level is critical, patients with hemophilia should be tested for vitamin D deficiency regularly.

In the present study, contrary to expectations, no significant difference was identified between the groups in terms of BMD Z-scores. However, previous studies have revealed that the development of hemophilic arthropathy, which has been accused as the main cause of impaired bone health for a long time, can be prevented by prophylaxis initiated at an early age so that the factor concentration does not fall below 1%.[10] Therefore, the prophylaxis group is expected to have better BMD results. The reasons beyond these results can be attributed to differences in patients' personal characteristics and compliance with treatment. Apart from these issues, there can be problems regarding

Table 2. *Comparison of bone mineral density results in groups receiving prophylaxis and on-demand treatment*

	Prophylaxis group (n=24)			On-demand group (n=12)			P value
	Osteoporosis	Osteopenia	Normal	Osteoporosis	Osteopenia	Normal	
L1-L4	N=5 (20.8%)	N=6 (25%)	N=13 (54.2%)	N=3 (25%)	N=3 (25%)	N=6 (50%)	0.86
Femur neck	N=4 (16.7%)	N=11 (45.8%)	N=9 (37.5%)	N=1 (8.3%)	N=3 (25%)	N=8 (66.7%)	0.88

factor supply and regular use in prophylactic treatment. Although improvements have been made recently in this regard, many of the subjects developed a target joint before regular prophylaxis. Another finding in this regard was the mean prophylaxis time of our patients, which was 8.3±1.4 years (5-10), whereas the mean age of the patients was 17.46±6.1 years (8-30). From this perspective, none of the patients in the prophylaxis group were receiving “primary prophylaxis”. All patients were receiving “secondary prophylaxis” or even “tertiary prophylaxis” according to the new definition.[13]

Studies in the literature evaluating bone metabolism are increasing day after day.[2,4,6,14,15] Nonetheless, research in the pediatric era is still scarce. The primary objective is not only to define the mechanism but also to invent cures. The degree of arthropathy, number of affected joints, avoidance of weight-bearing exercise, and early-onset prophylaxis are the most studied underlying factors.[6,16,17] The number of affected joints and degree of physical activity were not elucidated in the current study, which is a limitation of the findings. In addition to these factors, the presence of liver disease caused by the hepatitis C virus (HCV) was found to be responsible for affecting the vitamin D metabolism in the liver.[18,19] However, data about the HCV are conflicting because some studies conducted with HCV-positive and-negative patients revealed no difference in osteoporosis development.[2,20] Another infectious agent that directly elevates bone destruction via increased cytokine levels is the human immunodeficiency virus (HIV). HIV also impairs vitamin D absorption by causing chronic diarrhea.[21,22] Because our patients were not HCV or HIV-positive in our study, no evaluation was made in this regard.

Apart from the aforementioned occasions, FVIII itself has been demonstrated to play a role in bone metabolism by affecting the receptor activators of the nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) pathways. The RANKL-OPG pathway plays a key role in bone resorption via osteoclasts.[23] RANK binds to its ligand RANKL to activate osteoclast proliferation and differentiation. This pathway is controlled by OPG, which negatively regulates signaling and thus controls osteoclast activity.[23,24] FVIII and the von Willebrand factor complex downregulate the RANK-RANKL connection and promote OPG activity, resulting in inhibited osteoclastogenesis.[24,25] In addition, FVIII stimulates thrombin production, which stimulates osteoblasts via its receptors.[26,27] Another mechanism was proposed after studies in FVIII-knockout mice. The levels of trabecular bone formation and bone formation markers such as N-terminal propeptide of type 1 procollagen were decreased.[28]

Study Limitation

The current study has some limitations, as mentioned in the text prior. First, none of the patients received primary prophylaxis. The mean prophylaxis time was only 8.3±1.4 years, whereas the mean age was 17.46±6.1 years (8-30). This is a major limitation of our study. In addition, compliance with prophylaxis treatment is another issue affecting bone health. The Hemophilia Joint Health score was not evaluated in this study, which could have provided information about the arthropathy status of the patients and led to a better analysis.

Conclusion

Patients with hemophilia have an increased risk of impaired bone metabolism and the development of osteopenia and/or osteoporosis. The reasons beyond this and precautions are hot research topics. In this study, low BMD values were detected, consistent with the literature. Larger-scale studies are needed to evaluate the effects of treatment type on bone health.

Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Ege University Faculty of Medicine (decision no: 15-7/20 date: 27.07.2015).

Informed Consent: In addition, the family and/or patients signed an informed consent form.

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Evaluation of Patients with Cockayne Syndrome

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Abstract

Cockayne syndrome (CS) is a rare, severe, genetic neurodegenerative disorder. To better understand the condition, this article aimed to discuss the clinical manifestations and prognosis of CS. This clinical study was a retrospective review of the medical records of patients diagnosed with CS between January 2010 and January 2020. A total of 9 patients (6 males, 66.7%; 3 females, 33.3%) from 7 families were enrolled in the study. The median age of the patients was 94 (4-186) months. Genetic confirmation of CS was obtained in 5 of the patients and ERCC8 mutations were identified in all patients who underwent genetic confirmation of the disease. On admission, 8 patients were found to have microcephaly 4 patients were admitted for psychomotor retardation, 3 for seizures, and two for walking disabilities. The diagnosis of patients with CS can be challenging due to the wide range of symptoms. In patients who are normal at birth but develop microcephaly during follow-up, physicians should consider CS in addition to metabolic diseases in the differential diagnosis.

Keywords: Cockayne syndrome, microcephaly, premature aging

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Introduction

Cockayne syndrome (CS) is a rare, severe, genetic neurodegenerative disorder. The clinical features of this disease include failure to thrive, microcephaly, impaired development of the nervous system, sensitivity to sunlight, visual impairment, sensorineural deafness and premature aging[1]. There are two main types of CS: CS type A (CSA) and CS type B (CSB)[2]. CSA arises from mutations in ERCC8, whereas CSB results from mutations in ERCC6. It is possible to have problems that affect any internal organ and typically manifest in childhood. It is associated with a group of disorders called leukodystrophies, which are characterized by deteriorating white matter in the nervous system[3].

