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Invited Review

Legal and Ethical Approaches to the Usage of Blockchain and Artificial Intelligence Technologies in Healthcare in the Scope of Personal Data Protection

Kişisel Verilerin Korunması Çerçevesinde Sağlıkta Blockchain ve Yapay Zeka Teknolojilerinin Kullanımına Hukuki ve Etik Yaklaşımlar

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ABSTRACT

Latest developments in technology lead us to the blockchain and artificial intelligence (AI) technologies and these technologies were easily adopted in our daily lives via smartphones, tablets, and computers. However, the field of use of these technologies is not limited to individual usage. Thanks to them, public services have started to take a path in a quite positive direction. Even though it is predicted that these technologies will overstep their current benefits. Especially in healthcare, these technologies have many impacts that are determined to revolutionize medical science. Moreover, these technologies exceeded the pilot scheme and are currently integrated into the healthcare system. Apart from the interventional practices, AI technologies have started to impact children's health, and this makes sense when considering that today's children would live in the AI era. However, these technologies that can evolve rapidly and by themselves would raise questions, especially in healthcare. The right to health is one of the most important fundamental rights of humans as it is in direct relation with the right to health taking into account. When it comes to pediatrics, it is obvious that these concerns would reach higher levels, especially for the states who has special liabilities on protecting children's rights. In this study, we will explain the legal and ethical causes of these concerns and discuss possible solution.

Keywords: Blockchain, artificial intelligence, pediatrics, health, personal data protection

ÖZ

Son teknolojik gelişmelerin ürünleri olan öncelikle blockchain ve ardından yapay zeka teknolojileri, özellikle akıllı telefonlar, tabletler ve bilgisayarlar aracılığıyla gündelik yaşamlarımıza çok kolay bir şekilde entegre olan teknolojiler haline geldi. Şüphesiz ki bu teknolojilerin kullanım alanları bireysel kullanımlarla sınırlı kalmayacak ve özellikle hizmet alanında büyük adımların atılmasına sebep olacaktı. Hatta önümüzdeki yıllarda mevcut kullanımının da ötesinde faydaları ve etkileri olacağı öngörülmektedir. Özellikle sağlık alanında büyük adımların atılmasına ve tıp bilimini değiştirmeye kararlı bu teknolojiler yavaş yavaş pilot uygulamaların dışında sağlık hizmeti sunumuna entegre olmaya başlamıştır. Bu teknolojilerin kullanıldığı girişimsel işlemlerin dışında gelecek yılların yapay zeka çağına doğru insanlığı götüren yıllar olduğu düşünüldüğünde yapay zeka çağlarında yaşayacak olan çocukların sağlıkları noktasında da yapay zekanın şimdiden dahi etkilerini gösterdiği aşikardır. Fakat bu denli hızlı gelişen ve en önemlisi kendi kendine gelişebilen teknolojilerin, özellikle sağlık alanında birtakım şüpheleri de beraberinde getireceği aşikardır. Nitekim sağlık kişinin en temel, belki de yaşamıyla direkt bağlantısı sebebiyle en önemli haklarından birisidir. Devletlerin de çocukları koruma yönündeki özel önem gerektiren yükümlülükleri düşünüldüğünde söz konusu pediatri olduğunda bu şüphelerin daha da şiddetleneceği aşikardır. Bu çalışma ile bu şüphelerin hukuki ve etik gerekçeleri açıklanarak doktrindeki yaygın çözüm önerileri tartışılacaktır.

Anahtar kelimeler: Blockchain, yapay zeka, pediatri, sağlık, kişisel verilerin korunması

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INTRODUCTION

Blockchain and artificial intelligence (AI) technologies are quickly becoming a part of our daily lives. Not only for individual usage but also for public services. Healthcare is one of the popular and life-changing areas when it comes to the integration of blockchain and AI technologies into the service. As a service itself and also as the branches of the service separately, these technologies have so many benefits for the service itself and for improving human life and the treatment of diseases. Like many other branches

of medicine, pediatrics is one of the areas in which these technologies can show their significant impacts. As these technologies have many benefits for medicine and patients' health, they cause many concerns, especially at the point of fundamental rights and patients' security. Even these concerns outweigh the benefits when it comes to sensitive data and fundamental rights of the patients, especially of the children, for those states must provide higher protection. In this study, first, we will examine the benefits of these technologies separately in pediatrics. Then we will explain the term personal data and regulations on personal data protection which are effective in Turkey, such as General Data Protection Regulation (GDPR) and Kişisel Verilerin Korunması Kanunu/Turkish Personal Data Protection Act (KVKK), and we will discuss the regulations relevant to pediatrics. Finally, we will discuss legal and ethical questions about the usage of these technologies in pediatrics and we will discuss the probable solutions for these questions.

Blockchain Technologies in Pediatrics

Blockchain technology is simply defined as "Distributed database formed as a chain of data blocks and decentralizing the storage and processing of data" in the literature[1]. Even though its starting point was digital currency[2], now it has various areas of utilization such as finance, gaming, engineering, agriculture, and healthcare[3], which is one of the main subjects of this study. In healthcare, blockchain technologies offer various opportunities to use, such as; digital medical record storage, electronic prescription systems, intelligent hospital and telemedicine, clinical research, public health management, medical device tracking and drug tracking[4]. Even though the best-known and commonly used area of blockchain in healthcare is digital record storage, there is no usage of blockchain in healthcare in Turkey. Some may argue that there is a digital medical record storage system in Turkey called 'e-Nabız', but e-Nabız is not a product of blockchain technology, nor use the technology. That is why E-Nabız should not be confused with blockchain health record storage systems[5]. In this regard, Estonia is considered as a pioneer of the integration of blockchain technology in the storage of medical health records[6]. In pediatrics, studies show that implementation of electronic health records (EHR) facilitates monitoring diabetes, sickle cell disease and vital signs in pediatric intensive care and also facilitates the treatment of these diseases[7]. The same authors also emphasize the efficacy of the developments in the adaptation of the Telehealth system in pediatric care too[7]. So these systems allow children and their parents to reach healthcare services easily, especially for disease management at home. Apart from EHR, Internet of Things (IoT) devices integrated into the blockchain systems have a great impact on pediatric care too. IoT means devices that have an internet connection. These devices allow data sharing via internet connection and their main purpose is data collection and storage, then their flow to the bigger data systems without human intervention[8]. These devices are useful for monitoring patients' health status indicators[9] and provide real-time health data for healthcare professionals[8]. In pediatrics, there are some useful IoT devices such as; monitoring device for obesity prevention[10], monitoring device for diabetes, seizure detection device for epilepsy[11], device for management of asthma[12], IoT supported home mechanical ventilator[8], smart bracelets for children who have hearing loss[8], IoT supported smart pillbox, support device for autism spectrum disorder[13] and wearable IoT connected textile devices for neonatal monitoring[14].

AI Technologies in Pediatrics

Apart from blockchain technology, as AI technology can be integrated into the blockchain technology or stand alone AI have a huge impact on revolutionizing healthcare systems. AI technology's characteristics are potential human reasoning and decision-making[15]. These technologies work by learning, which happens by collecting and analyzing huge amounts of data and then by using these datasets to provide results or suggestions in the scope of their creation or use[16]. European Union (EU) Commission's High-Level Expert Group on AI defines clean and briefly how AI works as "perceiving their environment through data acquisition, interpreting the collected structured or unstructured data, reasoning on the knowledge, or processing the information, derived from this data and deciding the best action(s) to take to achieve the given goal and they can also adapt their behaviour by analyzing how the environment is affected by their previous actions"[17]. In healthcare, AI technology uses datasets from patients' health data and uses these datasets to make analyses and show its results in diagnostics or patient care[18]. European Parliamentary Research Service (EPRS) studies AI usage in healthcare into four main domains such as clinical practice, biomedical research, public health and health administration. Under the domain of clinical practice, AI's role is specified as image analysis, signal processing and integration and array of the results with the other health data. Under the domain of clinical research AI's role defined as retrieving clinical data by using machine learning algorithms and ranking the data.

In public health, AI's work as specified as risk analysis for diseases according to the demographics analysis. Lastly for healthcare administration, AI's role is defined as managing administrative workflow[19]. In the doctrine, even though some authors make similar classifications according to the medical field[20] like EPRS does, many authors address the issue according to its task. Today, the most popular and settled use of area of AI in healthcare is diagnosis and imaging[21] and also monitoring and remote care[18]. There are so many applications of these tasks fulfilled by AI[22]. In Turkey, there are some applications of AI in healthcare such as; integration of AI-based software to e-Nabız system[23], AI-based imaging devices, AI tools and software for early diagnosis and personalized cancer treatment, AI-based telemedicine applications[24], AI-based EHR and automation systems, biotechnology studies and clinical decision systems[25]. In pediatrics, AI is being used in personalized medicine[26], diagnostics and treatments[27], especially in imaging and monitoring[26], disease risk analysis[27] and clinical decision support[28]. Some authors also consider the usage of ChatGPT as a diagnostic or clinical decision support tool in pediatrics[27]. Despite the advantages of this advanced technology, it brings some concerns and questions, not only for its usage in pediatrics, but also for the whole healthcare system. However, we will discuss these concerns for pediatric health care deeply in this study for the delicate structure of children's personal data, especially in the context of children's health data and the field of pediatrics. In a study, authors indicated that pediatrics is a field that has more pressure for faster access to medical decisions and lower medical errors[29]. This can be explained by the parental observation on these patient-physician relationships. So the AI technologies cause anxiety among the parents for their high-risk, especially for the errors and concerns about the protection of personal health data, although this is not a priority[29].

Rules on Personal Data Protection Regulations about Pediatric Data

With the start of widespread use of the internet in our daily lives, concerns have been raised about personal data protection within the context of the right to respect for private life. All of these concerns led about the European Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data [Council of Europe Treaty Series (CETS) No.108] in 1981. Then today, it has evolved to the GDPR. In Turkey, as a product of the EU harmonization process, the KVKK/ Turkish Law no. 6698 came into force in 2016. Both GDPR and KVKK, define health data as a special data. There is no such specification for children's data, but GDPR has a regulation about the matter of consent regarding the children's personal data. In the following sections we will discuss these regulations.

Rules on Personal Data Protection Regulations about Children's Data

GDPR

For a lawful personal data collection, GDPR's article 6 requires the consent of the data subject for processing their personal data. Even though GDPR has no special regulation that regulates children's personal data under a special category. Therefore, Article 8 is about children's personal data. More specifically, Article 8 regulates the consent issue of the children's personal data. According to Article 8 of the GDPR, children at least 16 years old can consent to the processing of their own personal data by themselves. Nevertheless, children under the age of 16 cannot give consent to the processing and collection of their own personal data; their parents can give consent to the collection or processing of their children's personal data. Additionally, GDPR gives states a special responsibility over the activities for children. Also, GDPR suggests to the states to ensure special protection over children's personal data and this perspective is repeated in the recital 38 of GDPR, which is an explanatory text about the regulation, therefore there is no explanation of what can be done for the special protection of children's personal data. That is why this perspective of GDPR lawmakers is criticized in the doctrine[30].

KVKK

As a loyal follower of the GDPR, the Turkish legislator, did not recognize children's personal data as a special data category. Unlike GDPR, KVKK does not regulate the consent issue regarding children's personal data. This is because, children do not have legal capacity to act in Turkish law. Their parents do legal action in behalf of the children. Also, everyone under age 18 is considered a child in Turkish law. That is why the Turkish legislator found it unnecessary to regulate the consent issue on children's personal data[31]. Despite having no special regulations on children's personal data Turkish Ministry of National Education has a cautionary notice on sharing personal data of children in social media within education institutions both individually and institutionally[32]. Both GDPR and KVKK are criticized in the legal doctrine for not having a special regulation protecting children's personal data[33].

Rules on Personal Data Protection Regulations about Health Data

GDPR

Health data is regulated under a special category of the personal data, it is also called sensitive data, in the GDPR. Health data is also specified under a special category of personal data in the European Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (CETS No.108) in 1981. Regulating health data under a special category of personal data means it requires special protection and measures. In GDPR, health data is separated from genetic data and within the scope of health data, all of the data regarding the individual's health, including mental health are defined. Genetic data is also regulated under the same special category of personal data as health data. Collection and processing of sensitive personal data is only allowed if specific conditions are met, such as informed consent before collection[34]. Sensitive data must be collected and preserved in a secure environment and must meet required measures[35]. For example there is a prohibition for central data banks for health data and this prohibition is provided by the World Medical Association in 1983[35].

KVKK

As a loyal follower of GDPR, KVKK has similar regulations about health data, such as regulating health data under a special category and prohibiting the processing of the special personal data only if specific conditions are met such as informed consent. KVKK also pays great attention to informing data subject and includes a penal provision for contrary action[35].

In Turkish law, there is also a regulation about processing personal health data, called "The Regulation on Personal Health Data" which is regulated by the Turkish Ministry of Health. This regulation includes required protection measures for personal health data collection, processing and storage, further information on methods for collection, processing, storage and erasure of the health data, regulations about the e-Nabız central digital health system which is created via Ministry and also conditions for medical research and open health data. This regulation allows the usage of personal health data in medical research only if health data is anonymized and allows open health data only if required protection conditions are met.

Rules on Personal Data Protection Regulations about Children's Health Data

As we mentioned under the previous headings, both GDPR and KVKK do not provide special protection for children's personal data. According to both regulations, health data is considered as sensitive data and sensitive data requires special protection. So there is no special protection rule foreseen for children's personal health data. There are some differences between GDPR and KVKK regarding children's consent for processing personal data. As we mentioned in the previous headings. Process of health data requires informed consent. GDPR accepts children's consent as legal consent until the age of 16. Children under 16 years old cannot give legally valid consent for the processing their personal data according to the GDPR. Even though KVKK does not include any regulation about children's consent capability; general rules of Turkish law consider everyone under the age of 18 as a child and children do not have legal capacity to act. Their parents have the authority to act on their behalf of. That is why KVKK does not contain a special regulation for children's consent on the usage of their personal data. However, Article 8 of Turkish Regulation on Personal Health Data is about access to the children's health data and according to this article, parents can access to their children's health data through e-Nabız system but children who has the capacity of judgement can change the authorization of their parents for access to their health data through e-Nabız app. This article, seems to adopt the perspective of the GDPR on the matter in a way. In the doctrine, lack of special protection for children's personal data is criticized and it is suggested that children must be as fully informed as possible, even with games or cartoons, about the dangers of sharing their personal data with third parties[36]. Even so, children can be encouraged to participate in m-health apps which are helpful not only for tracking and monitoring chronic diseases and for treatments of mental diseases such as anxiety disorder, depression, etc.[36]. Besides, the same author, argues whether prenatal monitoring data is the mother's personal data or children's personal data according to the international organizations' official documents on this matter[36].

Personal Data Protection Regulations Applicable to Blockchain Technology

Even though there are many benefits of using blockchain technology in pediatrics, there are some compliance issues with the regulations arising from the nature of the technology. First of all, the problem

starts with the question "Is the data used and stored in blockchain a personal data?" If the answer is yes, then it should be emphasized that personal data is under the protection of both GDPR and KVKK. These regulations not only ensure the protection but also give individuals to control over their personal data[37]. Within the block, there might be data identifiable to the natural person[38]. So that means, the block can contain personal data and this is where blockchain gets on the radar of the personal data protection regulations such as GDPR and KVKK. In this case, the data subject can use their rights granted to them by these regulations. However, blockchain's nature cannot allow data subjects to use some of its rights, such as the right to erasure, destruction or anonymization of personal data. Because in a blockchain technology, data in the blocks cannot be changed or erased[37]. Even though there are some suggestions for compliance with these regulations but there is no exact solution for the rights of the data subject to be met as required[38]. Even when the sensibility of the health data is taken into account, as we mentioned before, all of the rights of the data subject on their health data must be overemphasized. Thus, management of the medical data causes a great challenge for the data controller[39].

Personal Data Protection Regulations Applicable to AI Technology

As we mentioned under the relevant heading, usage of AI technologies has many benefits in healthcare. Nevertheless, AI technologies require a vast amount of data for both learning and analyzing[17]. Within the vast amount of data, personal data may appear too. Thus, AI technologies can also get on the radar of the personal data protection regulations too. Collecting vast amount of data raises many concerns about personal data protection in AI technologies, such as re-identification, usage for the wrong purposes or usage beyond the data subject's consented purpose and transparency. While AI systems use big data to work, even the usage of anonymized data does not protect to data subject whose personal data is anonymized[40] because with the vast amount of data, anonymized data can be re-identified[17]. Thus, anonymized data can no longer be the non-personal data[17]. Besides, according to the relevant regulations, there is a 'purpose limitation' for the process of personal data. This means, personal data can only be used for the initial collection purpose. But AI technologies can reuse the data for a new purpose as out of control. The same logic applies at the point of consent. Because the consent of the data subject must be specific and the purpose limited[17]. When it comes to transparency, it is accepted that there is an uncertainty on the usage and the possible usage of the personal data in AI Technologies[17]. This uncertainty affects the usage of the right to erasure for the data subject. This is also a problem for the right to access to the personal data of the data subject. Apart from the personal data protection issues, the transparency problem causes mistrust in AI technologies especially in healthcare[19]. Besides, while considering the re-identification problem, since the health data is considered a sensitive data, it must be considered as a great risk of exposure and use of the sensitive personal data. In 2024, the EU AI Act came into force and this act ensures more security and more transparency for the AI users[41]. This act adopts a risk-based approach to AI technologies[42]. In the doctrine, this Act is considered as a great step for the development of AI systems in healthcare which protects and respects the fundamental rights of the patients[16].

Ethical Discussions on Using Blockchain and AI Technologies in Pediatrics

EPRS points out four ethical principles on the usage of AI, such as respect for human autonomy, prevention of harm, fairness and explicability/transparency[17]. Besides EPRS for the achievement of these principles, it sets seven requirements to be met such as, respect for the fundamental human rights, safety and security, respect for privacy and personal data, transparency, non-discrimination, sustainability and accountability [17]. When it comes to AI usage in medicine, transparency and respect for the patient's autonomy are the two moral principles that are generally put on the table. AI technologies have sophisticated self-learning algorithms, and these uninterpretable algorithms are called "The black box algorithms"[43]. This uninterpretable structure contradicts with the transparency principle and leads to the insecurity for the usage of these systems[44]. AI technologies also raise some concerns with respect to human autonomy especially, on respect to patients' autonomy in medicine. Some argue that AI can adopt a paternalistic model for decision making and discard the patient's decision for the treatment[43].

CONCLUSION

AI and blockchain technologies have a great impact in medicine, as in many other areas. Even in the different branches of medicine, we see that the use of AI has reached different levels of sophistication. Like the many other branches of medicine, AI and blockchain technologies, make a great contribution to pediatrics especially in monitoring diseases and ensuring the

participation and cooperation of the children in treatment.

In addition to its benefits, AI and blockchain technologies raise some legal and ethical concerns in widespread use. As legal concerns, we are commonly encountering the personal data protection issues. As we mentioned in the relevant headings, the usage of AI and blockchain technologies in medicine, currently makes it hard to usage of the data subjects' fundamental rights regarding their and their children's sensitive data and we observe the usage beyond the consent of the data subjects in these technologies. As an international authority, EPRS argues that GDPR and GDPR based regulations for personal data protection do not limit the capacity of the usage of these technologies but developers should harmonize their products with these regulations. We believe that EPRS's suggestions for these legal questions are acceptable. As for the ethical concerns, especially AI technologies, raise big question marks on transparency and respect for the patient's autonomy principles due to their structure. As the doctrine suggests, especially in medicine more transparent and explainable AI technologies must be chosen and physicians must intervene to the paternalist actions that might be caused by AI technologies in clinical decision making. This means physicians must play an active role with respect to the patient's autonomy when AI technologies are involved in the medical process.

Footnotes

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Original Article

Psychiatric Evaluation of Children and Adolescents Affected by the 2023 Kahramanmaraş Earthquake in Turkey

Türkiye'deki 2023 Kahramanmaraş Depreminden Etkilenen Çocuk ve Ergenlerin Psikiyatrik Değerlendirmesi

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ABSTRACT

Objective: There are a limited number of studies examining the effects of trauma on children and adolescents after the February 6, 2023 Kahramanmaraş earthquake in Turkey. The aim of this study is to investigate hospital records of pediatric patients directly affected by the earthquake among children admitted to child and adolescent psychiatry outpatient clinic.

Method: Between February and July 2023, medical records of 95 patients aged 0-18 years who applied to child and adolescent psychiatry outpatient clinic were examined. Sociodemographic characteristics, current psychiatric diagnoses, and treatment histories of the patients were assessed from their archive files.

Results: The mean age of 95 cases was 9.21±4.44 years (F: 51.6%). The most common indications for admissions were general counseling and sleep problems while 45.3% of the cases showed a grief reaction. The most frequent psychiatric diagnosis was attention-deficit/hyperactivity disorder (23.1%). Cases received the diagnosis of acute stress disorder (16.8%), and post-traumatic stress disorder (13.6%). After the disaster, 25.4% of the affected children were not attending school. Parents of 92.6% of cases were psychologically affected by the trauma. The group of children under 6 years of age most frequently received family counseling.

Conclusion: A high rate of parental impact from the disaster highlights the importance of psychosocial interventions that target both the children and their caregivers, as well as maintaining the child's integration in the school system as a guide for crisis management planning. The high application rates of children and adolescents with neurodevelopmental disorders to health care organizations after a disaster highlight the need to consider carrying out interventions tailored to the needs of earthquake victims.

Keywords: Disaster, earthquakes, trauma, child, adolescent, mental disorders, post-traumatic stress disorders

ÖZ

Amaç: 6 Şubat 2023'te Türkiye'de meydana gelen Kahramanmaraş depreminden sonra çocuklar ve ergenler üzerindeki travma etkilerini inceleyen sınırlı sayıda çalışma bulunmaktadır. Çalışmanın amacı bir üniversite hastanesi çocuk ve ergen psikiyatrisi polikliniğine başvuran çocuklar arasında depremden doğrudan etkilenen hastaların hastane kayıtlarını incelemektir.

Yöntem: Şubat-Temmuz 2023 tarihleri arasında çocuk ve ergen psikiyatrisi polikliniğine başvuran 0-18 yaş arası 95 hastanın tıbbi kayıtları incelenmiştir. Hastaların sosyodemografik özellikleri, mevcut psikiyatrik tanıları ve tedavi geçmişleri arşiv dosyalarından değerlendirilmiştir.

Bulgular: Doksan beş olgunun yaş ortalaması 9,21±4,44 yıl idi (kız: %51,6). Başvuru nedenleri arasında en yaygın olanı genel danışmanlık ve uyku problemleri iken, olguların %45,3'ünde yas tepkisi görüldü. En sık görülen psikiyatrik tanı dikkat eksikliği hiperaktivite bozukluğu (%23,1) idi. Olguların %16,8'i akut stres bozukluğu ve %13,6'sı travma sonrası stres bozukluğu tanısı aldı. Afet sonrasında olguların %25,4'ü okula devam etmiyordu. Tüm olguların %92,6'sının ebeveynleri travmadan psikolojik olarak etkilenmişti. Altı yaş altı gruba en sık aile danışmanlığı verildiği saptandı.

Sonuç: Afetten etkilenen ebeveynlerin yüksek oranı, hem çocuğu hem de bakım vereni içeren psikososyal müdahalelerin önemini ve çocuğun okul sistemine entegrasyonunun kriz yönetimi planlamasında bir rehber olarak korunması gerektiğini vurgulamaktadır. Afet sonrası çocuk ve ergenlerde nörogelişimsel bozuklukları olanların yüksek başvuru oranları bu bireylerin ihtiyaçlarına yönelik yapılacak müdahaleleri göz önünde bulundurmak gerektiğini ortaya koymaktadır.

Anahtar kelimeler: Afet, depremler, travma, çocuk, ergen, ruhsal bozukluklar, travma sonrası stres bozukluğu

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INTRODUCTION

Natural disasters may have profound and long-lasting effects on psychological well-being and physical health of the individuals[1]. Sudden and devastating effects of earthquakes cause intense feelings of fear, helplessness, insecurity and loss in individuals which expose victims of earthquake-especially developmentally vulnerable groups such as children and adolescents- to serious psychological risks[2,3]. The 7.7 and 7.6 magnitude earthquakes that occurred in Turkey on February 6, 2023, with the epicenter in the province of Kahramanmaraş, caused great destruction and loss of life in a large region covering 11 provinces in the southeast region of the country. According to official figures, the earthquakes claimed the lives of 50,783 individuals and injured 115,353 others. It was reported that 37,984 buildings collapsed as a result of the earthquakes[4]. In the initial phase, many people left the region to escape the destructive effects of the earthquake. It is estimated that approximately 2.2 million individuals evacuated or left the area on their own within about 10 days after the earthquake. According to the official registry of Turkish Department of Population 24,242 people migrated to Aydın province, although the number of migrants is probably higher than officially declared[5].

Psychiatric effects of disasters may differ according to age groups. The cognitive, emotional and social skills of children and adolescents, which are not yet fully developed, limit their capacity to cope with traumatic events[6]. In addition, the fact that adults experience mental problems such as post-disaster stress, depression or anxiety may make it difficult for them to provide emotional support to their children and adolescents and thus affect their mental health more adversely[7]. Moreover, this process is associated not only with the direct effects of the earthquake but also with secondary stress factors such as forced migration, changes in living conditions, disruptions in education and weakening of social support systems[8]. Children and adolescents who migrate after a disaster try to cope with the psychological effects of the trauma they have been exposed to while trying to adapt themselves to their new living conditions[9]. These unfavorable conditions lead to the development of post-traumatic psychiatric disorders and neurophysiological changes affecting emotional development of the victims. Post-traumatic responses can vary greatly depending on age, developmental stage, and variables inherent in the nature of the event (origin, severity, and duration), personal injury or injury to or loss of a family member, and the degree of life-threatening danger, as well as individual characteristics, family and social support[10]. Additionally, risk factors such as the source, severity, and duration of the traumatic event have been found to be related to the degree of vulnerability to post-traumatic symptoms. In a meta-analysis, the prevalence of post-traumatic stress disorder (PTSD) in children within the first six months after an earthquake was 19.2% and rised to 20.4% by the second year[11].

There is limited research in the literature on the psychological symptoms and psychopathological state of children and adolescents following the Kahramanmaraş earthquake[12,13]. The aim of this study is to contribute to the literature by presenting the descriptive sociodemographic and psychiatric clinical characteristics of children and adolescents who migrated to a city far from the landslide region within the first 6 months after the earthquake.

MATERIALS and METHODS

Between February and July 2023, the medical records of 97 patients aged 0-18 years who visited the child and adolescent psychiatry outpatient earthquake clinic at Aydın Adnan Menderes University Hospital following the disaster were retrospectively analyzed. A consent form was not obtained from the patients due to the retrospective nature of the study. Two cases with missing medical data were excluded from the study. The archive files of a total of 95 patients were included in the analysis.

Sociodemographic and psychiatric characteristics of the patients were retrospectively evaluated. Psychiatric diagnoses were established through psychiatric examinations performed according to the criteria stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[14]. The diagnoses determined at the time of first application were included in the current psychiatric diagnosis data files. Patients were admitted to the earthquake polyclinics without requiring an appointment and the follow-up frequencies varied according to the complaints of the patients and diagnoses they received. Accordingly, patients were called twice a week, weekly or once every 15 days for follow-up visits. Participants received individual psychotherapy or family counseling, and some were additionally provided with pharmacotherapy.

Ethics committee approval was received for this study from the Non-Interventional Local Ethics Committee of Aydın Adnan Menderes University (approval number: 2023/128, dated: 13.07.2023).

Statistical Analysis

The data of the cases were analyzed using the SPSS 29.0 for Windows (Armonk, NY: IBM Corp, USA) software package. Continuous variables were expressed as mean (± SD), while categorical variables as frequencies (n) and percentages (%). Chi-square test was used to compare categorical variables. McNemar's test, which is a two-group dependent two-sample comparison test, was used to compare the status of educational attendance before and after the disaster. A p-value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the total 95 cases including 49 (51.6%) female, and 46 (48.4%) male was 9.21±4.44 years. The respective number (%) of the study participants were ≤6 (n=31, 32.6%), 7-11 (n=34, 35.8%), and 12-18 (n=30, 31.6%) years old. The sociodemographic characteristics of the cases are presented in Table 1. The provinces from which the earthquake victims came from are shown in Figure 1. The mean time from the disaster to the referral to our hospital was 6.36±4.01 weeks (4-137 days). While 43.2% (n=41) of the cases applied to our hospital within the first 4 weeks after the earthquake, and 56.8% of them applied at a later date. The indicated mean number of psychiatric follow-up visits occurred immediately (2.17±1.51) or long after the earthquake (2.18±1.68). Before the disaster, 13.7% of cases were not attending school, whereas after the disaster, 25.3% were not attending school. There was a statistically significant difference in school attendance rates (p=0.012). Self-reports of the earthquake victims revealed incidents of self-harm (1.1%), suicide attempt (2.1%), cigarette (2.1%) and alcohol use (1.1%) before the disaster. The clinical characteristics of the cases before and after the earthquake are presented in Table 2.

The mean (± SD) household size was 5.57±1.82 individuals. Except for three cases (mild intellectual disability), all applicants had a normal level of intelligence. Five cases (5.3%) had physical illnesses including epilepsy (n=3), cleft palate (n=1), and neuroblastoma (n=1). Attention-deficit/hyperactivity disorder (ADHD) was the most common psychiatric diagnosis (7.3%) (Figure 2). There was no statistically significant difference among cases in terms of the presence of post-disaster psychiatric diagnosis and rates of social support provided to the victims (p=0.236). Earthquake victims were trapped under debris (5.3%), experienced peer bullying in their new schools (7.4%), and felt excluded (33.7%).

The most common indications for hospital admissions were general mental health assessment and counseling (n=33, 34.7%), sleep problems (n=20, 21.1%), and crying episodes (n=16, 16.8%). The victims most frequently reported their feelings of fear (45.3%), sadness (13.7%), anger (11.6%), unhappiness (7.4%), and guilt (1.1%). A total of 88 (92.6%) cases had parents affected by the trauma who were referred to psychiatry clinics.

Table 1. Sociodemographic characteristics of cases and parents

Characteristics	n	%
Gender		
Female	49	51.6
Age groups		
≤6 years	31	32.6
7-11 years	34	35.8
12-18 years	30	31.6
Education level		
Preschool	17	17.9
Primary school	31	32.6
Middle school	15	15.8
High school	19	20.0
Not attending school	13	13.7
Parental marital status		
Married	82	86.3
Divorced/separated	6	6.3
One parent deceased	5	5.3
Both parents deceased	2	2.1
Mother's education level		
Below high school	40	42.1
High school and above	55	57.9
Mother's employment		
Employed	33	34.7
Father's education level		
Below high school	33	34.7
High school and above	62	65.3
Father's employment		
Employed	93	97.9
Place of residence		
City center	58	61.1
District	35	36.8
Village	2	2.1
Financial status of the family		
Less income than expenditure	49	51.6
Equal income and expenditure	43	45.3
More income than expenditure	3	3.2

Figure 1. Provincial distribution of cases admitted to Aydın province from the earthquake region in Turkey

Upon reviewing psychiatric diagnoses, the most common psychiatric diagnoses were ADHD (23.1%), followed by acute stress disorder (ASD) (16.8%) and PTSD (13.6%) (Figure 3). The children diagnosed with ADHD (n=22), had specific learning disorders (n=9), ASD (n=2), and PTSD (n=1). Only one case among patients diagnosed with autism spectrum disorder (AD) (n=8), had a previous diagnosis of AD. Some earthquake victims had symptoms of grief (n=43, 45.3%), insufficient social support (32.6%) and a history of applying for a medical board report (14.7%). In terms of bereavement due to the disaster, the victims experienced the loss of a first-degree relative (n=3, 1%), friends, teachers, or neighbors (n=59, 62.1%). PTSD, and ASD were detected in 21.7%, and 23.4% of the cases that experienced a loss.

The earthquake victims received family counseling (n=40, 42.1%), both pharmacotherapy and psychotherapy (n=24, 25.3%), psychotherapy (n=23, 24.2%), and only pharmacotherapy (n=8, 8.3%). The most commonly used psychotherapy method was trauma-focused cognitive-behavioral therapy (TF-CBT), and eye movement desensitization and reprocessing therapy (EMDR) was applied to suitable cases. Family counseling was most commonly applied to children under -6 years of age (29.5%) (Figure 4). When analyzed based on the medications used in pharmacotherapy, selective serotonin reuptake inhibitors were the most commonly prescribed medication (13.6%), followed by methylphenidate (10.5%), antipsychotics (5.2%), atomoxetine (4.2%), propranolol (2.1%) and melatonin (2.1%). Multiple drug use was observed in 5 cases while 19 (20%) cases maintained their treatment.

DISCUSSION

The current study analyzes the sociodemographic and psychiatric clinical characteristics of children and adolescents who admitted to a distant city within the first six months following the earthquake in Kahramanmaraş province on February 6, 2023. The mean-age of the cases in our study was 9.2 years. Similarly, a study investigating the psychiatric clinical features of the Marmara earthquake reported that cases had a mean age of 9.7 years[15]. Additionally, it was observed that approximately half of all cases presenting to our clinic were primary school students and preschool children (48.4%). It is noted that the earthquake may more proundly affect younger children who are not yet fully developed both cognitively and verbally compared to children in other age groups[16]. This situation is anticipated to stem from the expectation of early protective intervention for children of families who have experienced a devastating earthquake.

In our study, when the cases were examined according to their regular attendance to formal education, we observed that 13 children (13.7%) did not attend school before, and 24 of them (25.4%) after the disaster with a statistically significant difference between pre- and post-disaster school attendance rates (p=0.012). The fact that those who attended to their new schools after the disaster experience peer bullying and exclusion, and the

low school attendance rates necessitate arrangements for the rapid orientation of children to school life through cooperation between institutions. In a study on surviving adolescents conducted five years after the 2010 Yushu Earthquake in China, the school attendance rate was comparable to ours (30.7%)[17]. Based on the results of studies demonstrating a strong association between school attendance status, psychopathology and well-being of children and adolescents after disasters, it is considered crucial to make necessary plans addressing devastating factors such as collapse of infrastructure system, destruction of buildings, and migration that disrupt the effective functioning of the education system[18].