Although the pathogenesis of this condition is not fully understood, it is known that basic deficiency is caused by deficiencies in DNA repair. In contrast to other defects in DNA repair, patients with CS have no predisposition to cancer or infection. The time of disease onset and the rate of disease progression differ significantly between the subgroups. CS is classified into three types: Type I (classical type), type II (congenital or severe type), and type III (late-onset or adult-onset type) based on the clinical features[4]. CS type I, the "classic" form, is characterized by normal fetal growth. Abnormalities typically develop within the first two years of life. Degeneration of the central and peripheral nervous systems leads to death in the first or second decade of life. CS type II is a congenital condition. It is significantly more severe than CS type 1. There is minimal neurological development after birth. Death typically occurs before age seven. Type III CS is characterized by later onset and is typically milder than types I and II[5].

Diagnosis of patients with CS can be challenging due to the wide range of symptoms. It is important to raise awareness among clinicians regarding disease severity. However, only a limited number of studies have been conducted on CS. To better understand the condition, this article aimed to discuss the clinical manifestations and prognosis of CS.

Highlights

- Cockayne syndrome (CS) is a rare, severe, genetic neurodegenerative disorder.
- CS is a heterogeneous disease that affects various systems, including the cardiovascular, genitourinary, and gastrointestinal systems.
- Patients with CS have been shown to have peripheral neuropathy, which may lead to muscle weakness and locomotion disturbances.
- Microcephaly, along with growth retardation, is a fundamental feature of CS.
- The presence of bilateral calcifications in the basal ganglia, dentate nucleus, and subcortical white matter is considered a diagnostic hallmark of CS.
- However, patients who are normal at birth develop microcephaly during follow-up, and it is recommended that vision and hearing tests be performed. In the differential diagnosis, physicians should consider CS in addition to metabolic diseases.

Material and Method

This clinical study was a retrospective review of the medical records of patients diagnosed with CS between January 2010 and January 2020 at the pediatric neurology department of Erciyes University. Individuals with a confirmed diagnosis of CS via molecular genetic testing were included in the study. A small number of patients were included in the study without confirmation of a clear clinical diagnosis of CS.

The perinatal history, presenting symptoms, systemic findings, psychomotor development, radiological assessment, mean age at diagnosis, and genetic results were collected from the electronic hospital records by a pediatric neurologist. Computed tomography (CT) or magnetic resonance imaging (MRI) was performed in all patients.

Informed consent was obtained from all participants before enrollment, and the study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2021/22 date: 06.01.2021).

Statistical Analysis

The statistical analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS) 22.0 package. In order to determine whether there was a normal or abnormal distribution, the Shapiro-Wilk test was applied to all variables. Non-normal data were expressed as median (minimum-maximum) and categorical data were expressed as counts and percentage.

Results

A total of 9 patients (6 males, 66.7%; 3 females, 33.3%) from 7 families were enrolled in the study. The median age of the patients was 94 (4-186) months. On admission, 8 patients were found to have microcephaly 4 patients were admitted for psychomotor retardation, 3 for seizures, and two for walking disabilities. All of our cases were defined as type 1 when evaluated according to their clinical features. The clinical features in our cohort are summarized in **Table 1**.

Genetic confirmation of CS was obtained in 5 of the patients and ERCC8 mutations were identified in all patients who underwent genetic confirmation of the disease. An antenatal ultrasound scan was performed on all patients in the cohort, and no abnormalities were found on the scans in any of the patients. Seven (77%) patients had a cesarean section and 2 (23%) had normal vaginal deliveries. It was found that no patients were admitted to the neonatal intensive care unit after birth. The weights of the patients at birth were all within the normal range, and based on the head circumference data at birth, all patients were found to be normocephalic.

Patients in the study were tested for hearing and vision problems. It was detected that 4 patients (45%) had normal audiological evaluations and 5 (55%) had bilateral sensorineural deafness. In the ophthalmological evaluation of patients, microphthalmia was detected in 7 (77%) cases, cataract in 2 (22%) patients, optic atrophy in 2 (22%) patients, and retinitis pigmentosa in

Table 1. *Clinical features and genetic consequences of Cockayne syndrome*

Case	Sex	Age	Birth weight	Developmental delay	Microcephaly	Characteristic physical appearance	Eyes symptoms	Teeth	Deafness	Contractures	Cutaneous photosensitivity	Seizure	CNS anomalies	Mutation	Type
1	M	6 y	2780 g	+	+	+	Microphthalmia	Hypoplastic teeth	+	-	-	+	Cortical atrophy/basal ganglia calcifications	ERCC8	CS 1
2	M	4 m	3120 g	+	-	+	-		-	-	-	-	Cortical atrophy/basal ganglia calcifications		CS 1
3	M	15 y	2670 g	+	+	+	Optic atrophy and microphtalmia	Dental caries, delayed eruption	-	+	-	+	Cortical atrophy/basal ganglia calcification, hypomyelination	ERCC8	CS 1
4	M	10 y	3410 g	+	+	+	Cataracts, microphtalmia	Dental caries	+	+	+	-	Cortical atrophy/basal ganglia calcifications, hypomyelination	ERCC8	CS 1
5	M	10 y 10 m	3080 g	+	+	+	Optic atrophy and microphtalmia	Dental caries and hypoplastic teeth	+	+	+	-	cortical atrophy/basal ganglia Calcifications, hypomyelination	ERCC8	CS 1
6	F	7-10 m	2960 g	+	+	+	Retinitis pigmentosa, microphtalmia	Delayed eruption, dental caries,	+	-	-	-	Cortical atrophy/basal ganglia calcifications, hypomyelination		CS 1
7	M	6-2 m	2850 g	+	+	+	Retinitis pigmentosa, microphtalmia	Hypoplastic teeth	-	-	-	-	Cortical atrophy/basal ganglia calcifications, hypomyelination		CS 1
8	F	3 y 10 m	3400 g	+	+	+	-	Malocclusion	-	-	+	+	Cortical atrophy/basal ganglia calcifications		CS 1
9	F	15 y 6 m	2910 g	+	+	+	Cataracts, microphtalmia	Delayed eruption, dental caries,	+	+	-	+	Cortical atrophy/basal ganglia calcifications, hypomyelination	ERCC8	CS 1