Table 2. Clinical characteristics of cases and parents		
Psychiatric illness of the mother	**n**	**%**
Yes	13	13.7
Psychiatric illness of the father		
Yes	6	6.3
Suicide attempts in the family		
Yes	5	5.3
Criminal records in the family		
Yes	2	2.1
Supportive relatives		
Yes	64	67.4
Psychiatric consultation before disaster		
Yes	33	34.7
Continuation of psychiatric follow-up before disaster		
Regular follow-up	8	8.4
Irregular follow-up	6	6.3
Lost to follow-up	19	20
Psychiatric diagnosis before disaster		
Yes	20	21.1
Use of psychiatric medication before disaster		
Yes	14	14.7
History of psychiatric disease before disaster		
Self-harm	1	1.1
Suicide attempts	2	2.1
Cigarette use	2	2.1
Alcohol use	1	1.1
Indications for hospital admission after disaster		
General mental health assessment and counseling	33	34.7
Sleep problems	20	21.1
Crying episodes	16	16.8
Difficulty focusing	11	11.6
Requirement for health board report	5	5.3
Other*	10	10.7
Treatments received after disaster		
Family counseling	40	42.1
Pharmacotherapy and psychotherapy	24	25.3
Individual psychotherapy	23	24.2
Pharmacotherapy alone	8	8.3
*Withdrawal: 4.2%, inability to study: 3.2%, bereavement/loss: 1.1%, self-harming behavior: 1.1%, behavioral problem: 1.1%		

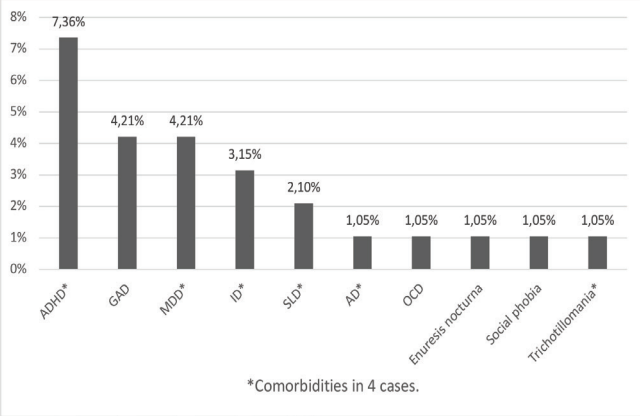

Figure 2. Distribution of pre-disaster psychiatric diagnoses

ADHD: Attention-deficit/hyperactivity disorder, PTSD: Post-traumatic stress disorder, SLD: Specific learning disability, AD: Autism spectrum disorder, MDD: Major depressive disorder, ASD: Acute stress disorder, OCD: Obsessive-compulsive disorder, GAD: Generalized anxiety disorder, ID: Intellectual disability

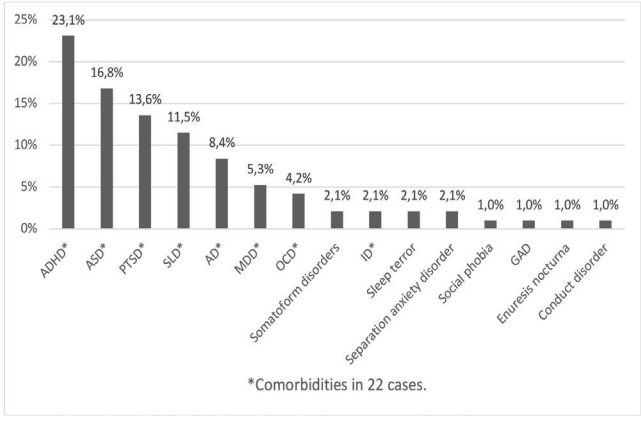

Figure 3. Post-disaster psychiatric diagnosis distribution

ADHD: Attention-deficit/hyperactivity disorder, PTSD: Post-traumatic stress disorder, SLD: Specific learning disability, AD: Autism spectrum disorder, MDD: Major depressive disorder, ASD: Acute stress disorder, OCD: Obsessive-compulsive disorder, GAD: Generalized anxiety disorder, ID: Intellectual disability

We have observed that assessment of general mental health state and counseling consisted 34.7% of the indications for hospital referrals. In our study, sleep disorders were the most common complaints following seeking general counseling. A cohort study conducted on 1573 adolescents who survived the Wenchuan earthquake in China revealed a prevalence of poor

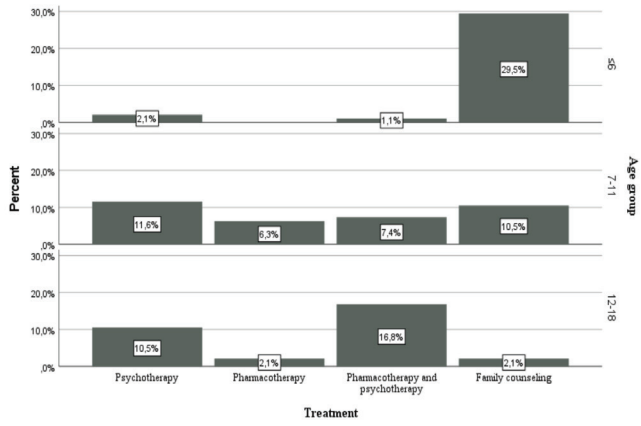

Figure 4. Treatments applied for different age groups

sleep quality of 22.6%[18]. A subsequent study conducted in Türkiye on children and adolescents following the Kahramanmaraş earthquake revealed that sleep disturbances were the most prevalent complaints[13]. In our study, sleep problems were evaluated under a single category; however, there is a need for conduction of more detailed studies examining sleep disorders, which are considered a core component of PTSD, in the literature[19,20].

In the current study, the most common psychiatric diagnoses received by the cases were ADHD, ASD, and PTSD. Additionally, neurodevelopmental disorders constituted 33.6% of all diagnoses established. Upon reviewing the literature, a strong association between ADHD and PTSD has been noted, indicating that the clinical presentation is more severe when ADHD accompanies PTSD, functionality is more severely impaired, and accompanying behavioral problems are more frequently seen[21]. In our study, 22 cases of ADHD were accompanied by 2 cases of ASD and 1 case of PTSD. The lower rate of this comorbidity compared to the rates reported in the literature may be due to the cases presenting to us in the early period after the disaster (within an average of 6.3 weeks), during which some symptoms may not have become clinically significant. However, considering that these cases may be at serious risk in the subsequent periods, we strongly emphasize that appropriate treatment and psychosocial interventions in the early period are of utmost importance.

Among referrals to our clinic, 8 cases were diagnosed with AD, and three of these cases had additional psychiatric disorders. A study conducted in Italy following the 2009 L'Aquila earthquake examined the adaptive behaviors of children and adolescents with

AD who had, and had not experienced the earthquake. The results indicated a significant decrease in adaptive behaviors among the former group during the initial months following the earthquake[22]. Parents of children and adolescents diagnosed with neurodevelopmental disorders may have referred more frequently to child psychiatry clinics for counseling or treatment adjustments due to changes in their routines, disruptions in their formal and special education, and difficulties in maintaining their current psychiatric treatments during the earthquake and thereafter. In times of disaster, it is important to promptly arrange the treatment of children with special needs and individuals under psychiatric follow-up. Evaluating the effects of trauma and PTSD in children diagnosed with AD is also an important consideration[23]. There is a need for further research examining adaptive processes in children and adolescents diagnosed with AD in the post-earthquake period.

The prevalence of PTSD and depression following major earthquakes varies across studies, with PTSD ranging from 15.7% to 58.3% and depression ranging from 16.8% to 64.5%[24-28]. The prevalence of PTSD in children and adolescents after an earthquake varies depending on assessment methods, the time elapsed since the event, and the distance from the epicenter of the earthquake[25,29,30]. In a study examining the psychiatric characteristics of children and adolescents after the Marmara earthquake in Turkey, it was found that 25.5% of the cases met the diagnostic criteria for PTSD, 16.5% for ASD and 38% for adjustment disorder[15]. After the Van earthquake, 40.6% of adolescents reported severe PTSD symptoms, while 37.7% met criteria for clinical depression[31]. Researches conducted following the Turkish earthquake indicates prevalence rates of PTSD, and ASD among children and adolescents ranging from 28% to 75% and 31% to 42%, respectively[32-35]. The rates of PTSD and depression observed in our study were lower than those reported in the literature. This could be attributed to several factors including the diagnoses being determined by child psychiatrists based on clinical interviews according to DSM-5 criteria, the absence of scale-based diagnoses, the inclusion of cases referred to the outpatient clinic, the lower mean-age of the cases, the timing of the initial six-month referrals, and the results being from a single center. These factors may have contributed to the lower rates of PTSD observed in our study compared to those reported in the literature.

Common risk factors for developing these disorders include female gender, direct exposure to earthquake, injury or death of family members, and adverse life events[27,28,36]. Some studies have found that symptoms persist over time, while others have observed a decrease in their prevalence[28,37]. Protective factors identified include social support and mental resilience[28,36].

These findings highlight the need for early interventions and long-term mental health support for adolescent earthquake victims. In our study, it was observed that social support was inadequate in 31 (32.6%) cases, and furthermore, 32 (33.7%) cases reported feeling socially excluded. Perceived social support is defined as the interaction process in relationships that fosters coping, respect, belongingness, and competence through the real or perceived exchange of physical or psychological resources[38]. Likewise, individuals with weak social and family support systems are more likely to develop ASD or PTSD following a traumatic event[39,40]. Consequently, research indicates that social support may protect children from developing psychiatric symptoms following a disaster, while inadequate social support may be a significant risk factor for PTSD[41,42].

In the literature, disruption in family functioning is considered an important risk factor for emotional disturbances in children, and post-earthquake parental psychopathology has been associated with the development of PTSD in children. Moreover, strong family support is highlighted as a protective factor[15,43-45]. Our study found that 92.6% of the parents of the cases were affected by trauma, and parents who were also significantly affected by trauma were insufficient in providing the necessary social support to their children. Therefore, all parents were provided with necessary psychoeducation, and referrals to psychiatry were made. It has been noted that the death of a family member or the person the victim cares about and parental injury during an earthquake are significantly associated with adverse emotional outcomes among children and adolescents[35,43,46-48]. In many studies in the literature, it has been observed that witnessing injury or death, as well as the loss or injury of family members and/or relatives, play a significant role in the development of PTSD among adolescents[35,49,50]. In our study, nearly half of the cases who experienced a loss were diagnosed with ASD or PTSD. It is considered essential to closely monitor individuals who have experienced loss of a relative or a close friend for the development of PTSD and to implement protective measures.

Approximately half of the cases (49.5%) received psychotherapy in our study. International treatment

guidelines for the treatment of PTSD recommend TF-CBT as the first-line treatment for children. Additionally, various studies have demonstrated the effectiveness of EMDR in the treatment of children and adolescents[51-53]. In our study 19 cases (20%) continued with treatment, and the mean number of psychiatric consultations was found to be 2.17±1.6 times. Unfortunately, the limited number of follow-ups did not allow for an evaluation of the effects of the treatments. Scarce number of follow-up consultations attended by the earthquake victims could be attributed to financial issues, access to healthcare services, distance of accommodation centers from healthcare facilities, changes in accommodation, prioritizing basic personal needs over seeking psychiatric help, or the spontaneous reduction of some symptoms.

Strengths of the Study

There is a paucity of studies investigating psychiatric evaluation in children and adolescents affected by the 2023 Kahramanmaraş earthquake in Turkey. This study offers valuable insights by addressing a significant research gap and providing a comprehensive epidemiological perspective on the post-earthquake period in Türkiye through a detailed psychiatric evaluation. The study was conducted on 95 cases from diverse age groups. A comprehensive evaluation was conducted for a number of factors, including sociodemographic characteristics, pre-existing psychiatric diagnoses, and treatment history. Furthermore, a comprehensive analysis was performed using a variety of scales to assess different psychiatric conditions, including depression, anxiety, and PTSD. An alternative perspective is provided by the incorporation of gender-specific analyses. Furthermore, the identification of psychiatric conditions both prior to and following the earthquake will inform the implementation of appropriate psychosocial interventions in the post-earthquake period.

Study Limitations

Single-center setting of the study may limit the generalizability of its findings. Additionally, its retrospective design may result in retrieval of incomplete data and limitations in case follow-up. A six-month post-earthquake timeframe may not fully capture psychiatric condition which might develop in the long-term. Although we applied certain assessment scales to eligible patients during initial assessments and follow-ups within the scope of the study, the fact that these scales were not applicable across different age groups (e.g., adolescents, school-age, and preschool children), the inability to conduct follow-up assessments for patients who lost to follow-up, and insufficient number of follow-up visits (n=2) attended by the earthquake victims, prevented comparisons at specific time points (e.g., acute phase, 3 and 6 months later) and limited the generalizability of the results to the entire study sample. The fact that assessment scale scores were not estimated before and after the therapeutic interventions may also be a limitation regarding the evaluation of the effectiveness of the medical intervention. Therefore, data of the assessment scales have not been presented in this study.

CONCLUSION

Life-saving interventions following disasters such as earthquakes are important for both preserving the mental health of children and organizing psychiatric treatment promptly due to the significant risk factors that childhood traumatic events pose for psychopathology that might develop later in life. Our study observed high rates of neurodevelopmental disorders (AD and ADHD diagnoses), correlating with the high impact of the disaster on parents. Integrating post-disaster psychosocial interventions for both children and caregivers, identifying factors that impede children's continued participation in the school system after addressing their basic needs, will be instructive in crisis management planning. Furthermore, this study, conducted in a western province of Turkey, provides insights into disaster-related psychosocial interventions and planning of the provision of geographical needs by comparing earthquake-affected and unaffected distant centers in terms of psychiatric referrals.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from The Non-Interventional Ethics Committee of Aydın Adnan Menderes University (approval number: 2023/128, dated: 13.07.2023).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept: B.G.Ö., H.A., Design: B.G.Ö., H.A., Data Collection or Processing: S.A., M.K.Ç., A.K.Ç., B.C.Ö., Analysis or Interpretation: S.A., M.K.Ç., A.K.Ç., B.C.Ö., B.G.Ö., Literature Search: S.A., M.K.Ç., A.K.Ç., B.C.Ö., Writing: S.A., M.K.Ç., B.C.Ö.

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Original Article

The First Description of Acidic Blood-Induced Kidney Injury Following Subarachnoid Hemorrhage: The First Experimental Study

Subaraknoid Kanamayı Takip Eden Asidik Kana Bağlı Böbrek Hasarının İlk Tanımı: İlk Deneysel Çalışma

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ABSTRACT

Objective: One of the complications of subarachnoid hemorrhage (SAH) is the acidity of blood and cerebrospinal fluid if carotid body/glossopharyngeal-nerve chemoreceptor networks are disrupted. This study aimed to investigate whether the renal arteries and glomeruli are affected by acidic blood pH following SAH.

Method: Twenty-six hybrid rabbits were selected of which 5 were used to analyze interactions between carotid bodies and kidneys, 5 were allocated as the sham group that received injections of 1 cc saline, and 16 of them constituted the SAH group in which 1 cc of autologous arterial blood was injected into the cisterna magna. Deaily pH and blood pressure values of all animals were measured before, during, and after surgery for 2 weeks, and then all animals were decapitated. Carotid bodies and atrophic glomeruli of all animals were determined histopathologically. Only pH values, and number of atrophic glomeruli per mm^3 (n/mm^3) were analyzed statistically.

Results: In the study group severe degeneration of perirenal vagal ganglia, renal artery vasospasm, intrarenal hemorrhage, and renal glomerular degeneration were observed. The mean density of atrophic glomeruli in control, sham, and study groups were estimated as 13±37/mm^3, 24±5/mm^3, and 67±11/mm^3, respectively which differed statistically significantly between control, and sham ($p<0.005$), sham and study ($p<0.0005$), control and study ($p<0.00001$) groups.

Conclusion: The study showed that acidic blood results in degeneration of the epithelial cells and causes severe vasospasm in renal arteries and glomerular atrophy following SAH, which has not previously been described.

Keywords: Subarachnoid hemorrhage, renal artery injury, acidosis, glomerulus atrophy

ÖZ

Amaç: Subaraknoid kanamanın (SAH) komplikasyonlarından biri, karotis cisimcik ve glossofaringeal sinir ağlarının bozulmasına bağlı olarak kan ve beyin omurilik sıvısında gelişen asidozdur. Bu çalışmanın amacı, SAH sonrası asidik kan pH'ının renal arterler ve glomerüller üzerindeki etkisini araştırmaktır.

Yöntem: Çalışmada 26 melez tavşan kullanıldı. Beş tavşan karotis cisimcik ve böbrek ağı analizleri için ayrıldı. Beş tavşan, 1 cc serum fizyolojik uygulanarak SHAM grubuna dahil edildi. On altı tavşana ise sisterna magnaya 1 cc otolog arteriyel kan enjekte edilerek SAH modeli oluşturuldu. Tüm hayvanların pH ve kan basıncı değerleri, ameliyat öncesinde, ameliyat sırasında ve sonrasında 2 hafta boyunca günlük olarak kaydedildi. Çalışma sonunda tüm hayvanlar dekapite edilerek karotis cisimcikleri ve böbrek dokuları histopatolojik olarak incelendi. pH değerleri ve atrofik glomerül sayıları (n/mm^3) istatistiksel analiz edildi.

Bulgular: Çalışma grubunda perirenal vagal ganglion dejenerasyonu, renal arter vazospazmı, intrarenal hemoraji ve glomerüler dejenerasyon saptandı. Kontrol, SHAM ve SAH gruplarında ortalama atrofik glomerül yoğunluğu sırasıyla 13±3, 24±5 ve 67±11 n/mm^3 olarak hesaplandı. Atrofik glomerül sayısı arasındaki ilişki gruplar istatistiksel olarak anlamlı bulundu ($p<0.005$ kontrol/SHAM; $p<0.0005$ SHAM/SAH; $p<0.00001$ kontrol/SAH).

Sonuç: Bu çalışma, SAH sonrası gelişen kan asidozunun epitel hücre dejenerasyonuna yol açtığını ve daha önce tanımlanmamış bir şekilde renal arterlerde artmış vazospazm ile glomerüler atrofiye neden olduğunu ortaya koymaktadır.

Anahtar kelimeler: Subaraknoid kanama, renal arter yaralanması, asidoz, glomerulus atrofisi

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INTRODUCTION

The kidneys are innervated by a complex network that includes thoracolumbar somatosensory fibers, the abdominal sympathetic chain, and vagal nerves. These neural pathways play a crucial role in regulating renal blood flow, blood pressure, and electrolyte balance[1]. Subarachnoid hemorrhage (SAH) is a life-threatening condition that not only affects the central nervous system but also has severe systemic adverse outcomes, including acute kidney injury (AKI)[2]. SAH increases the incidence of AKI and worsens survival outcomes, emphasizing the need to better understand the underlying mechanisms of renal dysfunction in this context[3,4]. While electrolyte imbalances, such as hypokalemia, are known to contribute to SAH-induced renal pathology[5,6], the impact of autonomic nervous system (ANS) dysregulation on renal function is still incompletely understood. The sympathetic and parasympathetic nervous systems exert opposing effects on renal function. Excessive sympathetic activation secondary to vagal nerve dysfunction can lead to renal artery spasms, increased renal blood pressure, and ultimately, renal hypertension[7-9]. Experimental models have demonstrated that vagal nerve lesions, such as cervical vagotomy, exacerbate renal sympathetic activity, triggering renal hypertension[10-12]. Furthermore, ischemia-reperfusion injury, a common complication of SAH, has been linked to sympathovagal imbalances, which further elevate renal arterial pressure and worsen kidney damage[13]. These findings highlight the critical role of dysregulation of ANS in the pathogenesis of SAH-associated renal complications.Although the effects of SAH on kidney function have been well documented, the mechanisms through which acidotic blood contributes to renal injury remain insufficiently explored. Acidosis is a common consequence of SAH and has been implicated in systemic hypoxia, carotid chemoreceptor activation, and increased sympathetic drive, all of which contribute to the development, and exacerbation of renal hypertension. However, direct effects of acidic blood on renal epithelial cells and glomerular anatomy have yet to be fully elucidated. Previous studies have primarily focused on sympathetic overactivation and electrolyte disturbances as key contributors to SAH-induced renal dysfunction, often overlooking the potential role of acidosis played in the pathogenesis renal pathologies. This study aims to bridge this gap by investigating the mechanisms through which acidic blood contributes to the development of renal epithelial cell degeneration and glomerular atrophy following SAH. While existing research has predominantly attributed SAH-related renal damage to excessive sympathetic activation and electrolyte imbalances, the specific effects of acidosis on renal structure and function remain largely undefined. By building on current knowledge of SAH-associated renal complications, this study seeks to provide novel insights into the pathophysiology of SAH-induced kidney injury and identify potential therapeutic targets for mitigating renal damage.