CNS; Central nervous system, M; Male, F; Female, M; Month Y; Year

3 (33%) patients. Echocardiographic and genitourinary ultrasonographic evaluation of the patient did not reveal any abnormal findings. Hepatic involvement was accepted based on elevated transaminase levels and elevated levels of transaminase were found in 5 (55%) patients without concomitant cholestasis.

Seizures occurred in 4 (44%) patients, and the analysis of the patients' electroencephalography showed focal sharp wave activity in addition to irregular ground activity. Seven patients underwent CT imaging, and cranial MRI was performed in all patients. Calcifications were observed in the bilateral basal ganglia in all cases. The MRI evaluation showed cerebral atrophy and cerebellar involvement in all patients, and hypomyelination was found in 6 cases **(Figures 1, 2 and 3).**

In our study, 1 (11%) patient was able to ambulate, while the others were unable to walk. Seven (77 %) patients had muscle weakness, 4 (44%) had joint contractures, 6 patients had tremor, 3 (33.3%) had scoliosis, 5 (55%) had photosensitivity **(Figures 4, 5 and 6).**

Discussion

CS is a rare disorder that can be extremely difficult to detect early in life due to phenotypic variability. Fundamental conditions like growth retardation and microcephaly develop rapidly over time, resulting in the loss of acquired skills like sitting, walking, swallowing, self-feeding, and speaking. In this study, we evaluated data from 9 subjects for a better understanding of clinical characteristics of the disorder. To the best of our knowledge, this study is one of the few to evaluate the clinical outcomes of CS in the literature.

CS is a rare and fatal disorder that typically causes death within the first or second decade. Out of the 140 cases reviewed by Nance and Berry[6], 37 had a mean age at death of 12 years, and 22% of these patients died at least 20 years old. The underlying disease is a defect in one of the repair mechanisms of the DNA. Patients with CS do not have a predisposition to cancer or infection, in contrast to those with other DNA repair defects[3].

The genetic types of CS are type A ERCC8 (also known as CSA), type B ERCC6 (also known as CSB), and type C. Based on previous research, there was no significant correlation between the type of mutation and the severity of CS[7]. In our cohort, whole exome sequencing was performed in 5 of the patients and the ERCC8 mutation was detected in all. Additionally, a review of all cases revealed that they exhibited type 1 characteristics when evaluated according to their clinical features.

It is believed that the CSA and CSB proteins help RNA polymerases overcome transcriptional blockages caused by DNA damage. Cells that are deficient in CSA and CSB are unable to repair the DNA damage caused

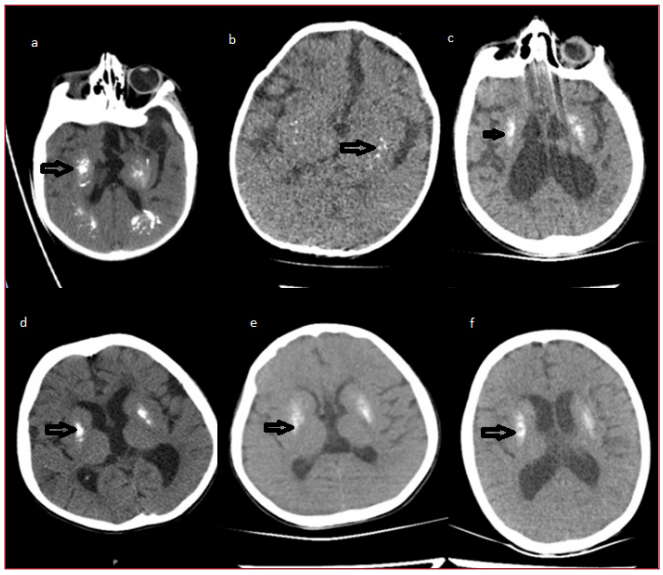

Figure 1. Axial non-contrast brain CT images
Basal ganglia and white matter calcifications and varying degrees of cerebral atrophy
CT: Computed tomography

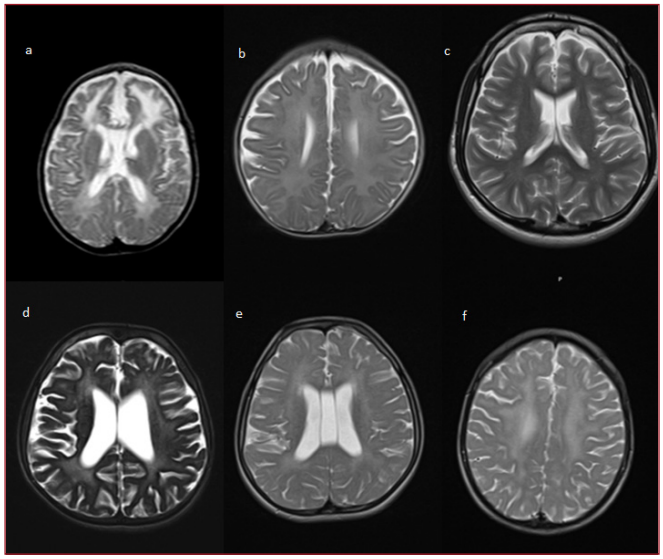

Figure 2. Axial T2 non-contrast brain MRI images
T2A hyperintense hypomyelinated areas in periventricular white matter
MRI: Magnetic resonance imaging

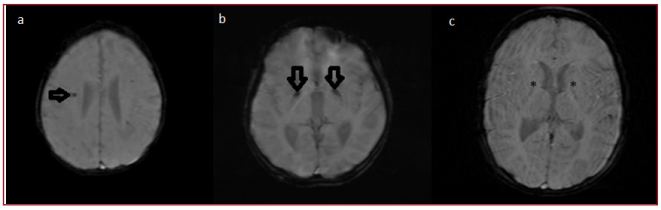

Figure 3. SWI sequence images
A) Punctate calcification at the level of the right centrum semiovale (a)
B) Calcification is present in both basal ganglia (b,c)
SWI: Susceptibility weighted imaging

Figure 4. Microcephally, small chin, prominent ear structure, sunken and prominent eyes, and prematurely aged appearance

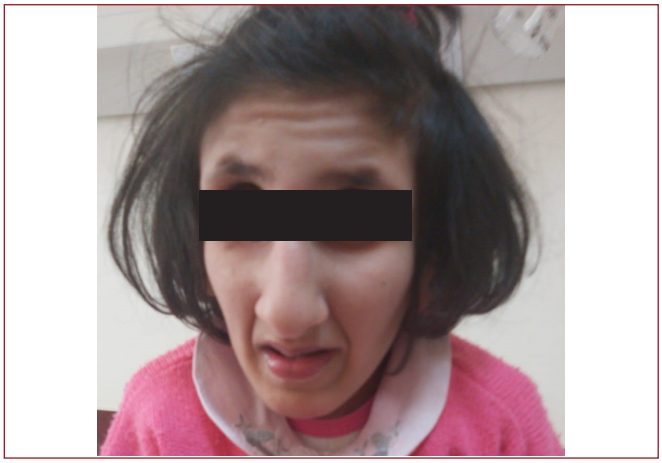

Figure 5. Microcephally, small chin, elongated nose, sunken and prominent eyes, prematurely aged

Figure 6. Kyphosis: They might be very cachetic because of the loss of subcutaneous

by ultraviolet light, in contrast to normal repairing cells[8]. Deficiencies in DNA repair are likely to be responsible for some patients with CS who have an extreme sensitivity to sunlight and may have premature aging. In a study that was conducted by Wilson et al.[8] it has been reported that 40 out of 99 patients were photosensitive and developed blisters after exposure to sunlight. In our study, 3 (33%) of 9 patients had photosensitivity.

The neurological symptoms of CS are severe and have a significant impact on morbidity. The presence of bilateral calcifications in the basal ganglia, dentate nucleus, and subcortical white matter is considered a diagnostic hallmark of CS[9]. In rare cases, confirmed by genetic testing, CS without calcification has been reported[9]. Even in severe cases, brain calcifications may not be visible before the age of 1 year; however, almost all patients with CS tend to develop calcifications after the age of 3[10]. Severe white matter atrophy has also been demonstrated in CS on imaging[11]. In one series, all patients who underwent MRI showed brain atrophy, with white matter loss being the earliest neuro-radiological finding[10]. In our study, including two patients aged 1 year, in all cases calcifications were seen in the basal ganglia, and hypomyelination was detected in 5 of the patients.

Patients with CS have been shown to have peripheral neuropathy in several studies[12].This condition may lead to muscle weakness and locomotion disturbances[13]. This study showed that individuals with CS experience walking disability, muscle weakness, and contractures. We observed that 1 patient was capable of ambulation, 7 patients had muscle weakness, 4 patients had joint contractures, and 3 patients had scoliosis **(Figures 4, 5 and 6).**

Microcephaly, along with growth retardation, is a fundamental feature of CS. Except for the severe infantile variants, the circumference of the head at birth is usually within the normal range, and its growth gradually slows with age, often stopping completely between the ages of 1 and 2 years[3]. Head circumference at birth is within the normal range, indicating the absence of any developmental disorder in patients with CS. Although it is true that the majority of patients with CS over the age of 2 have microcephaly, it is important to note that a small percentage may have normal measurements. Therefore, if a patient is suspected of having CS but does not have microcephaly, alternative diagnoses may be necessary. One study documented that the autopsied brains of patients with CS were generally 50% or less weightless than expected[5]. Normal in utero growth followed by early postnatal microcephaly without gross brain structural abnormalities suggested that transplacental growth factors may be lost. Although the birth weights and head circumferences of all patients were within the normal range, microcephaly was detected in 8 of the patients in our study.

The involvement of the nervous system in most patients may result in cognitive impairment, developmental delay, motor dysfunction, and ambulatory difficulties. The loss of neurons in auditory and visual pathways can also lead to hearing and vision problems[14]. Cataracts are frequently reported in patients with CS. The presence of cataracts before the age of 3 years is considered a significant prognostic factor for survival in individuals with CS[6]. In our study, 7 patients had ocular involvement, including 2 patients (patient 4, patient 9) who were diagnosed with cataracts. Hearing loss is a significant feature of CS[6]. Audiometry testing may be unavailable for various reasons, including difficulties associated with testing in children and individuals with neurological or cognitive impairments. However, if it is not recognized in the early stages of CS, hearing loss can lead to a more withdrawn demeanor. In our study, 4 patients (45%) had normal audiological evaluations and 5 had bilateral sensorineural deafness. It has been observed that a significant proportion of patients with CS, approximately 23%, may experience seizure disorders, and approximately 66% may experience tremors[8]. The majority of patients experience ongoing seizures without a predominant seizure type, and intention tremor is the most common type of tremor observed. In our cohort, seizures occurred in 4 out of 9 (44%) patients, without a predominant seizure type, and intention tremors were observed in 6 patients, which is consistent with the literature.