MATERIALS and METHODS

The animals used in this experimental study were owned and managed by our institution. Ethical approval for the study was obtained from the Institutional Review Board of Animal Experiments Local Ethics Committee of Atatürk University (approval number: E-2200369130, dated: 29.06.2022). The study was conducted on 26 rabbits; five of which were used to analyze the normal structures of the carotid bodies and kidneys. Twenty-one rabbits consisted of both sham surgery group (n=5) that received an injection of 0.5 cc saline solution, and study (n=16) group received an injection of 0.5 cc of autologous-auricular arterial blood into cisterna magna following surgical preparation of suboccipital-cervival region under general anesthesia. SHAM and study group animals received these injections once a day for three-day period. Before surgery, the SHAM and study group animals were anesthetized with an injection of 1 mg/kg acepromazine, 25 mg/kg ketamine hydrochloride, and 15 mg/kg lidocaine hydrochloride combination. After a followed-up of two weeks, all animals were sacrificed under general anesthesia before surgery. Their carotid bodies and kidneys were removed and fixed in a 10% formalin solution for one week. Then, these samples were embedded in paraffin blocks, and 20 consecutive 5 µm sections were taken from these paraffin blocks for the stereological analysis. Specimens were stained with hematoxylin and eosin method. Histopathologically, condensed cytoplasm, shrinking nuclei, angulated cells, and pericytoplasmic halo formation around cytoplasm due to cytoplasmic regression were accepted as epithelial degeneration criteria for carotid body neurons and kidneys. The physical dissector method was used to evaluate the number of atrophic glomeruli by refereces to glomerular cells like our previous studies. Stereological methods were used to estimate the number of atrophic glomeruli; and the corelation between the pH values and the number of atrophic glomeruli was analyzed using IBM SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA) software. Shapiro-Wilk tests were used to evaluate variabilities in distribution for normalizing descriptive data expression of mean ± standard deviation. Variabilities in distributed

data were analyzed by Analysis of Variance test. Kruskal-Wallis test was also used when the results were considered statistically significant at $p<0.05$.

RESULTS

Two out of 16 rabbits died within the second week, likely due to cardiorespiratory disorders, and replaced by additional new animals for restudy. The mean blood pH values were: 7.346±0.032 in the control (n=5), 7.315±0.062 in the sham (n=5), and 7.20±0.014 in the study groups (n=16) (Figure 1). Circulatory and respiratory changes were detected in the study groups. Systolic blood pressure was measured as 99±7/mmHg in normotensive, 106±8/mmHg in sham, and 117±13/mmHg in the study rabbits.

The mean density of atrophic glomeruli of the control, sham, and study groups were estimated as 13±3/mm^3, 24±5/mm^3, and 67±11/mm^3, respectively (Figure 2). The levels of significance noted in statistical analyses performed between pH values and number of atrophic glomeruli were: $p<0.005$ in control vs sham; $p<0.0005$ in sham vs study; $p<0.00001$ in control vs study groups.

Number of degenerated carotid body neurons and pH changes were comparable to those found in our previous relevant studies[13,14].

Histopathological Results

Hilar renal artery vasospasm, vagal nerve axonal injury with degeneration of perirenal ganglia, atrophic glomeruli, degenerated perirenal ganglia, inflamed degenerated vagal plexus around renal artery and kidney, stenotic renal artery, degenerated perirenal ganglia, intrarenal artery covered with lymphoid tissue, slightly edematous glomeruli, and atrophic glomeruli, hemorrhagic parenchymal edema with ghost degenerated glomeruli and atrophic glomeruli were detected in SAH created rabbits.

Figure 3 shows the binuclear neurons of carotid bodies in control (A), moderately deformed neurons in sham (B), and severely deformed neurons in study (C) groups. Figure 4 shows cross-sectional view of the renal artery on computed tomography (RA) in a normal rabbit (A). Moreover, histopathological appearances of control (B), moderately stenotic renal artery in a sham (C), and severely stenotic renal artery in a study animal (D) are shown in Figure 4. The method of estimating number of glomeruli is demonstrated in Figure 5: In order to predict the number of glomeruli stereologically, the cross-sectional region (A) of the kidney was taken into consideration, n pairs of physical dissectors designed in a 3-dimensional form consisting of consecutive sections taken at 100-micron intervals in the glomeruli thickness and the method for estimating the number of glomeruli (G) in two consecutive pairs at 100 microns apart were used. Figure 6 shows normal glomerulus in the control (A), moderately deformed glomerulus in the sham (B), and severely deformed glomerulus in the study (C) groups.

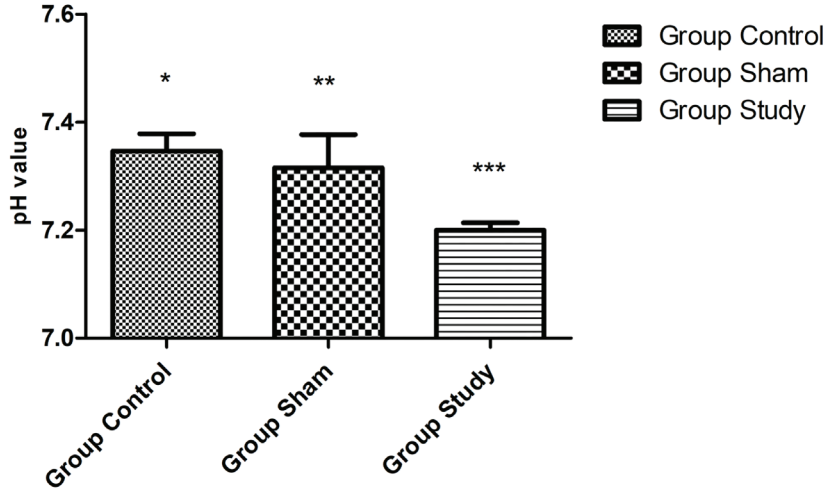

Figure 1. pH Value of the groups. *p<0.005 in control/SHAM; **p<0.0005 in SHAM/study; ***p<0.00001 in control/study
SHAM: Sham-operated group

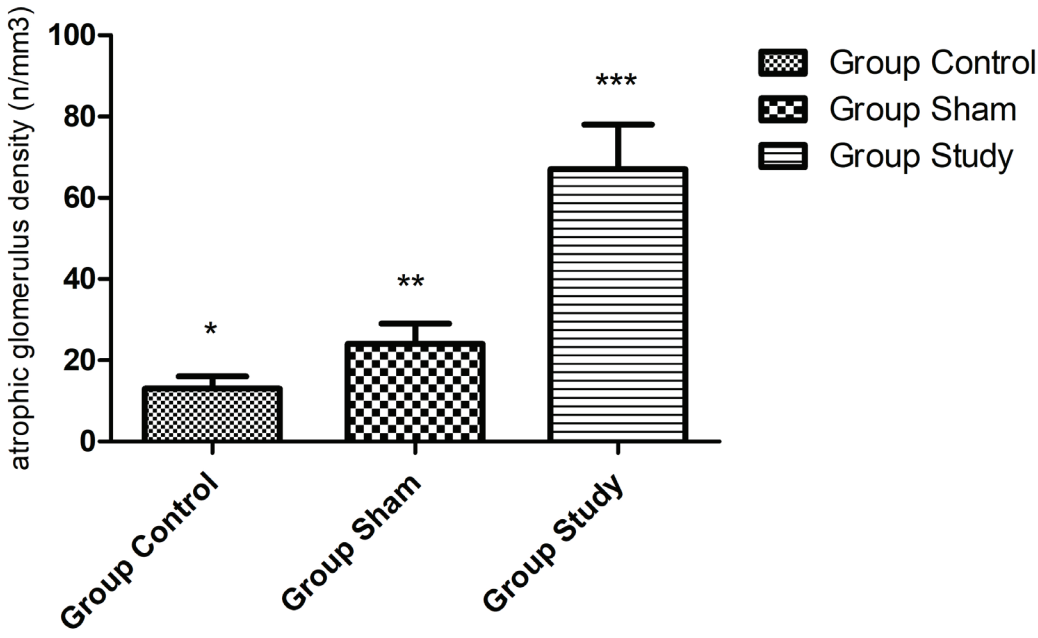

Figure 2. The mean atrophic glomerulus density (n/mm^3) of the groups. *p<0.005 in control/SHAM; **p<0.0005 in SHAM/study; ***p<0.00001 in control/study

SHAM: Sham-operated group

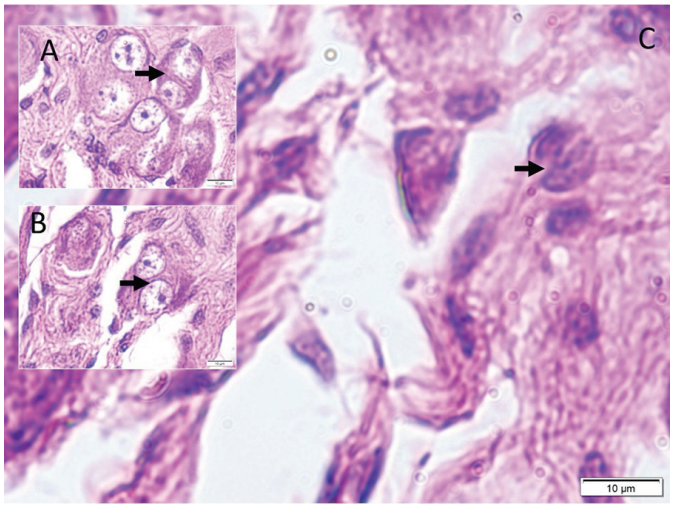

Figure 3. Carotid body's binuclear neurons in control (A), moderately deformed neurons in SHAM (B) and severely deformed neurons in study (C) groups (arrow-LM, HE, x100/A,B,C)

SHAM: Sham-operated group, LM: Light microscopy, HE: Hematoxylin and eosin staining

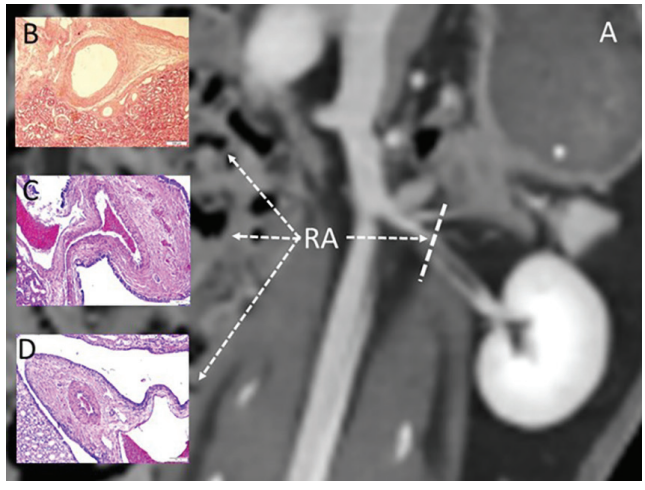

Figure 4. Tomographycal appearances of a renal artery with the section level (RA) in a normal rabbit (A). And histopatholgical appearances of a control (B), moderately constructed renal artery in a SHAM (C) and severely constructed renal artery in a study animal (D) (LM, HE, x10/A, B, C)

RA: Renal artery, SHAM: Sham-operated group, LM: Light microscopy, HE: Hematoxylin and eosin staining

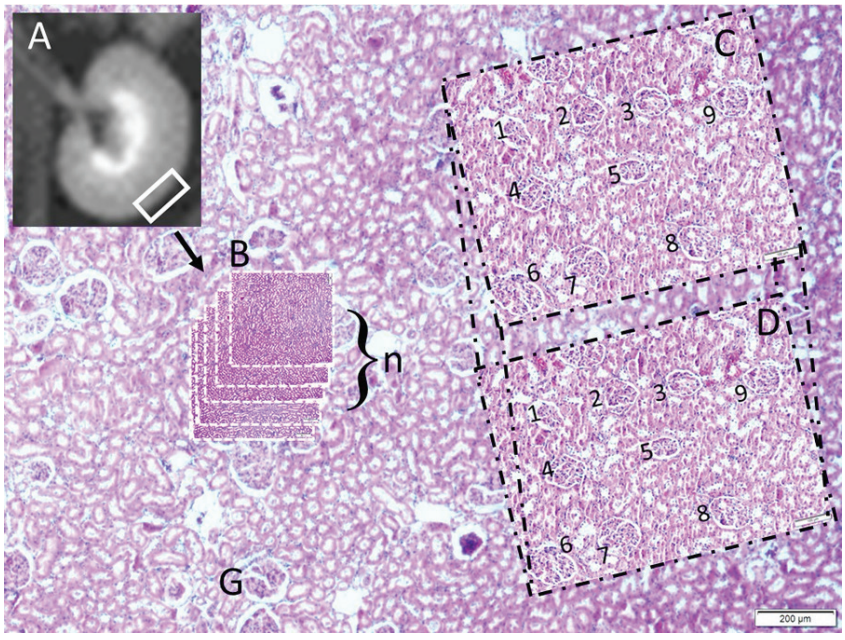

Figure 5. Glomerulus numbers estimation method is seen (LM, HE, x4). In order to predict the glomerulus number stereologically, the cross-sectional region (A) taken from the kidney, a series of n consecutive 1-mm sections (B) were obtained from this section, n pairs of physical dissectors designed in 3-dimensional form consisting of consecutive sections taken at 100 micron intervals in the glomeruli thickness and the method for estimating the glomeruli (G) number in two consecutive pairs 100 microns apart are followed. Sections C and D are consecutive sections. If a glomerulus present in section C is not found in section D, it is considered a disappearing glomerulus pair and included in the count. If no corresponding glomerulus is identified, it is excluded from the analysis

LM: Light microscopy, HE: Hematoxylin and eosin staining

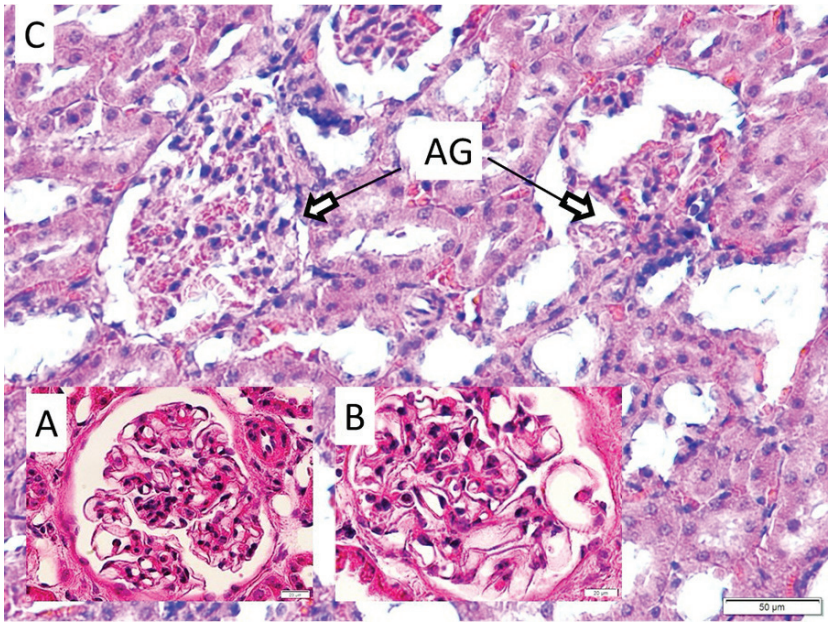

Figure 6. Normal glomeruls in control (A), moderately deformed glomerulus in SHAM (B) and and severely deformed glomerulus study (C) group (LM, HE, x40/ B, C, D)

SHAM: Sham-operated group, LM: Light microscopy, HE: Hematoxylin and eosin staining

DISCUSSION

SAH is a neurovascular emergency that can lead to severe complications affecting renal function. This study investigates the underlying mechanisms of histopathological changes in the kidneys following SAH, with a particular focus on the role of ANS dysfunction in renal impairment and hypertension. The findings provide valuable insights into the pathophysiology of renal complications following SAH, contributing to a deeper understanding of this complex interaction.

Renal Autonomic Innervation and Its Relationship with SAH

The kidneys receive innervation from somatosensory, sympathetic, and vagal nerves[15]. The sympathetic nervous system plays a crucial role in regulating renal function and arterial blood pressure, whereas vagal nerves exert antihypertensive and homeostatic effects via parasympathetic activity[16,17] In conditions such as SAH, vagal ischemia or dysfunction may be a key factor in the pathogenesis of neurogenic renal hypertension[18].

Parasympathetic preganglionic neurons in the renal hilus and around the suprarenal glands modulate parasympathetic functions[19]. Vagal efferent fibers are distributed among microganglia, including the periarterial plexuses surrounding renal arteries[7]. Vagal afferents contribute to regulation of blood volume, homeostasis and can modulate activity of the renal nerve following SAH[20]. Studies have shown that interventions such as bilateral vagotomy[21], vagal blockage[22], vagal efferent dysfunction[23], an increase in hypertensive molecules in the solitary nucleus-vagal ganglion[24], and metabolic conditions like diabetes[25] can all lead to heightened renal sympathetic activity and renal hypertension[26]. These findings underscore the critical role of sympathovagal balance in maintaining renal function.