CS is a heterogeneous disease that affects various systems, including the cardiovascular, genitourinary, and gastrointestinal systems. The cardiovascular system exhibits an advanced degree of arteriosclerosis according to the age of the patient[13]. Renal failure may occur in some patients and is believed to be secondary to hypertension and atherosclerosis[15]. The endocrine system appears to be functioning normally, and no deficiencies in hormones have been reported. In our study, echocardiographic and genitourinary evaluation of the patients did not reveal any abnormal findings; however, elevated levels of transaminase were found in 5 patients and feeding difficulties were detected in all patients.

Study Limitations

This study demonstrated the clinical features of CS. However, there are a number of important limitations to this study that should also be noted, including the limited number of patients, single-center design, and lack of genetic confirmation of all patients. Another limitation was that electromyography could not be performed in our patients.

Conclusion

Many questions remain regarding the molecular mechanisms underlying this disease. However, patients who are normal at birth develop microcephaly during follow-up, and it is recommended that vision and hearing tests be performed. In the differential diagnosis, physicians should consider CS in addition to metabolic diseases.

Ethical Approval: The study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2021/22 date: 06.01.2021).

Informed Consent: Consent was obtained from the parents of the patients.

Author Contributions: Acer H: Design, Data Collection or Processing, Writing.; Özçora GD: Design, Literature Search.; Canpolat M: Concept, Writing.; Doğan ME: Analysis or Interpretation.; Karaman ZF: Analysis or Interpretation.; Kumandaş S: Concept.

Conflict of Interest: Mehmet Canpolat is Editorial Board Member in the Journal of Pediatric Academy. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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Effective Use and Cost-Evaluation of Erythrocyte Suspension in Surgical Branches of Tertiary Hospital

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Abstract

Blood has been accepted as the basic symbol of life from the past to the present. Transfusion is the transfer of blood and blood components to a patient due to various health problems. The present study aimed to evaluate the effective use and cost of erythrocyte suspension in surgical branches in a tertiary hospital. In this study, the use and cost-effective evaluation of erythrocyte suspension, a blood component, after surgical intervention in brain and nerve diseases surgery, orthopedics and traumatology, general surgery, gynecology and obstetrics, and organ transplantation clinics between 01/01/2023 and 31/12/2023 were retrospectively evaluated. Because blood products are provided as voluntary donations, their appropriate use will help reduce hospital and patient costs. We believe that strict compliance with national and international standards and guidelines, quality management, and good clinical practices, as well as ensuring continuity of training on these issues, will enable more efficient product acquisition and decrease blood component disposal in all blood services units.

Keywords: Erythrocyte suspension, transfusion, surgical clinics, cost, disposal

Introduction

Blood has been accepted as the basic symbol of life from the past to the present. Transfusion is the transfer of blood and blood components to a patient due to various health problems. The present study aimed to evaluate the effective use and cost of erythrocyte suspension in surgical branches in a tertiary hospital.

Material and Methods

In this study, the use and cost-effective evaluation of erythrocyte suspension, a blood component, after surgical intervention in brain and nerve diseases surgery, orthopedics and traumatology, general surgery, gynecology and obstetrics, and organ transplantation clinics between 01/01/2023 and 31/12/2023 were retrospectively

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evaluated. Because the hospital serves as a transfusion center, blood products are supplied by the Turkish Red Crescent. The cross-matching technique is used, which is one of the eligibility criteria for erythrocyte suspension prepared for the patient.

Social Security Institution Community on Healthcare Practices (SUT) is a legislative notification that allows the implementation of the state's health-related social policies, pricing, regulations, and containing all other application details. The regulation is regulated within the framework of Social Security Institution (SGK) law no. 5502, law no. 5510, and the General Health Insurance Procedures Regulation. Payment principles for all transactions made at health centers are regulated according to these codes. Therefore, knowing SUT disease, procedure, and surgery codes, transaction scores, and pricing, and reporting and pricing transactions completely in line with these codes are very important in terms of both recording the work done and preventing disposals.

Highlights

- The increasing average life expectancy and the increasing use of medical interventions have increased the need for blood products whose sole source is humans.
- The correct use of an erythrocyte suspension is cost effective.

The cross-match value of the SUT updated by the SGK on 19/10/2023 was 75. The Turkish lira (TL) equivalent of the SUT is 29.64 TL. The cost of erythrocyte suspension provided by the Red Crescent is 1519 TL for 1 unit. The study protocol was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 1484 date: 01.07.2021). This study does not require informed consent in terms of method; it is a retrospective study.

Statistical Analysis

Only tables reporting on the situation have been created. No statistical analysis was performed.

Results

The number of erythrocyte suspensions planned to be used for patients and the actual amounts used for patients at each clinic are presented in **Table 1**. As can be seen, the difference between the planned and used amounts is considerable. Except for the orthopedics and traumatology clinic, below 30% of planned suspensions are used, with the gynecology and obstetrics clinic having the minimum ratio of 12%. In the orthopedics and traumatology clinic, this ratio is 37%, which is still well below the desired level.

Table 2 lists the reasons for the disposal of blood components in our study. It can be noted that the dominant reason is expiration, which accounts for 92% of all disposals.

Discussion

In this study, it was determined that the total number of erythrocyte suspensions requested from surgical clinics was 24931 (100%) units, with 5941 (24%) used units and 18990 (76%) unused units. The cost loss is calculated as 1899075 SUT points. It has been determined that the hospital has suffered significant financial losses. Cost studies are important in the literature[1-3].

Preparing more erythrocyte suspension than necessary causes disposal due to reasons related to the blood component, such as blood component procurement, production, and use, transportation and transfer, storage, storage process, or the component reaching its expiry date before being used for the recipient, or user-related reasons, such as keeping the component released to the service in an inappropriate environment for a long time, wrong indication, or lack of training. The suspension can be disposed of before or after its use[4-6]. In our study, the main reasons for erythrocyte suspension disposal were its expiration date, storage conditions, and damage during transportation and transport, as presented in **Table 2**.

According to the hospital's quality standards, the erythrocyte suspension destruction rate was determined to be below 3%. This rate was calculated as 1.5% from the 2023 disposal data of the transfusion center. This rate can be further reduced by appropriate blood management[7,8].