Chronic Kidney Disease (CKD) and Sympathovagal Balance

CKD is associated with increased central sympathetic activity and reduced cardiac vagal tone[9]. Metabolic disorders such as diabetes may exacerbate this process due to an impaired anti-inflammatory role of the vagus nerve[8]. Acute hypothermia has been suggested as a potential approach to suppress renal sympathetic nerve activity[27]. Prolonged renal ischemia has also been linked to both vagal and sympathetic afferent activation during reperfusion[28]. Experimental models, including cervical vagotomy, disruption of vagal impulses, and increased renal sympathetic activity in vagotomized rats further support the role of ANS dysfunction in renal hypertension[10-12]. These observations highlight the significance of ANS imbalance in the pathogenesis of CKD.

Renal Innervation and Vagotomy

Renal sympathetic neurons increase renal blood flow in hypotensive subjects[29]. Since baroreceptors and chemoreceptors in the carotid sinus modulate blood pH and blood pressure[30], SAH-induced ischemia of glossopharyngeal nerve-carotid body chemoreceptor network can lead to development of dangerous acidosis and hypertension[14] and renal insufficiency[31]. As a result, excess renal sodium retention leads to nephrotic syndrome-like disorders[32]. Decreased vagal inputs related to baroreceptor reflex[33] disorders lead to renal vascular hypertension[34]. Systemic hypoxia markedly potentiates the renal constriction caused by the baroreflex, caused by the carotid chemoreceptor afferent input[35].

Subarachnoid Hemorrhage and Renal Disease

SAH can impair renal function, leading to serious complications such as AKI and renal failure. Moreover, kidney disease is a recognized risk factor for stroke, and stroke itself may exacerbate renal dysfunction[36,37]. In this study, post-SAH metabolic acidosis was found to contribute to vascular and structural damage in the kidneys, including renal artery vasospasm and glomerular atrophy. Notably, our findings suggest a previously undescribed mechanism in the literature, in which SAH-induced acidosis directly contributes to renal epithelial cell degeneration and vascular dysfunction.

SAH, Acidosis, and Multiorgan Dysfunction

The effects of SAH-induced acidosis are not confined to the kidneys but extend to other organ systems, potentially leading to widespread tissue damage. Conditions such as degeneration of the chemoreceptor network, consisting of the glossopharyngeal nerve and carotid body (GPN-CB) carotid body-glossopharyngeal[14] and cervical trauma[13] can result in severe acidosis in both blood and cerebrospinal fluid. This process has been implicated in pathological changes such as "burned-out" spinal cord lesions[38], degeneration of choroid plexus[39] and intestinal injury[40]. These findings suggest that post-SAH acidosis may be a critical driver of multiorgan failure, underscoring the need for further investigation into its systemic effects.

Study Limitations

One of the primary limitations of this study is the absence of biochemical data, which could have provided further insights into the observed findings. Future research incorporating biochemical analyses or novel biomarkers will be essential to strengthen and validate the results of our research study. Another limitation of this study is the relatively small sample size. We, the authors, acknowledge that sample size is a critical component of any study, as an insufficient number of subjects may lead to the oversight of significant differences within the population. However, increasing the number of experimental animals beyond what is necessary could result in unnecessary sacrifice of greater number of animals. Based on our experiences derived from our previous eresearch studies, this study was therefore conducted using twenty-six adult rabbits, ensuring a balance between scientific rigor and ethical considerations.

CONCLUSION

This study sheds light on the mechanisms underlying renal pathology following SAH, particularly the disruption of sympathovagal balance and the impact of acidosis on renal dysfunction. Moving forward, recognizing acidosis as a key contributor to multiorgan failure may help to initiate the development of targeted therapeutic strategies. Additionally, our findings offer new perspectives for preventing and managing renal complications following SAH.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Institutional Review Board of Animal Experiments Local Ethics Committee of Atatürk University (approval number: E-2200369130, dated: 29.06.2022).

Informed Consent: Not applicable.

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Footnotes

Author Contributions

Surgical and Medical Practices: B.F., M.D.A, Concept: B.F., M.D.A, Design: B.F., M.D.A, Data Collection or Processing: B.F., M.D.A, Analysis or Interpretation: B.F., M.D.A, Literature Search: B.F., M.D.A, Writing: B.F., M.D.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Predictive Factors for Failure of High-Flow Nasal Cannula Therapy in Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesinde Yüksek Akışlı Nazal Kanül Tedavisinin Başarısızlığı için Öngörücü Faktörler

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ABSTRACT

Objective: High-flow nasal cannula (HFNC) therapy is widely used to manage respiratory distress in children. However, treatment failure requiring advanced respiratory support is associated with increased rates of morbidity and mortality. Identifying predictive factors for HFNC failure is crucial for optimizing patient outcomes. This study aimed to determine the predictive factors associated with HFNC therapy failure in pediatric patients with moderate to severe respiratory distress managed in the pediatric intensive care units (PICU).

Method: This cross-sectional study included patients aged one month to 18 years with moderate to severe respiratory distress treated with HFNC therapy in the PICU between October 2018 and January 2020. Patients with chronic lung disease or cyanotic congenital heart disease were excluded from the analysis. Clinical and laboratory data, including modified Respiratory Distress Assessment Instrument (mRDAI) scores and treatment outcomes, were analyzed. Statistical methods including Mann-Whitney U test, χ^2 test, receiver operating characteristic curve and multivariate logistic regression analyses were used.

Results: Analysis of 114 patients revealed an HFNC treatment failure rate of 31.6%. Multivariate logistic regression analysis revealed that the presence of medical comorbidities [odds ratio (OR): 25.8; 95% confidence interval (CI): 2.61-254.5; p=0.005], an increased mRDAI scores at the first hour of HFNC therapy (OR: 2.9, 95% CI: 1.32-6.48, p=0.008), and higher pediatric risk of mortality (PRISM) (OR: 2.1, 95% CI: 1.44-3.07, p<0.001) were significant predictors of HFNC failure.

Conclusion: Early identification of predictive factors such as medical comorbidities, mRDAI and PRISM scores can help improve management strategies and outcomes for pediatric patients with respiratory distress undergoing HFNC therapy.

Keywords: Risk factors, HFNC, non-invasive ventilation, treatment failure, pediatric intensive care unit, pediatrics

ÖZ

Amaç: Yüksek akışlı nazal kanül (HFNC) tedavisi çocuklarda solunum sıkıntısını yönetmek için sıklıkla kullanılmaktadır. Bununla birlikte, ileri hava yolu desteği gerektiren tedavi başarısızlığı, artmış morbidite ve mortalite ile ilişkilidir. HFNC başarısızlığı için öngörücü faktörlerin belirlenmesi, hasta sonuçlarının optimize edilmesi için hayati önem taşımaktadır. Bu çalışmanın amacı, çocuk yoğun bakım ünitesinde (ÇYBÜ) orta ila şiddetli solunum sıkıntısı olan çocuk hastalarda HFNC tedavi başarısızlığı ile ilişkili öngörücü faktörleri belirlemektir.

Yöntem: Bu kesitsel çalışmaya, Ekim 2018 ile Ocak 2020 tarihleri arasında ÇYBÜ'de HFNC tedavisi ile tedavi edilen orta ila şiddetli solunum sıkıntısı olan bir ay ila 18 yaş arasındaki hastalar dahil edildi. Kronik akciğer hastalığı veya siyanotik konjenital kalp hastalığı olan hastalar çalışma dışı bırakıldı. Solunum skorları modifiye solunum sıkıntısı değerlendirme aracı (mRDAI) ve tedavi sonuçları dahil olmak üzere klinik ve laboratuvar verileri analiz edildi. İstatistiksel yöntemler arasında Mann-Whitney U testi, χ^2 testi, alıcı işletim karakteristik analizi ve çok değişkenli lojistik regresyon yer aldı.

Bulgular: Yüz on dört hastanın analizi, HFNC tedavi başarısızlığı oranının %31,6 olduğunu ortaya koydu. Çok değişkenli lojistik regresyon, tıbbi komorbiditelerin varlığının [olasılık oranı (OR): 2,8, %95 güven aralığı (CI): 2,61-254,5, p=0,005], HFNC tedavisinin ilk saatinde artmış mRDAI skorunun (OR: 2,9, %95 CI: 1,32-6,48, p=0,008) ve daha yüksek pediatrik ölüm riski (PRIM) skorlarının (OR: 2,1, %95 CI: 1,44-3,07, p<0,001) HFNC başarısızlığının anlamlı öngörücüleri olduğunu göstermiştir.

Sonuç: Tıbbi komorbiditeler, mRDAI skorları ve PRISM skorları gibi öngörücü faktörlerin erken tanımlanması, solunum sıkıntısı nedeniyle HFNC tedavisi alan çocuk hastalar için yönetim stratejilerinin ve sonuçların iyileştirilmesine yardımcı olabilir.

Anahtar kelimeler: Risk faktörleri, HFNC, non-invaziv mekanik ventilasyon, tedavi başarısızlığı, çocuk yoğun bakım ünitesi, pediatri

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INTRODUCTION

High-flow nasal cannula (HFNC) therapy is a relatively safe and easily applicable management of respiratory distress in children[1-3]. It delivers heated and humidified oxygen at high flow rates through the nasal cannula, which creates positive airway pressure and improves gas exchange[1,3,4]. HFNC therapy is generally used safely in pediatric wards, pediatric emergency departments, and pediatric intensive care units (PICUs)[4-6]. Studies have shown that HFNC therapy reduces respiratory effort/scores, the need for advanced respiratory support, and the length of hospitalization by clearing the nasopharyngeal dead space, improving lung mucociliary clearance, and oxygen delivery[2,3,7-11].

However, despite its many advantages and widespread use, failure rates of HFNC therapy ranging between 12.7-31.9% have been reported[1,12-16]. HFNC therapy failure, defined as the transition to advanced airway support therapies in patients who do not respond to HFNC therapy, is associated with increased mortality and morbidity[13].

HFNC therapy may delay the inevitable need for advanced respiratory support therapy by masking signs of respiratory distress. Identifying the predictors of HFNC therapy failure, early diagnosis, and optimization of patient care are important factors for preventing adverse outcomes. This study aimed to determine the factors affecting HFNC therapy failure in patients with moderate to severe respiratory distress treated in the PICU.

MATERIALS and METHODS

Study Design and Setting

This is an observational, cross-sectional study conducted in a single center in Turkey. Behçet Uz Children's Hospital, which was included in the study as a single center, is a tertiary-level training and research hospital for pediatrics in İzmir. It has a 14-bed pediatric emergency department, a 24-bed third-level PICU, and three general pediatric wards with a total of 46 beds.

Sample Size

The sample size was calculated as 70 (at least 35 for each of the successful and failed HFNC therapy groups using G*Power[17] with 80% power and a 0.05 type 1 error rate, and using the data derived from the study of Er et al.[14]

Participants

Inclusion Criteria

All patients aged between 1 month and 18 years who were followed up in the PICU with the indication of moderate and severe respiratory distress and received HFNC respiratory support therapy between October 2018 and January 2020 were included in our study.

Exclusion Criteria

Patients aged over 18 years and younger than one month, those with chronic lung disease and cyanotic congenital heart disease (those with CO_2 retention or hypoxia in daily life, those receiving home oxygen therapy), patients with craniofacial malformations, trauma patients, hypotonic patients, patients with tracheostomy, patients using HFNC therapy for respiratory support after extubation, and those who did not agree to participate in the study were excluded.

HFNC Therapy Protocol

The HFNC device-flow driver and humidifier-(AIRVO 2® Nasal High Flow System, Fisher & Paykel Healthcare, Auckland, New Zealand) in our hospital consisted of an air-oxygen mixer and a heating and humidification system capable of providing fraction of inspired oxygen (FiO_2) from 21% to 100% and an airflow of 2-60L/min. The gas mixture was delivered to the patient via an age-appropriate nasal cannula (Optiflow™ interfaces, Fisher & Paykel Healthcare, Auckland, New Zealand) at 34 °C.

In patients receiving HFNC therapy, the nasal cannula was set to an initial flow rate of 2 L/kg/min. in infants and 1 L/kg/min. in children, and the flow rate was changed according to the discretion of the clinician who monitored the patient and symptomatic changes in the patient's respiratory distress (respiratory retraction, nasal flaring, and tachypnea)[8]. FiO_2 was initially adjusted appropriately according to the patient's requirements and then adjusted so that the patient's oxygen saturation (SpO_2) was maintained between 92-97%[1,3,10].

Data Collection and Measurements

Patient information, laboratory results, and nurse and physician records registered in electronic patient database of our hospital were investigated. Sex, age, diagnoses, pediatric risk of mortality (PRISM) III scores, cardiovascular system history, intubation history, indications, and duration of HFNC therapy, medical comorbidities, nasal respiratory polymerase chain

reaction results, hematocrit values, and incidence of mortality (if any) were recorded. Blood gas test results, respiratory rates (RRs), heart rates (HRs), SpO_2, FiO_2 values, SpO_2/FiO_2 (S/F) ratios, modified Respiratory Distress Assessment Instrument (mRDAI) and Pediatric Respiratory Severity Scores (PRESS), sedation, and side effects were recorded before, during the first hour, and in cases of failure of HFNC therapy.

Severity of respiratory distress was assessed using mRDAI and PRESS scores. Failure of HFNC therapy was defined as the need for advanced respiratory support treatment modalities [non-invasive mechanical ventilation (NIMV), continuous airway pressure and bilevel positive airway pressure or invasive mechanical ventilation (IMV)] within the first seven days after onset of respiratory distress. A 7-day failure period was chosen so as to evaluate both early and late HFNC therapy failures, providing a comprehensive assessment of its efficacy in our PICU population, where shorter periods may miss delayed deteriorations[16,18,19]. Intubation criteria were based on the discretion of the attending physician on the overall clinical situation, including breathing effort (chest retractions, and nasal flaring) and the ability to sustain this respiratory effort[20-22]. In addition, lethargy, cyanosis, poor perfusion, apnea, or inability to maintain adequate oxygen saturation were indications for intubation.

Study Registration and Guidelines

This study was registered at ClinicalTrials under the identifier NCT06146439. The design of our study adhered to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis + artificial intelligence (AI) statement (Appendix)[23].

Statistical Analysis

Distribution of data was checked using histograms, Q-Q plots, and the Kolmogorov-Smirnov test. Normally distributed quantitative data were expressed as mean (± Standard Deviation), whereas data that were not normally distributed were indicated as median and interquartile range (IQR=Q3-Q1). Categorical variables were expressed as numbers and percentages. Variables with more than 25% missing data were excluded from the analysis. Missing data were analyzed using Little's missing completely at random test. The missing data were determined to be missing completely at random mechanism, and the datasets were completed using the expectation-maximization algorithm. To eliminate the effect of extreme outliers in the data, we excluded these data using (25^{th} percentile - 3IQR) and (75^{th} percentile + 3IQR).

For comparisons of numerical data between paired groups, the Student's t-test was used for comparisons between normally distributed groups, and the Mann-Whitney U test for comparisons among non-normally distributed groups. Nominal and ordinal variables were compared by the χ^2 test. If a significant difference was found between the groups after application of the χ^2 test, the group or groups from which the difference originated from were evaluated by post hoc analysis using Tukey and Bonferroni tests.

Variables with a p-value less than 0.20 were included in univariate analyses to determine the factors affecting the risk of HFNC therapy failure. Nominal independent variables were designed as n-1 dummy variables. Multivariate logistic regression (LR) analysis was performed by including independent variables that were significant in the univariate analysis. The variance inflation factor (VIF) was used to detect multicollinearity among independent variables. Variables with a VIF of >3 were excluded from the analysis. Predictive factors were reported using multivariate odds ratios (ORs) and levels of significance (p) were adjusted for 95% confidence intervals (CIs). In the LR analysis, the fit of the predictions to the established model was tested using the Hosmer-Lemeshow test, and the ability of the independent variables to explain the dependent variables was tested using the Nagelkerke R^2 value. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic decision-making properties of independent variables in predicting HFNC therapy failure. The area under curve (AUC) was used to determine the discrimination power of the variables and the Youden index (sensitivity+specificity-1) was used to determine the most appropriate threshold value and the best sensitivity and specificity values.

Statistical analyses and data visualization were performed using Jamovi (The Jamovi Project 2023, Sydney, Australia, version 2.3) and SPSS® (IBM® SPSS Statistics for Windows, version 26.0, Armonk, NY, USA). All analyses were conducted using two-tailed tests with a significance level of 0.05.

Ethical Considerations

Our study was conducted after receiving approval from Behçet Uz Children's Hospital Ethics Committee (approval number: 2018/239, dated: 10.08.2018). Informed consent was obtained from all participants or their parents.

RESULTS

A total of 187 patients applied to our Pediatric intensive care unit between October 2018 and January 2020 were included in our study (Figure 1). Sixty-three patients were excluded owing to missing data and reasons for exclusion. Of the 114 patients included in the analysis, 61.4% (n=70) were male, the median age was 6 (IQR:3-13) months, and the median weight was 7.0 (IQR:5.0-9.5) kilograms. The demographic and medical characteristics of the patients are shown in Table 1.

HFNC therapy was successful in 78 (68.4%) and failed in 36 (31.6%) patients. After the failure of HFNC therapy, 16.7% (n=6) of the patients received NIMV treatment, whereas 83.3% (n=30) of them received invasive ventilation after endotracheal intubation. The history of intubation, place of transfer to intensive care, diagnosis on hospitalization, indications, respiratory distress, medical comorbidity, PRISM scores, mortality rates, breastfeeding history, side effects, and duration of HFNC therapy were significantly different between the groups. History of intubation, transfer to the intensive care unit from another hospital, bronchopneumonia, type 1 respiratory failure, medical comorbidity (immunodeficiency), side effects (inability to tolerate HFNC therapy), and mortalities were significantly more frequent in the failure group (Table 1).

At the beginning of HFNC therapy, FiO_2 was higher, and the mRDAI score and S/F were lower in the failure group. In the first hour of HFNC therapy, pCO_2, lactate, HR, RR, FiO_2, mRDAI, and PRESS scores were higher, and the pH, SpO_2, and S/F ratio were lower in the failure group. A comparison of the clinical and laboratory data between the successful and failed groups at the beginning and first hour of HFNC therapy is presented in Table 2.