Table 1. *Erythrocyte suspension use and cost evaluation at each clinic*

Clinic	Number of requested erythrocyte suspensions for patients	Number of erythrocyte suspensions	Number of erythrocyte suspensions not used for patients	Cost of erythrocyte suspensions for patients (ES*SUT value)	Cost of erythrocyte suspensions not used for patients (ES*SUT value)
Brain and nerve diseases	5904 (100%)	1694 (29%)	4210 (71%)	5904*75	4210*75
Orthopedics and traumatology	3670 (100%)	1369 (37%)	2301 (63%)	3670*75	2301*75
General surgery	4733 (100%)	1361 (29%)	3372 (71%)	4733*75	3372*75
Organ transplantation	1077 (100%)	327 (30%)	750 (70%)	1077*75	750*75
Gynecology and obstetrics	9547 (100%)	1190 (12%)	8357 (88%)	9547*75	8357*75

ES; Erythrocyte suspension, SUT; Social Security Institution Community on Healthcare Practices

Table 2. *Reasons for blood component disposal*

Reason for disposal	Expiration	Explosion	Storage conditions	Due to services	Other	Manufacturing defect	Total
Number of suspensions	711 (92.1%)	23 (3.0%)	21 (2.7%)	8 (1.0%)	9 (1.2%)	0	772 (100%)

Generally, the first cause of disposal in transfusion centers is outdated components, as in our study. In order to reduce the disposal of expired blood components, as stated in the 2016 National Blood and Blood Components Preparation, Use and Quality Assurance Guide, good planning of stock management, accurate determination of the critical stock level, and notification to the regional blood center are necessary. When these precautions are taken, the transfusion center will have a regular stock of ready-to-use blood components, and at the same time, it will be ensured that blood component disposal is minimized and the required blood component is kept ready in case of emergency. In stock management, it is important to act according to the "first in, first out" principle, except for special cases requiring fresh blood components, to follow the expiry date preferably with online systems, to create a good warehouse order and to train personnel accordingly.[9]

Measures can be taken to increase the possibility of using blood components by cross-matching more than one patient (double cross match) for erythrocyte concentrates nearing their expiration date in transfusion center stocks[10,11].

More than one cross-match study of erythrocyte suspensions increases personnel testing time. In cross-match tests, which should take approximately 1 hour to complete, this time is doubled. Heat and energy losses are also important in the preparation of erythrocyte suspensions and were not included in this study. We believe that further studies on these subjects will contribute to the literature.

Results

In parallel with the increase in average life expectancy, the increase in medical interventions and the development of treatment methods, the need for blood and blood products, the sole source of which is humans, has also increased. Because blood products are provided as voluntary donations, their appropriate use will help reduce hospital and patient costs. Employees in all blood service units and blood and blood component users are required to work diligently and carefully to minimize blood component disposal in all processes that involve safe, accurate, and efficient supply, preparation, and use of blood components. We believe that strict compliance with national and international standards and guidelines, quality management, and good clinical practices, as well as ensuring continuity of training on these issues, will enable more efficient product acquisition and decrease blood component disposal in all blood services units.

Conclusion

The increasing average life expectancy and the increasing use of medical interventions have increased the need for blood products whose sole source is humans. The correct use of an erythrocyte suspension is cost effective. Ensuring the training of blood bank employees reduces the destruction of blood components.

Ethical Approval: The study protocol was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 1484 date: 01.07.2021).

Informed Consent: Retrospective study.

Author Contributions: Tuncel DA: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Yiğit Sönmez A: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors declare no conflicts of interest. The authors are responsible for the content and writing of this article.

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Median Arcuate Ligament Syndrome Involving a Celio-Mesenteric Trunk-a Lesson Learnt

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Abstract

Celio-mesenteric trunk (CMT) is a rare vascular variation of the ventral branches of the abdominal aorta that supply blood to the mesentery and the gut. This rare variation is seen in 2/100.000 population. The presence of this anomaly is associated with an increased risk of mesenteric ischemia in the case of proximal occlusion. Median arcuate ligament (MAL) syndrome is a controversial entity characterized by compression of the celiac axis by MAL causing post-prandial pain. We report the fourth case of MAL compression syndrome involving a CMT in the world

Keywords: Celio-mesenteric trunk, computed tomography, median arcuate ligament syndrome

Introduction

Vascular compression syndromes are a group of disorders characterized by external compression of healthy arteries or veins, as well as accompanying nerve structures. These syndromes can severely impact the quality of life in affected individuals, who are typically young and otherwise healthy. The celio-mesenteric trunk (CMT) is a rare anatomical variation where the celiac artery (CA) and the superior mesenteric artery (SMA) arise from a common origin. It occurs in 0.5% to 3.4% of the general population.[1,2] This variation can complicate the planning and implantation of surgical procedures involving the areas supplied by these vessels. A new classification system for celio-mesenteric trunk based on multi-detector computed tomography (CT) angiographic (CTA) results and possible embryological mechanisms has been proposed recently.[3] CA branch stenosis or occlusion can accompany this anatomical aberrancy, but vascular compression syndrome of CMT by the median arcuate ligament (MAL) is extremely rare.[4] It is important to be aware of this variation to avoid complications during interventions. Multi-detector row CTA is an excellent tool for detecting the celio-mesenteric trunk before surgical and interventional procedures. The author clarifies that written informed consent was obtained from the parents and the anonymity of the patient was ensured. The study submitted to this journal has been conducted in accordance with the Declaration of Helsinki and according to the requirements of all applicable local and international standards.

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Case Report

An 8-year-old male child was brought to the emergency reception of North Bengal Medical College and Hospital, West Bengal, India with complaints of intermittent abdominal pain that worsened with food intake. The pain was described by the parents as diffuse and intermittent and increasing in intensity within an hour of food intake due to which the child had barely eaten for the last year and had lost around 10 kg body weight. The child rated the pain as 7 on a scale of 0 to 10. The child was admitted to a local private hospital a few days back where after a lot of investigations including endoscopy a diagnosis of SMA syndrome was done on sonography and the patient was treated with a gastrojejunostomy. The parents could not show the imaging reports but the diagnosis was documented on the discharge certificate of the child. However, even after the surgery, the complaint persisted due to which the child was brought to our institute.

On examination, the child appeared malnourished and his weight for his age fell below the 3rd percentile as per the Indian Association of Pediatrics growth charts. Pallor was present but the rest of the general survey was unremarkable. An abdominal examination could not be done as the child was resisting it due to pain from the recent midline incision site. For the same reason, an ultrasound examination could not be performed after routine blood tests the patient was posted for a contrast enhanced CT (CECT) of the abdomen.

CECT abdomen revealed unremarkable solid organs and normal bowel loops. There was no evidence of intramural gas or bowel wall edema. A gastrojejunostomy was seen in place (**Figure 1**). A common CMT was identified on CECT opposite to the 1st lumber vertebrae (**Figure 2**). It was classified as a Morita type 2 CMT. The left gastric artery was seen to arise as a thin branch below the CMT and was seen to anastomose with the left hepatic artery (**Figure 3**). The common trunk measured 8 mm and was seen to be compressed in its proximal part by the MAL with post-stenotic dilation (**Figures 4 and 5**). A 58% stenosis was identified. The patient was planned for a conventional angiography of the vessels but the parents declined due to their concerns about radiation exposure. The patient was offered a laparoscopic release of the MAL to which they consented and was referred to Nil Ratan Sarkar Medical College, the apex center of pediatric surgery in the state where he underwent the procedure. Three months post-operative there is near total resolution of symptoms and the patient is eating well. He is under regular follow-up under the department of general surgery and awaiting a reversal of the gastrojejunostomy.

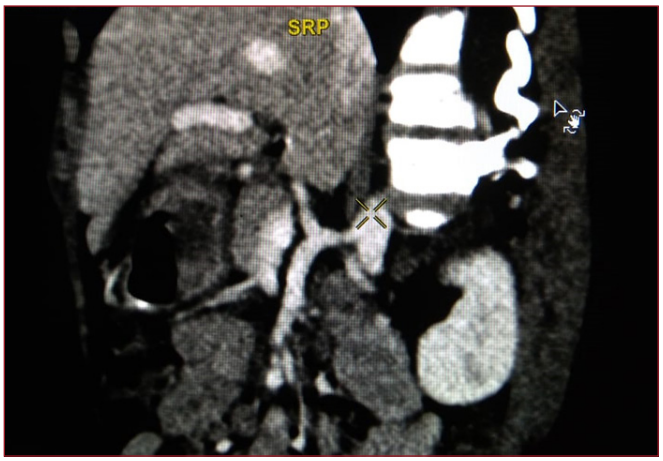

Figure 2. The first ventral branch from the abdominal aorta is seen to arise as a CMT (cursor over the origin of the CMT)
CMT: Celio-mesenteric trunk

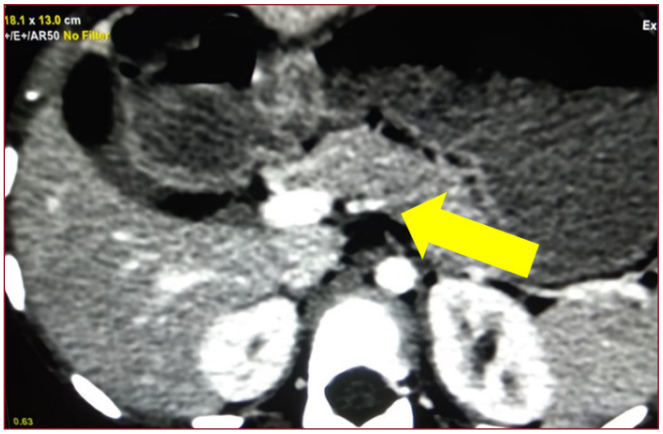

Figure 3. Left gastric artery (Yellow arrow) arising as a separate ventral branch of the abdominal aorta below the CMT
CMT: Celio-mesenteric trunk

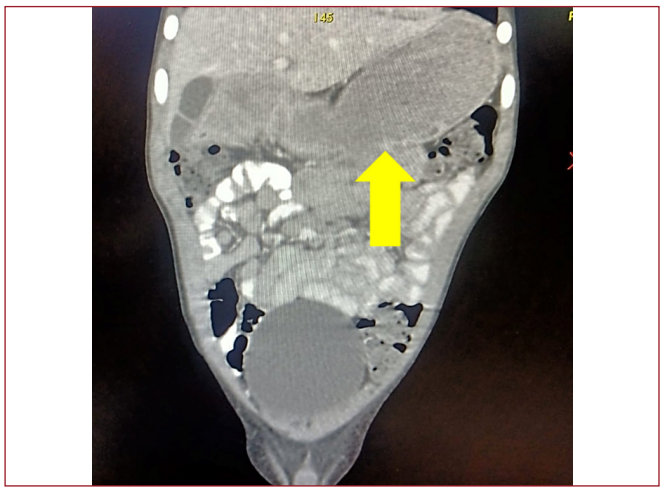

Figure 1. CT scan of abdomen was done and a gastro-jejunostomy was seen in place (Yellow arrow)
CT: Computed tomography