When the variables found to be significant in the univariate LR analysis were evaluated using multivariate LR analysis, the variables given in Table 3 formed the most appropriate model. The predictability and goodness-of- fit of the model were found to be high according to the Hosmer-Lemeshow test (χ^2: 3.5, degree of freedom 8, p=0.899), and its fit (Cox&Snell R^2=0.546 and Nagelkerke R^2=0.773) was similar to the real situation. According to the multiple LR model, the presence of medical comorbidities (OR:25.8, 95% CI:2.61-254.50, p=0.005), the mRDAI scores at the first hour of HFNC therapy (OR:2.9, 95% CI:1.32-6.48, p=0.008) and the PRISM scores (OR:2.1, 95% CI:1.44-3.07, p<0.001) were significantly associated with failure. The mRDAI scores at the beginning of HFNC therapy (OR:0.2, 95% CI:0.08-0.44, p<0.001) were significantly associated with success of the HFNC therapy. The results of the multiple LR model are presented in Table 3.

In the ROC analysis performed to determine the optimal cut-off values for quantitative variables for predicting HFNC failure, cut-off values of 17 for the PRISM score (AUC:0.736, p<0.001) and 4.5 for the mRDAI score in the first hour of HFNC therapy (AUC:0.779, p<0.001) were found (Table 4).

Table 1. Demographic and clinical data of the patients

Characteristics	Successful (n=78)	Failure (n=36)	Total (n=114)	p-value
Gender, % (n)				
Male	56.4 (44)	72.2 (26)	61.4 (70)	0.107
Female	43.6 (34)	27.8 (10)	38.6 (44)	
Age, median (IQR), months	5.75 (3-11)	9 (2.25-16.75)	12.1 (3-6)	0.326
Weight, median (IQR), kg	7 (5.5-9.57)	6.6 (4.5-9.75)	7.8 (5-7)	0.475
Congenital heart disease, % (n)	10.3 (8)	5.6 (2)	8.8 (10)	0.401
Intubation history, % (n)	15.4 (12)	33.3 (12)	21.1 (24)	**0.029**
Patients transferred to the PICU from, % (n)				
Another hospital	8.9 (7)	25 (9)*	14.03 (16)	**0.039**
Pediatric emergency room	79.4 (62)*	58.3 (21)	72.8 (83)	
Pediatric ward	11.5 (9)	16.7 (6)	13.1 (15)	

Table 1. Continued				
Characteristics	**Successful (n=78)**	**Failure (n=36)**	**Total (n=114)**	**p-value**
Indications for its use, % (n)				
Respiratory distress	94.9 (74)*	63.9 (23)	85.1 (97)	**<0.001**
Type 1 respiratory failure	5.1 (4)	25.0 (9)*	11.4 (13)	
Type 2 respiratory failure	0.0 (0)	11.1 (4)	3.5 (4)	
Respiratory distress according to mRDAI scores, % (n)				
Moderate	30.7 (24)	50 (18)	36.8 (42)	**0.048**
Severe	69.3 (54)	50 (18)	63.2 (72)	
Respiratory distress according to PRESS scores, % (n)				
Moderate	1.2 (1)	11.1 (4)	4.3 (5)	**0.034**
Severe	98.8 (77)	88.9 (32)	95.7 (109)	
PRISM scores, median (IQR)	14 (11-16)	18 (12-21)	14 (11-16)	**<0.001**
Baseline diagnoses, % (n)				
Bronchopneumonia	47.4 (37)	72.2 (26)*	55.2 (63)	**0.017**
Bronchiolitis	35.9 (28)*	11.1 (4)	28.1 (32)	
Reactive Airway Disease	14.4 (11)	0.0 (0)	9.6 (11)	
ARDS	0.0 (0)	11.1 (4)	3.5 (4)	
Chest X-ray findings, % (n)				
Normal	12.8 (10)	5.5 (2)	10.5 (12)	0.368
Consolidation	24.3 (19)	77.7 (28)	41.2 (47)	
PBM	53.8 (42)	75.0 (27)	60.5 (69)	
Air trapping	35.8 (28)	8.3 (3)	27.1 (31)	
Nasopharyngeal swap PCR, % (n)				
RSV	31.8 (14)	29.0 (9)	30.6 (23)	0.206
Rhinovirus	31.8 (14)	3.2 (1)	20.0 (15)	
Negative	4.5 (2)	12.9 (4)	8.0 (6)	
Medical comorbidities, % (n)				
None	71.6 (58)	41.6 (15)	64.0 (73)	**0.017**
Immunodeficiency	1.2 (1)	13.7 (5)*	5.2 (6)	
Prematurity	6.1 (5)	8.3 (3)	7.0 (8)	
Septic shock	6.1 (5)	0.0 (0)	4.3 (5)	
Epilepsy	3.7 (3)	11.0 (4)	6.1 (7)	
Inherited metabolic disorders	6.1 (5)	8.3 (3)	7.0 (8)	
Cerebral palsy	3.7 (3)	5.5 (2)	4.3 (5)	
Side effects, % (n)				
None	73.1 (57)	55.6 (20)	67.5 (77)	**<0.001**
Nasal trauma	24.4 (19)	16.7 (6)	21.9 (25)	
Intolerance	2.6 (2)	27.8 (10)*	10.5 (12)	
Sedation, % (n)				
No	80.8 (63)	77.8 (28)	79.8 (91)	0.711
Yes	19.2 (15)	22.2 (8)	20.2 (23)	

Table 1. Continued

Characteristics	Successful (n=78)	Failure (n=36)	Total (n=114)	p-value
Breastfeeding history, % (n)				
Never	6.4 (5)	27.8 (10)	13.2 (15)	**<0.001**
Still breastfeeding	78.2 (61)	36.1 (13)	64.9 (74)	
Weaned breastfeeding	15.4 (12)	36.1 (13)	21.9 (25)	
Hematocrit, mean (± SD), %	31.94 (3.94)	30.3 (4.99)	31.5 (4.31)	0.082
HFNC duration, median (IQR), hour	72 (60-96)	15 (4.5-35.5)	48 (16-84)	**<0.001**
Death, % (n)	0 (0)	25.2 (7)	6.14 (7)	**<0.001**

A p-value <0.05 marked in bold. *Indicates statistical significance in post-hoc analysis (p<0.05). ARDS: Acute respiratory distress syndrome, HFNC: High-flow nasal cannula, IQR: Interquartile range, mRDAI: Modified respiratory distress assessment instrument, PBM: Prominent broncho-vascular markings, PICU: Pediatric intensive care unit, PRESS: Pediatric Respiratory Severity score, RSV: Respiratory syncytial virus, SD: Standard deviations, PRISM: Pediatric risk of mortality score, PCR: Polymerase chain reaction

Table 2. Data at the beginning and first hour of HFNC treatment

	Successful (n=78)	Failure (n=36)	Total (n=114)	p-value
At the onset of HFNC therapy, median (IQR)				
pH	7.36 (7.3-7.4)	7.32(7.24-7.4)	7.35 (7.29-7.4)	0.08
pCO_2, mmHg	44.3 (37.9-48.5)	46 (41.5-55)	44.7 (39-50)	0.104
Lactate, mmol/L	2.1 (1.32-3)	2.1 (1.58-2.79)	2.1 (1.5-3)	0.91
HR, bpm	166 (155-180)	162 (146-175)	166 (150-180)	0.19
RR, bpm	60 (56-62)	60 (51-65)	60 (55-64)	0.85
SpO_2, %	90 (88-90)	88 (88-90)	90 (88-90)	0.19
FiO_2, %	21 (21-30)	30 (30-40)	30 (21-40)	**<0.001**
S/F ratio	419 (300-423)	293 (218-300)	313 (237-419)	**<0.001**
mRDAI scores	9 (8-10)	9 (7-9)	9 (8-10)	**0.04**
PRESS scores	4 (4-5)	4 (4-5)	4 (4-5)	0.499
First hour of HFNC therapy, median (IQR)				
pH	7.38 (7.35-7.4)	7.33 (7.28-7.38)	7.37 (7.33-7.4)	**<0.001**
pCO_2, mmHg	41 (38-44)	47 (40-53)	41.5 (38-46.6)	**0.001**
Lactate, mmol/L	1.45 (1.17-2.1)	2.16 (1.37-3.4)	1.6 (1.2-2.36)	**0.004**
HR, beats/min.	138 (125-148)	150 (141-167)	140 (130-154)	**<0.001**
RR, beats/min.	42 (40-50)	50 (44-55)	44 (40-50)	**<0.001**
SpO_2, %	98.5 (96-100)	94 (94-98)	98 (96-100)	**<0.001**
FiO_2, %	40 (30-40)	40 (40-50)	40 (30-40)	**<0.001**
S/F ratios	250 (245-320)	225 (188-246)	247 (235-320)	**<0.001**
mRDAI scores	3.5 (3-4)	5 (4-6)	4 (3-5)	**<0.001**
PRESS scores	2 (1-2)	3 (2-4)	2 (2-3)	**<0.001**

A p-value <0.05 marked in bold. FiO_2: Fraction of inspired oxygen, HFNC: High Flow Nasal Cannula, IQR: Interquartile range, pCO_2: Partial pressure of carbon dioxide, HR: Heart rate, mRDAI: modified respiratory distress assessment instrument, PRESS: Pediatric Respiratory Severity Score, RR: Respiratory rate, SpO_2: Oxygen saturation, S/F: Oxygen saturation/fraction of inspired oxygen ratio

Table 3. Results of multivariate logistic regression analysis

A. Model fit measures

Model summary			Hosmer and Lemeshow test			
-2 LogL	Cox & Snell R^2	Nagelkerke R^2	Step	χ^2	df	p-value
47.543	0.546	0.773	7	3.505	8	0.899

B. Model co-efficients

Predictors	B	SE	Wald	OR	95% CI		p-value
Medical comorbidities, Yes vs. No[a]	3.249	1.16	7.73	25.8	2.61	254.5	**0.005**
PRISM scores	0.741	0.19	14.64	2.1	1.44	3.07	**<0.001**
mRDAI scores, first hour of HFNC	1.074	0.40	7.01	2.9	1.32	6.48	**0.008**
mRDAI scores, beginning of HFNC	-1.664	0.43	14.74	0.2	0.08	0.44	**<0.001**
pCO_2, first hour of HFNC, mmHg	0.060	0.04	2.14	1.1	0.98	1.15	0.143

[a]Reference value. A p-value <0.05 is marked in bold. χ^2: Chi-square, CI: Confidence interval, df: Degree of freedom, HFNC: High-flow nasal cannula, LogL: Log-likelihood, mRDAI: Modified respiratory distress assessment instrument, pCO_2: Partial pressure of carbon dioxide, PRISM: Pediatric risk of mortality score, OR: Odds ratio, SE: Standard error

Table 4. ROC analysis results

Independent variables	AUC	SE	p-value	%95 CI			
mRDAI scores, first hour of HFNC	0.779	0.051	<0.001	0.678	0.879		
PRISM scores	0.736	0.060	<0.001	0.619	0.854		
Independent variables	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**	**LR test**	**Youden index**
mRDAI scores, first hour of HFNC	4.5	60	90	57.9	90.9	5	1.497
PRISM score	17	57.1	92.3	76.9	81.8	7	1.495

AUC: Area under the curve, CI: Confidence interval, HFNC: High-flow nasal cannula, LR: Likelihood ratio, mRDAI: Modified respiratory distress assessment instrument, PRISM: Pediatric risk of mortality score, SE: Standard error, ROC: Receiver operating characteristic

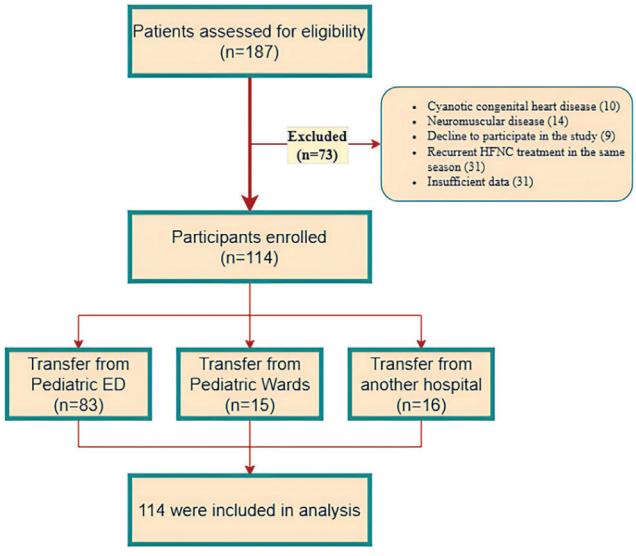

Figure 1. Flow diagram. Flowchart showing the stages of the study and the number of participants

DISCUSSION

Our study aimed to determine the factors affecting HFNC therapy failure in children with moderate to severe respiratory distress and revealed that HFNC therapy failure was 31.6%. The presence of medical comorbidities was associated with 25.8 times greater odds of HFNC therapy failure. The PRISM and mRDAI scores estimated at the first hour of treatment were associated with HFNC therapy failure, whereas interestingly, the mRDAI scores at the beginning of treatment were associated with successful HFNC therapy.

Studies to detect HFNC therapy failure in children have been conducted in pediatric emergency departments[14,15,24-26], pediatric wards[1,12,26-29], and PICUs[5,10,12,13,15,16,26,30-37] as in our study. To the best of our knowledge, we have reported one of the highest failure rates[1,12-16,32,36]. Pediatric HFNC failure has been evaluated at varying time intervals (30 minutes to 96 hours)[13,19,38].

Many studies[16,18,19] have evaluated HFNC failure within the first 24-hours after its application, whereas our study employed a 7-day assessment window. This extended duration of follow-up period likely allowed us to capture delayed failures that occur beyond the initial 24 hours, thereby contributing to a higher observed failure rate. In addition, this high failure rate we observed may be attributed to the exclusion of patients with mild respiratory distress and focusing on patients admitted to the PICU. The inclusion of patients with a higher prevalence of medical comorbidities, as confirmed by our LR analysis, further distinguishes our study from others that may have enrolled a broader, less critically ill pediatric population. Besides, higher proportion (83.3%) of the patients in our failure group required intubation and invasive respiratory support therapy when compared with HFNC therapy failure rates reported in other studies[5,14,36]. Only İleri et al.[15] reported the need for IMV similar to our study. This finding suggests that our cohort may represent a population in which HFNC is being used in patients near the threshold for invasive support, or that certain underlying pathologies common in our center are less responsive to HFNC alone. Additionally, variations in clinical management protocols, including different criteria for transition to invasive ventilation and local practices regarding monitoring respiratory parameters, may have contributed to the observed discrepancies.

The presence of medical comorbidities, which was the predictor factor with the highest odds ratio in our study, was reported to be significant in only one study[32]. Comorbidities of congenital heart disease were reported more frequently in patients who experienced HFNC failure in two studies[12,28]. Of these studies, only Sunkonkit et al.[12] applied LR analysis (RR: 6.36, 95% CI: 1.74–23.17; p = 0.005). In another study, the presence of hemato-oncologic disease was associated with treatment failure (OR: 3.79, 95% CI: 1.12–12.78, p=0.031)[39]. While other studies have identified comorbidities as risk factors, in our study a particularly striking link was detected between HFNC failure rates and these comorbidities. This finding may be indicative of the specific patient profile, severity, or multiplicity of comorbidities that are prevalent in the population that is served by our tertiary referral center. The broad CI (95% CI: 2.61-254.5) also suggests variability, emphasizing the need for future research to identify which specific comorbidities drive this profound risk.

To the best of our knowledge, the PRISM score, another important predictive factor in our study, was reported to be significant in three studies[13,16,34]. In their study evaluating both HFNC therapy and NIV, Ongun et al.[34], reported that the cut-off value for the PRISM score was lower than that in our study. The Pediatric Index of Mortality^2 Risk of Death score in one study and the Pediatric Early Warning System respiratory score in another study were reported to be associated with failure of HFNC therapy[10,36].

A study conducted in infants with bronchiolitis managed in the PICU reported that a modified Tal score greater than five at the fourth hour of HFNC therapy was a predictive factor (OR: 2.81, 95% CI: 1.04, 7.64; p=0.042) [33]. In our study, we found that the mRDAI score at the first hour of treatment was associated with treatment failure. This seemingly paradoxical result requires careful interpretation. One potential explanation for this phenomenon is that patients presenting with more pronounced, readily apparent respiratory distress (higher initial mRDAI scores), perhaps due to conditions highly responsive to the mechanisms of HFNC (e.g., work of breathing reduction), may exhibit a more dramatic and rapid positive response when therapy is initiated promptly. Conversely, patients with lower initial scores might harbor underlying pathologies less amenable to HFNC support, such as severe parenchymal disease or impending fatigue not yet fully reflected in the score. This phenomenon underscores the notion that a baseline score alone is insufficient to evaluate the efficacy of HFNC therapy; the trajectory of the score and the overall clinical picture, including factors like comorbidities and PRISM score have a paramount importance. The dynamic nature of respiratory distress in pediatric patients necessitates continuous reassessment, rather than reliance on initial presentations alone.

In addition to the predictive factors we found in our study; younger age[33], higher RR at triage[25,30,35], lower SpO_2 at admission[14], higher FiO_2 at admission[10], lower S/F ratio at admission[5,14,16,39], lower venous pH at admission[14,25], greater venous pCO_2 at admission[14,25,32,35,37], no improvement or decrease in RR[1,10,12,14,24,29,32], no improvement in the S/F ratio[14,39], low S/F ratio[5], no improvement in HR[10,12,24,32], decreased $PaCO_2/PaO_2$ ratio[13], decreased ROX index[13,40,41], lowest diastolic blood pressure[32], lobar infiltration on chest radiography[12], and maximum FiO_2[27,28] were also reported.

The diagnosis of bronchiolitis[25], duration of HFNC therapy[33], and a significant increase in the S/F ratio in the first hour of HFNC therapy[14] were reported as factors

affecting the success of HFNC therapy. In our study, the initial mRDAI score was associated with successful HFNC therapy.

HFNC is a relatively new treatment on which pediatricians have focused. HFNC therapy has several benefits. Clinical practice and the literature have reported these benefits many times. However, similar to any other therapy, HFNC therapy can fail. We must not forget its negative consequences.