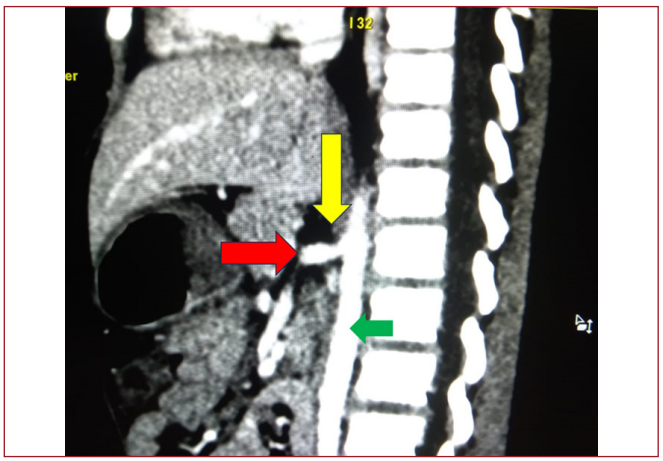

Figure 4. Compression of the proximal portion of CMT by the arcuate ligament (Yellow arrow) with post-stenotic dilation (Red arrow). Abdominal aorta (Green arrow)
CMT: Celio-mesenteric trunk

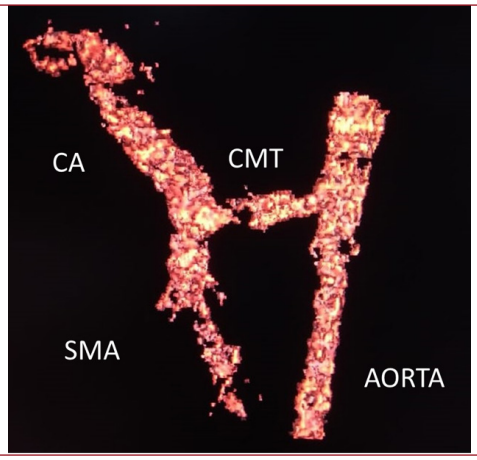

Figure 5. Angiographic anatomy after volume rendering of the vessels showing the aorta, CMT with focal compression, CA, and the SMA
CMT: Celio-mesenteric trunk, CA: Celiac artery, SMA: Superior mesenteric artery

Discussion

The MAL is a fibrous arcade that unites both crura of the diaphragm on either side of the aortic. It usually passes over the aorta over the CA origin. In between 10% and 24% of the population, ligaments may pass through the proximal part of the CA and cause indentation.[1,5] Generally, CA arises as the 1st ventral branch of the abdominal aorta around 1 cm below the MAL however in a small subset of the population in about 10% to 24%, the ligament may cross over the proximal portion of the celiac axis and cause a characteristic indentation that is usually asymptomatic. Most such patients are asymptomatic however a rare controversial entity called MAL syndrome is described where compression of CA by an indenting MAL causes epigastric pain exacerbated by food intake, weight loss, and nausea.[6] Although discovered several years ago the existence of this entity is still debated. The pathophysiology postulated is a combination of vascular occlusion and neuropathic pain due to compression of celiac ganglion which is increased during inspiration due to downward displacement of the diaphragm.[5,6] The diagnosis of this condition is even more challenging due to the non-specific nature of the presentation. There is no consensus yet on the diagnostic criteria for this condition. Generally, doppler sonography of the CA in inspiration and expiration shows stenosis and turbulence in the post-stenotic dilated portion.[6] In our case, the child would not allow a Doppler study due to the pain in his abdomen from the recent surgery,

CTA or conventional angiography is considered the gold standard for documenting compression. Axial sections are often inadequate to fully assess the CT findings typical with MAL compression. The best CTA plane to assess CA focal constriction is the sagittal plane. The distinctive hooked appearance of the focal narrowing can aid in differentiating it from other causes of CA constriction, such as atherosclerosis disease. Additionally, post-stenotic dilatation and large collateral arteries may be seen on CT.[5,7] The CMT is a rare anatomical variation first described by Lipshutz. He used the term “truncus celiaco-mesenterica” to describe the variant anatomy found in two cadavers where the CA and SMA had a common origin from the abdominal aorta. Due to the rare nature of the variant anatomy, the exact prevalence is known but it is estimated to be around 0.42% to 2.7%.[6,8] The identification of this variant anatomy can have serious implications related to patient symptomatology. Dual origin of vessels and multiple mutual anastomoses have a protective effect against mesenteric ischemia if either of the major ventral branches of the aorta supplying the gut is blocked. In the case of a CMT this benefit is lost in case an obstructive or a stenotic lesion occurs at the common origin. Hence such a case would have serious ischemic consequences like acute or chronic mesenteric ischemia which we suspect was the cause of abdominal pain in our patient. To the best of our knowledge, this is the fourth case in the literature reporting a case of MAL syndrome associated with a CMT.[5,6,9] Treatment is targeted towards the restoration of normal mesenteric vascular perfusion. Both open and laparoscopic management are done in various tertiary care centers. The MAL is divided along with the removal of the periarterial neural ganglionic tissue to relieve the neuropathic pain.[5,10] SMA syndrome also known as Wilkie’s syndrome, is a condition that can cause duodenal obstruction. It occurs when the SMA compresses the third part of the duodenum due a reduced aorto mesenteric angle, leading to inadequate drainage of duodenal contents into the jejunum. This can result in weight loss and malnutrition. Aortomesenteric angles less than 22 to 28 degrees with an acute otitis media distance between 2-8 mm are strongly suggestive of SMA syndrome. Although sonography can be used as a rapid and effective modality to screen for the condition but definitive diagnosis can be made only on CTA or conventional angiography.[11-13]

Conclusion

CMT is a rare vascular variant where the CA and SMA have a common origin. Due to a lack of collateral supply, a proximal occlusion can result in acute or chronic mesenteric ischemia. Clinical diagnosis of this condition is virtually impossible and diagnosis is based on radiological findings of CTA. Although to be considered as a diagnosis of exclusion we highlight the role of radiology in the successful diagnosis of MAL compression syndrome in a CMT along with its successful management. Also, we strongly discourage the use of sonography as a sole modality to diagnose SMA syndrome to guide treatment options and recommend all such cases to be considered for CECT abdomen to clearly define and describe the vascular anatomy.

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Conflict of Interest: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study received no financial support.

Informed Consent: The author clarifies that written informed consent was obtained from the parents and the anonymity of the patient was ensured.

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