Study Limitations

This study had several limitations. The study was conducted at a single center. We could not evaluate confounding factors such as clinicians' different approaches to HFNC therapy. This single-center design and the variabilities in the applications of HFNC therapy and disease management practices may limit the generalizability of our findings. Furthermore, the extended observation period used to define HFNC failure could have contributed to our higher reported failure rate compared to studies with shorter monitoring windows. In addition, we should have included patients on HFNC therapy whose transfer from the pediatric emergency department. to the PICU was delayed due to the heavy bed occupancy in the PICU in the comparative analyses which may have affected both the results and the validity of the predictive model. It is also important to note that variations in sample size, statistical methodologies, and the operational definition of HFNC failure across studies may have contributed to the observed discrepancies. Future multicenter studies with standardized protocols are needed to validate these results and further refine the predictive models.

CONCLUSION

Early identification of predictive factors -medical comorbidities, elevated mRDAI scores at the first hour, and higher PRISM scores- can guide clinicians in optimizing HFNC therapy and improving outcomes of pediatric respiratory distress managed in the PICUs.

Ethics

Ethics Committee Approval: Our study was conducted after receiving approval from Behçet Uz Children's Hospital Ethics Committee (approval number: 2018/239, dated: 10.08.2018).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Footnotes

Author Contributions

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

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Original Article

Examination of Factors Affecting the Development of Osteoporosis in Children with Duchenne Muscular Dystrophy

Duchenne Musküler Distrofisi Olan Çocuklarda Osteoporoz Gelişimini Etkileyen Faktörlerin İncelenmesi

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ABSTRACT

Objective: Duchenne muscular dystrophy (DMD), which is primarily treated with glucocorticoids, is the most common genetic progressive neuromuscular disease in children, which can lead to osteoporosis and fractures. This study analyzed factors affecting osteoporosis before and after loss of ambulation and its relationship with fractures in DMD patients.

Method: This retrospective study included 40 DMD patients. Clinical and laboratory findings and bone mineral densitometry (BMD) values were analyzed.

Results: The median age at diagnosis was 3 years (Q1-Q3: 1-3.5). Osteoporosis was detected in 80% by femoral neck Z-score and 40% by vertebral Z-score, with all vertebral osteoporosis cases also meeting femoral neck osteoporosis criteria. Femoral neck Z-score worsened after loss of ambulation ($p<0.05$), while the lumbar Z-score remained stable. Fractures occurred in 35% of patients, with vertebral fractures in 17.5%. All vertebral fractures were associated with vertebral osteoporosis. No correlation was found between fractures and Dual-energy X-ray absorptiometry scores before loss of ambulation ($p>0.05$), and Z-scores were not significant predictors of fractures. The median age for glucocorticoid initiation was 48 months, with no significant difference between prednisolone and deflazacort regarding osteoporosis duration, scoliosis, or loss of ambulation ($p>0.05$). Scoliosis was present in 60% of patients before loss of ambulation, but no significant relationship was found between BMD and scoliosis.

Conclusion: The results of this study did not show a direct correlation between BMD before the loss of ambulation and the future risk of fractures. Therefore, BMD alone may not be a sufficient predictor of scoliosis progression in DMD patients.

Keywords: Duchenne muscular dystrophy, bone density, osteoporosis, fractures

ÖZ

Amaç: Duchenne musküler distrofisi (DMD), çocukluk çağında en sık görülen genetik ve ilerleyici nöromusküler hastalık olup, tedavisinde glukokortikoidler kullanılmaktadır. Hastalık, osteoporoz ve kırıklara yol açabilmektedir. Bu çalışmada, DMD hastalarında ambulasyon kaybı öncesi ve sonrası osteoporozu etkileyen faktörler ile kırıklarla olan ilişkiler değerlendirilmiştir.

Yöntem: Çalışmaya retrospektif olarak 40 DMD hastası dahil edilmiştir. Klinik ve laboratuvar veriler ile kemik mineral dansitometri (KMD) sonuçları analiz edilmiştir.

Bulgular: Hastaların tanı aldıkları medyan yaş 3 yıl (Ç1-Ç3:1-3,5) olarak bulunmuştur. Femur boynu Z-skoruna göre hastaların %80'inde, vertebra Z-skoruna göre ise %40'ında osteoporoz tespit edilmiştir. Vertebral osteoporoz saptanan tüm hastalarda femur boynu osteoporozu da bulunmuştur. Ambulasyon kaybı sonrasında femur boynu Z-skorlarında anlamlı bir kötüleşme gözlenirken ($p<0,05$), lomber Z-skorlarında değişiklik izlenmemiştir. Kırıklar hastaların %35'inde, vertebral kırıklar ise %17,5'inde görülmüştür. Tüm vertebral kırıkların, vertebral osteoporozla ilişkili olduğu belirlenmiştir. Ambulasyon kaybı öncesi çift enerji X-ışını absorbsiyometrisi skorları ile kırıklar arasında anlamlı bir ilişki saptanmamıştır ($p>0,05$) ve Z-skorlarının kırık riskini öngörmede anlamlı bir belirteç olmadığı gösterilmiştir. Glukokortikoid tedavisine başlanma medyan yaşı 48 ay olarak kaydedilmiş, prednizolon ve deflazakort grupları arasında osteoporoz süresi, skolyoz gelişimi ve ambulasyon kaybı açısından anlamlı bir fark bulunmamıştır ($p>0,05$). Ambulasyon kaybı öncesi hastaların %60'ında skolyoz tespit edilmiş, ancak KMD ile skolyoz arasında anlamlı bir ilişki gösterilememiştir.

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Sonuç: Elde edilen bulgular, ambulasyon kaybı öncesinde ölçülen kemik mineral yoğunluğunun ilerleyen dönemde kırık riskini öngörmede yeterli olmadığını göstermiştir. Bu nedenle BMD'nin tek başına skolyoz progresyonu için güvenilir bir prediktör olmayabileceği düşünülmektedir.

Anahtar kelimeler: Duchenne musküler distrofi, kemik dansitesi, osteoporoz, kırıklar

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common neuromuscular disorder caused by mutations in the dystrophin gene on the X chromosome, affecting one in 3600 male births[1]. These mutations in the dystrophin gene lead to progressive muscle fibre degeneration and weakness.This weakness may initially present as difficulty in walking, but gradually progresses to the point where affected patients are unable to perform activities of daily living and have to use a wheelchair[2].

Clinical signs usually appear in the first few years of life[3-5]. Muscle weakness is more pronounced, especially in proximal muscles. Although the clinical course of skeletal muscle and cardiac involvement can be variable, death usually occurs as a result of cardiac or respiratory failure[4-6].

Creatinine kinase is highly sensitive in the presence of physical examination findings that may be consistent with DMD[7]. DMD is an inherited X-linked recessive trait and the diagnosis should be confirmed by genetic testing[8,9]. Dystrophin immunocytochemistry can also be used to detect cases not identified with polymerase chain reaction testing[10,11]. The most important cause of osteoporosis in DMD patients is thought to be glucocorticoid use and decreased mechanical stimuli due to loss of ambulation[12]. In addition, nutritional deficiencies, hormonal imbalances, systemic inflammation, myokine release from dystrophic muscle, and vascular dysfunction also play a role in osteoporosis[12,13]. All these factors disrupt bone homeostasis by affecting the activity of osteoblasts and osteoclasts, and affect osteoporosis to varying degrees[12,13]. Glucocorticoids are the main treatment for DMD and early initiation has been shown to prolong ambulation[14]. Glucocorticoids improve muscle function, delay the development of respiratory complications and have been reported to delay scoliosis and even cardiomyopathy[15]. However, glucocorticoid therapy is associated with side-effects such as weight gain, cushingoid appearance, behavioral changes, delayed puberty, reduced growth, increased risk of fractures, cataracts, and hair growth[14,16]. Low-energy trauma vertebral fractures, long bone fractures, and osteoporosis are frequently seen in patients with DMD who are taking glucocorticoids[17]. It has been reported that 20-60% of boys with DMD have low-energy trauma extremity fractures (usually distal femur, tibia or fibula), while up to 30% develop symptomatic vertebral fractures[18,19]. The aim of this retrospective study was to analyse the clinical, demographic, and treatment-related factors associated with the development of osteoporosis before and after loss of ambulation in patients under the age of 18 years with genetically confirmed DMD, and to evaluate the relationship between osteoporosis and bone fractures based on Dual-energy X-ray absorptiometry (DXA) measurements, glucocorticoid use, and fracture history.

MATERIALS and METHODS

Patient data were obtained from hospital electronic medical records system. The study included patients under the age of 18 years with a diagnosis of muscular dystrophy, who were followed up at the Muscle Centre between 2013 and 2023, and who developed gait loss. Patients who were diagnosed with Becker muscular dystrophy, who did not continue follow-up in our centre, and who were not diagnosed with DMD by genetic tests were excluded from the study. Forty patients who attended regular follow-ups and had complete accessible records were included in the study

The diagnosis of DMD was based on clinical findings and genetic testing[20]. Clinical and demographic characteristics, laboratory tests and bone mineral densitometry values were analyzed before and after loss of ambulation. Body weight percentiles were calculated according to the Center for Disease Control and Prevention (CDC).

Glucocorticoid (prednisolone or deflazacort) treatment was started in all patients after an average age of 4 years. The choice of deflazacort or prednisolone was based on availability of treatment. Prednisolone treatment was started at 0.5-0.75 mg/kg/day and deflazacort at 0.5-0.9 mg/kg/day. Dose adjustment was made according to the clinical follow-up of the patients. All patients were referred to a dietician at least once and were recommended a calcium-rich diet. Annual height and weight follow-up was performed, and body weight percentiles were calculated according to the CDC. Vitamin D supplementation was adjusted according to annual blood calcium and vitamin D values.

Ambulation loss was classified according to the Ambulatory Functional Classification System for DMD (AFCSD). The AFCSD consists of 5 levels, defined as follows: level 1, walking at normal speed and with normal postural alignment; level 2, walking independently without an assistive device or support, with abnormal walking patterns such as tiptoeing or waddling and impaired postural alignment such as excessive trunk lordosis; level 3, walking only short distances using a hand-held mobility device such as a walker or crutches; level 4, unable to walk and using a battery powered wheelchair; and level 5, needing manual wheelchair transportation[21]. According to the AFCSD classification, levels 4-5 were considered immobilized (non-ambulant).

Regular bone mineral density (BMD) measurements are recommended after the initiation of glucorticoid therapy for the monitoring of bone health and early diagnosis of osteoporosis in patients with DMD[22,23]. DXA is used for this purpose. All DXA scans were performed using a DMS Group IMD device (model: HF1 F/12; X-ray tube: OX/110-5). Device calibration was conducted routinely in accordance with the manufacturer's guidelines to ensure measurement accuracy and reliability. The DXA scans taken before and after loss of ambulation were analyzed to examine BMD. PA lumbar vertebral and femoral (femoral neck) imaging was performed[24]. The age- and height-adjusted Z scores were used in the evaluation of DXA scans[25]. The patients were separated into two groups as those with a BMD Z-score of ≤-2 standard deviation score (SDS) or >-2 SDS. The parameters affecting BMD were analyzed.

The diagnosis of osteoporosis is established based on the criteria outlined in the 2019 Pediatric Position Statement of the International Society of Clinical Densitometry. The presence of one or more vertebral compression fractures, in the absence of local pathology or high-energy trauma, is considered indicative of osteoporosis. In cases where vertebral compression fractures are not present, the diagnosis requires both a clinically significant fracture history and a BMD Z-score of ≤-2.0. A clinically significant fracture history is defined by at least one of the following: (1) two or more long bone fractures occurring by the age of 10 years or (2) three or more long bone fractures at any age up to 19 years[26].

The study was approved by the Ethics Board of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval number: 2023/06-41, dated: 13.07.2023).

Statistical Analysis

The analyses were conducted using SPSS software. Normality of data distribution was evaluated with the Shapiro-Wilk test. Quantitative variables were expressed as mean and standard deviation values for normally distributed data, and as median and interquartile range values for non-normally distributed data. Categorical data were assessed using chi-square tests or Fisher's exact tests. Comparisons of continuous variables between two groups were performed with the Independent Samples t-test or the Mann-Whitney U test, and for more than two groups, ANOVA or Kruskal-Wallis tests were utilized. Post-hoc analyses were conducted to determine specific group differences. The level of statistical significance was set at $p<0.05$

RESULTS

Evaluation was made of 40 male patients diagnosed with DMD, with a median age of 12 (Q1-Q3:11-14) years. A history of DMD in siblings was present in 3 patients and 3 patients had a history of DMD in uncles. The median age at diagnosis of DMD was 3 years (Q1-Q3:1-3.5). The diagnosis of 6 patients was made during screening because of a family history of DMD, and 34 patients (85%) were diagnosed incidentally in further investigations due to elevated liver function tests. The median age of onset of walking was 12 months (min 11- max 30 months). The median age at which gait deterioration began was 4 years and the median age at loss of ambulation was 10 years. Scoliosis was found in 24 patients (60%). According to the femoral neck Z score, 32 (80%) patients met the definition of osteoporosis, while only 16 (40%) patients met the definition of osteoporosis according to the vertebral Z score. All patients with osteoporosis according to the vertebral Z-score also met the definition of osteoporosis according to the femoral neck Z score. In 14 patients there was a history of low-energy trauma bone fracture during the mobilized period. Six patients (15%) had long bone fractures. The distribution of these fractures was as follows: three patients (7.5%) had humerus fractures, two patients (5%) had femur fractures, and one patient (2.5%) had a tibia fracture. Treatment was started of deflazacort in 17 (42.5%) patients, and prednisolone in 23 (57.5%) (Table 1).

The laboratory parameters before and after loss of ambulation showed a significant decrease in the creatinine kinase value after loss of ambulation. Lumbar spine Z-score values were similar, but femoral neck Z-score values worsened after loss of ambulation (Table 2).

Patients who did not have vertebral osteoporosis before loss of ambulation had a similar age at diagnosis and onset of walking, but a younger age at immobilisation [9.5 (9-10), p=0.046)]. These patients had higher vitamin D levels [15.5 (10.4-21.1) vs. 11.9 (8.9-14.9) (p=0.051)]. The rates of long bone fractures and scoliosis were similar in other patients, but all vertebral fractures were observed in these patients (Table 3). There was no difference between the Ca, P, vitamin D, ALP, PTH and CK values of patients with lumbar spine Z osteporosis and other patients after loss of ambulation.

Table 1. The clinical and demographic characteristics of the patients with DMD	
Current age (years) (Median Q1-Q3)	12 (11-14)
Age at diagnosis (years) (Median Q1-Q3)	3 (1-3.5)
Family history of DMD	6 (15%)
Brother	3 (7.5%)
Uncle	3 (7.5%)
Diagnostic sign	
Incidental liver function test elevation	29 (72.5%)
Family screening	6 (15%)
Gait impairment	5 (12.5%)
Independent walking age (months) (median; min-max)	12 (12-36)
Age of gait impairment (years) (median; min-max)	4 (3-5)
Age of immobilization (years) (median; min-max)	10 (7-15)
Vertebral osteoporosis before loss of ambulation, n (%)	16 (40)
Femoral neck osteoporosis before loss of ambulation, n (%)	32 (80)
Scoliosis, n (%)	24 (60)
Bone fracture n (%)	14 (35)
Vertebral	7 (17.5)
Non-vertebral	7 (17.5)
Steroid preference, n (%)	
Deflazacort	17 (42.5%)
Prednisolone	23 (57.5%)
Daily dose of vitamin D supplements (IU)	2000 (min 750-max 3000)
IU: International units, DMD: Duchenne muscular dystrophy	

Table 2. Laboratory findings and bone mineral densitometry values of the patients with DMD before and after loss of ambulation			
	Before loss of ambulation	**After loss of ambulation**	**p-value**
Ca (mg/dL)	9.72±0.31	9.79±0.38	0.379
P (mg/dL)	4.94±0.53	4.74±0.65	0.107
Alp (U/L)	108.2±33.6	104.2±40.3	0.356
TSH (ng/dL)	2.69±1.31	2.74±1.67	0.859
T4 (ng/dL)	1.16±0.42	1.14±0.48	0.772
Vit D (µg/L)	14.99±5.97	16.83±6.46	0.07
PTH (µg/L)	39.56±14.39	42.31±35.6	0.653
CK (U/L)	7218±3880	4422±2659	**0.001**
Weight SDS	0.16±1.31	0.34±1.44	0.114
Femoral neck Z score	-2.64±1.03	-2.87±1.04	**0.03**
Lumbar spine Z score	-1.21±1.69	-1.63±1.72	0.09
Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, TSH: Thyroid stimulating hormone, T4: Thyroxine, VitD: Vitamin D, PTH: Parathyroid hormone, CK: Creatinin kinase, SDS: Standard deviation score, DMD: Duchenne muscular dystrophy			

There was no difference between the Ca, P, ALP, vitamin D, PTH and CK levels of the patients with femoral neck osteoporosis before loss of ambulation and the other patients (p>0.05). There was no difference between the Ca, P, ALP, PTH and CK values of patients with femoral neck osteoporosis and other patients after loss of ambulation, but vitamin D levels were higher in patients with osteoporosis (Table 4).

There was no correlation between bone fracture and femoral neck and vertebral DXA scores before the loss of ambulation. Before the loss of ambulation, the vertebral Z-score was -1.06±1.62 SDS (n=33) in patients without vertebral compression fractures, compared to -1.87±1.97 SDS (n=7) in patients with fractures, with no significant difference determined between the two groups (p=0.346).

Glucocorticoid therapy was initiated for the patients at a median age of 48 months (minimum 44 months, maximum 54 months). Steroid preference (prednisolone or deflazacort) had no effect on the development of osteoporosis and no effect on the development of scoliosis according to the vertebral Z-score of the laboratory parameters. No significant difference was determined between patients on prednisolone and patients on deflazacort in respect of the incidence of bone fractures, scoliosis and osteoporosis (p=0.792). The delay in loss of ambulation was similar in both groups (p=0.71).

Table 3. The relationship between the parameters of the patients and the presence of vertebral osteoporosis before loss of ambulation

	Vertebral osteoporosis before loss of ambulation		
Parameter	**No (n=24)**	**Yes (n=16)**	**p-value**
Age of immobilization (years) (median), IQR	9.5 (9-10)	10 (10-11.5)	**0.046**
Independent walking age (month) (median), IQR	12 (12-16.5)	12(12-12)	0.071
Age at diagnosis (years)	3(1-4)	2(1.5-3)	0.308
Vit D (µg/L), IQR	15.5 (10.4-21.1)	11.9 (8.9-14.9)	**0.051**
TSH (ng/dL), IQR	2.7(1.0-4.2)	2.3(1.2-2.7)	**0.020**
T4 (ng/dL), IQR	1.1(0.9-1.2)	1.1(1-1.2)	0.841
Ca (mg/dL), IQR	9.7(9.4-9.9)	9.7(9.6-10.1)	0.442
P (mg/dL), IQR	4.9 (4.5-5.3)	5.1(4.5-5.3)	0.981
CK (U/L), IQR	7028 (4823-9040)	7396(3239-8413)	0.420
Alp (U/L), IQR	109 (79-136)	100(81-131)	0.625
Bone fracture	6(25%)	8(50%)	0.104
Vertebral compression fracture	-	7(43.8%)	**0.001**
Non-vertebral fracture	6(25%)	1(6.3%)	0.210
Scoliosis	14(58.3)	10(62.5)	0.792

Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, TSH: Thyroid stimulating hormone, T4: Thyroxine, VitD: Vitamin D, PTH: Parathyroid hormone, CK: Creatinin kinase, SDS: Standard deviation score, IQR: Interquantile range

Table 4. Relationships between femoral neck Z scores and laboratory findings before and after loss of ambulation

Femoral neck Z scores						
Before loss of ambulation osteporosis				**After loss of ambulation osteporosis**		
	No n=8	**Yes n=32**	**p**	**No n=6**	**Yes n =34**	**p-value**
Ca (mg/dL)	9.6±0.3	9.7±0.3	0.461	9.9±0.29	9.8±0.4	0.519
P (mg/dL)	4.7±0.6	5±0.5	0.214	4.8±0.7	4.7±0.6	0.793
Alp (U/L)	130±40.5	103±30.5	0.139	127±37	100±40	0.152
VitD (µg/L)	16.3±4.1	14.7±6.4	0.376	14±2	17.3±6.8	0.029
PTH (µg/L)	45.2±9.7	38.1±15.1	0.121	73.5±84.1	36.8 ±14.7	0.335
CK (U/L)	7939±2529	7037±4163	0.446	4269±2568	4450±2712	0.879

Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, TSH: Thyroid stimulating hormone, T4: Thyroxine, VitD: Vitamin D, PTH: Parathyroid hormone, CK: Creatinin kinase, SDS: Standard deviation score, IQR: Interquantile range

The weight percentile of 3 patients was >2 SDS before loss of ambulation, and only 1 patient had body weight percentile >2 SDS after loss of ambulation. When patients with and without bone fracture were compared, the vertebral and femoral Z scores before and after loss of ambulation were not determined to predict bone fracture (p=0.104).

DISCUSSION

DMD is a progressive disease diagnosed at an early age in children, causing muscle weakness, severe disability and early death with pulmonary and cardiac complications in addition to neuromuscular symptoms[5]. The disease was first described by the French electrophysiologist and neurologist Guillaume-Benjamin-Amand Duchenne (de Boulogne) in 1868 and can cause neuromuscular disease as well as cognitive impairment, learning and behavioural problems[4]. The mean age at diagnosis ranges from 4.3-4.11 years, and there has been significant progress in recent years[3]. In this study, the median age at diagnosis was 3 (1-3.5) years. Patients with DMD usually become wheelchair-dependent before the age of 12 years. The average age at which patients lose the ability to walk has been reported to be 9.4±2.4 years[27]. In this study, the age at diagnosis appears to be better than in the current literature, with the median age at which loss of ambulation occurred being 10 years, which is similar to the literature.

DMD is a serious, progressive muscle disease that can result in death at a young age. Although there is currently no definitive cure, glucocorticoids are the main treatment[28]. However, long-term use of glucocorticoids in DMD patients and progressive loss of muscle strength due to the nature of the disease lead to adverse effects on bone such as osteoporosis[29].

Low BMD is often underestimated despite causing significant morbidity. Osteoporosis/osteopenia is common, especially in patients receiving glucocorticoid therapy, and this condition poses a significant risk for pathological fractures[12]. Mechanical stress is important in maintaining bone volume and structure. Motor paralysis, long-term bed rest, and situations that may cause immobilization (such as putting a cast on the fractured area) cause rapid bone loss. It is known that bone resorption is accelerated and bone formation is suppressed due to bone remodeling disorder that occurs after immobilization. Therefore, it is important to prevent disuse osteoporosis[30,31]. Loss of ambulation can cause further demineralization of bone, further altering bone health and increasing the fracture risk[32].

In this study, vertebral osteoporosis was found in 40% and femoral neck osteoporosis in 80% of patients before loss of ambulation. It was also observed that BMD decreased after loss of ambulation, especially in the femoral neck. This was consistent with the findings of Larson and Henderson[17], who reported that in children with DMD, lumbar spine bone density decreases only slightly in ambulatory individuals, but drops significantly with the loss of mobility. These results support the mechanical stress theory, which posits that mechanical load plays a critical role in preventing bone resorption.

DXA is the most widely used technique for the assessment of BMD in children[33]. In patients with DMD, DXA should be performed before starting glucocorticoids, every 1-2 years if glucocorticoids are used, and annually if bisphosphonate therapy is used[24]. In children, posteroanterior lumbar vertebral and femoral neck measurements are performed[24]. A difference of approximately 0.5 SDS can be seen between the femoral neck Z-score and the lumbar vertebral Z score. This difference increases further below Z-score -3 SDS. Immobile children such as those with DMD may have preserved lumbar DXA but low femoral neck DXA[34].

In this study, femoral neck measurements were found to be lower than the lumbar vertebral BMD measurements. A difference of approximately 1 SDS was determined between the lumbar and femoral neck Z-scores, consistent with the literature. This was attributed to the fact that DXA measurements of the hip region (total hip or femoral neck) in children are less reliable due to the difficulties in determining the area to be measured[25]. In addition, the measurement differences detected in this study may lead to differences in the diagnosis of osteoporosis. Although DXA is a routinely recommended method for BMD monitoring in DMD patients, it has some disadvantages[35,36]. It is known that DXA may give inaccurate results due to spinal deformities or anatomical changes[36]. Therefore, quantitative computed tomography (QCT) is one of the methods that has been recommended for the diagnosis of osteoporosis in DMD patients in recent years[35]. QCT has the advantage of being able to directly measure trabecular bone density in the vertebrae, which shows greater changes than cortical bones in osteoporosis and responds rapidly to treatment[35,36]. It can be considered that QCT will be used more widely in the future and provide better predictions.

Detection and prevention of osteoporosis in patients with DMD is crucial to reduce complications such as

vertebral fractures, long bone fractures and scoliosis. In a two-year follow-up study of 6,213 children by Clark et al.[37], a weak inverse association was identified between BMD and subsequent fracture risk. The study also suggested that childhood fracture risk is associated with volumetric BMD and that cortical thickness, as one of the determinants of volumetric BMD, has a significant impact on skeletal fragility. While bone size was not found to have a direct relationship with fracture risk, children who sustained fractures tended to have relatively smaller skeletal structures compared to their overall body size[37]. Corticosteroids are thought to delay the loss of muscle strength through anti-inflammatory action. Despite the beneficial effects, corticosteroids have negative side-effects on bone health, resulting in low bone mass and increased bone fragility[38,39]. King et al.[19] reported that long bone fractures were 2.6-fold more common in DMD patients treated with steroids compared to patients who did not use steroids. In addition, vertebral compression fractures were reported in 32% of the steroid-treated group, while vertebral fractures were not seen in the steroid-naive group.[19] According to a study by Tian et al.[40], the prevalence of fractures in DMD patients increases with age. The prevalence of vertebral fractures was reported as 4.4%, 19.1%, and 58.3% at ages 5, 10, and 18 years, respectively. In addition, no significant association was determined between vertebral Z-scores and vertebral compression fractures in the current study, which was consistent with the literature[41]. The prevalence of vertebral compression fracture was 17.5% in the current study. Although this rate is a relatively low rate compared to the literature, it is thought that this rate may increase during the follow-up of the patients. The data in the current study do not support the value of Z scores as predictors of future fractures. However, fractures were observed in 35% of the patients and vertebral fractures were observed in 17.5% of the patients (all of these patients had vertebral osteoporosis). This suggests that it is difficult to use the bone health status of the patients for fracture prediction, or that different methods such as QCT should be tried for prediction. As Z-scores are limited in fracture prediction, it is thought that fracture risk assessment should be supported by advanced imaging methods such as QCT, especially in clinically high-risk patients. Long bone fractures also occur in patients with DMD. In a study of 378 patients with DMD from 4 neuromuscular centres, McDonald et al.[18] reported that 79 patients had long bone fractures, and most fractures were reported in mobile patients (47%). Lower limb fractures can significantly reduce a patient's function and accelerate the decline in walking ability due to prolonged immobilization and/or restriction of activities[42]. In a 2020 study of 287 patients, Yıldız et al.[43] reported that bone fractures were identified in 51 patients, and 36.4% of those with fractures subsequently lost the ability to walk. In a study by King et al.[19], it was reported that humerus fracture was more common in the non-steroid group and femur fracture was more common in the steroid group. In this study, all patients were on long-term steroid therapy and humerus fracture was observed more frequently than in the literature. This finding may be due to the small sample size. In the current study, bone fracture was seen in all the patients during the mobile period, but no patient was immobilized due to fracture.

The development of scoliosis in DMD is thought to be related to decreased mobility and paraspinal muscle weakness[44,45]. Prolonged ambulation and corticosteroid use may delay scoliosis onset and reduce the need for surgery[46-50]. Although low BMD is common in idiopathic scoliosis, Tsaknakis et al.[51] found no correlation between BMD and scoliosis severity in DMD. In this study, 60% of patients developed scoliosis before ambulation loss, despite early steroid use. No significant association was found between BMD and scoliosis or osteoporosis, suggesting that BMD alone may not predict scoliosis severity or osteoporosis risk in these patients.

Many treatment methods are used to prevent osteoporosis and fractures and improve bone health in patients with DMD. Regular monitoring of bone health and early diagnosis, exercise therapies, alternative treatments to corticosteroids, anti-resorptive agents, vitamin D supplements and hormone therapies are among these methods. Vitamin D deficiency affects approximately 50% of the global population. Since vitamin D is synthesized in the skin through sunlight exposure, its deficiency is primarily attributed to lifestyle changes that limit ultraviolet B-induced production[52]. Patients with DMD tend to be less exposed to sunlight, especially after immobilization. Periodic monitoring of calcium intake and serum 25-hydroxyvitamin D concentrations is recommended for patients with DMD. If calcium intake is below the recommended age-appropriate amount or if serum 25-hydroxyvitamin D levels fall below 30 ng/mL, patients should be fed a calcium-rich diet and supplemented with vitamin D[23]. All the patients in our centre were checked annually for blood calcium, phosphorus, and vitamin D values. The blood calcium and phosphorus values of all the current study patients were found to be within normal limits.

Nevertheless, nutritional recommendations were made for all the patients whether or not a deficit was detected. Patients without osteoporosis before loss of ambulation had higher vitamin D values [15.5 (10.4-21.1) versus 11.9 (8.9-14.9) p=0.051]. This finding is very valuable in terms of emphasizing the protective effect of vitamin D.

Physical therapy is an important part of DMD treatment, but there is no standard physiotherapy protocol[42]. Bisphosphonates are one of the options used in the treatment of osteoporosis, but there is not enough evidence for young DMD patients[34,53]. Denosumab and Tocilizumab have shown promising results as monoclonal antibodies that regulate osteoclastic activity and reduce bone mineral loss[34,54]. The effects of growth hormone and testosterone on bone density have been investigated within the scope of hormone treatments, but definitive results have not been reached[34]. Teriparatide (PTH analog) has the potential to improve bone quality, but there is not enough data on its use in DMD patients[55].

Study Limitations

The limited number of patients and the retrospective design can be considered limitations of the study.

CONCLUSION

This study focuses on bone problems developing in DMD patients, such as osteoporosis, fractures, and scoliosis. The median age of the patients at the time of diagnosis was 3 years, and the median age for starting to walk was 12 months. These findings indicate that the symptoms began early and were also recognized early in our clinic. In 80% of the patients, there was femoral neck osteoporosis, and in 40%, there was vertebral osteoporosis. In all patients with vertebral osteoporosis, femoral neck osteoporosis was also present. The study also found that, particularly in the femoral neck, BMD decreased after the loss of ambulation, but no change in Z scores was observed in the vertebrae after the loss of ambulation. Fractures were observed in 35% of the patients, and vertebral fractures were seen in half of these patients (17.5% of all patients). In particular, all patients with vertebral fractures had vertebral osteoporosis. The study results did not show a direct correlation between BMD before the loss of ambulation and the future risk of fractures. Scoliosis was present in 60% of the patients before the loss of ambulation, but no significant relationship was found between BMD and the severity of scoliosis. This suggests that BMD alone may not be a sufficient predictor of scoliosis progression in DMD patients. Patients who did not develop osteoporosis before loss of ambulation had higher vitamin D levels.

An important contribution of this study to the literature is the high rate of osteoporosis in the femoral neck region in the pre-ambulatory period. A unique aspect of this study is that it is one of the first series to show a high rate of femoral neck osteoporosis in the pre-ambulatory period. This finding shows the need for closer monitoring of bone health, especially in the phase before the immobility period begins, and for early preventive approaches to be planned. In addition, these data may guide the timing of treatment protocols to be applied in the future.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Board of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval no: 2023/06-41, dated: 13/07/2023).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept: Y.G., F.B., B.N.D., N.O.D., Design: Y.G., P.G., F.B., B.N.D., N.O.D., Data Collection or Processing: Y.G.,S.M.D.,Ö.A.Y., A.Ö.Y., B.T., H.B., Analysis or Interpretation: Y.G., Ö.Al., B.T, Literature Search: Y.G., Writing: Y.G.

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Original Article

An Overview of Treatment in Pediatric Bladder-bowel Dysfunction: A Single-Center Experience

Pediatrik Mesane Bağırsak Disfonksiyonunda Tedaviye Bakış: Tek Merkezli Deneyim

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ABSTRACT

Objective: This study aimed to evaluate the clinical characteristics, treatment responses, and outcomes of pediatric patients diagnosed with bladder-bowel dysfunction, highlighting a structured management approach including urotherapy, pharmacotherapy, and rehabilitation techniques.

Method: A retrospective study was conducted with 1846 children aged 5-18 years diagnosed with bladder-bowel dysfunction at Bakırçay University Çiğli Training and Research Hospital between 2022 and 2025. Patients with neurological disorders were excluded. Data on demographics, bladder-bowel symptom scores, treatment modalities, uroflowmetry results, and treatment outcomes were collected. Conservative treatments included use of osmotic-laxatives and urotherapy. Patients unresponsive to initial therapies received treatment with antimuscarinics, biofeedback, and transcutaneous electrical nerve stimulation where appropriate.

Results: The mean age of the patients was 104.4 months. Female predominance (67%) was observed. Conservative management alone successfully resolved symptoms in 512 patients without vesicoureteral reflux or recurrent urinary tract infections. Patients with higher bladder-bowel symptom scores (>20) and pathological uroflowmetry results required biofeedback and, in some cases, transcutaneous electrical nerve stimulation. No relapse was observed in any subgroup of patients during the 6-month follow-up period. Effective management of constipation and lifestyle modifications were critical for treatment success.

Conclusion: A stepwise treatment protocol focusing on bowel regulation, urotherapy, and individualized interventions provides effective symptom control and prevents disease progression in pediatric bladder-bowel dysfunction. Early diagnosis, attention to modifiable risk factors such as constipation, and long-term adherence to behavioral strategies are essential for optimal treatment outcomes. Prospective studies with extended follow-up periods are warranted.

Keywords: Bladder-bowel dysfunction, children, urotherapy, constipation, biofeedback, TENS

ÖZ

Amaç: Bu çalışmada, pediyatrik yaş grubunda mesane-barsak disfonksiyonu tanısı alan hastaların klinik özellikleri, tedavi yanıtları ve sonuçları değerlendirilmiş; üroterapi, farmakoterapi ve rehabilitasyon tekniklerini içeren yapılandırılmış bir tedavi yaklaşımı vurgulanmıştır.

Yöntem: 2022-2025 yılları arasında Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi'nde mesane-barsak disfonksiyonu tanısı konulan, 5-18 yaş aralığındaki 1846 çocuk retrospektif olarak incelenmiştir. Nörolojik bozukluğu olan hastalar çalışmaya dahil edilmemiştir. Demografik veriler, mesane-barsak semptom skorları, tedavi yöntemleri, üroflowmetri sonuçları ve tedavi sonuçları toplanmıştır. Koruyucu tedaviler arasında ozmotik laksatifler ve üroterapi yer almıştır. Başlangıç tedavilerine yanıt vermeyen hastalara uygun durumlarda antimuskarinikler, biofeedback ve transkutanöz elektriksel sinir stimülasyonu uygulanmıştır.

Bulgular: Ortalama yaş 104,4 ay olarak bulunmuştur. Hastalarda kız cinsiyet baskınlığı gözlenmiştir (%67). Vezikoüreteral reflü veya tekrarlayan idrar yolu enfeksiyonu olmayan 512 hastada yalnızca konservatif tedavi ile semptomlar başarıyla düzelmiştir. Yüksek mesane-barsak semptom skoruna (>20) sahip olan ve patolojik üroflowmetri sonuçları bulunan hastalarda biofeedback ve bazı durumlarda transkutanöz elektriksel sinir stimülasyonu gerekmiştir. Altı aylık takip sürecinde hiçbir alt grupta nüks gözlenmemiştir. Etkili konstipasyon yönetimi ve yaşam tarzı değişiklikleri tedavi başarısı için kritik bulunmuştur.

Sonuç: Barsak düzenlenmesine, üroterapiye ve bireyselleştirilmiş müdahalelere odaklanan basamaklı bir tedavi protokolü, pediyatrik mesane-barsak disfonksiyonunda etkili semptom kontrolü sağlamakta ve hastalık progresyonunu önlemektedir. Erken tanı, konstipasyon gibi değiştirilebilir risk faktörlerine dikkat edilmesi ve davranışsal stratejilere uzun vadeli uyum, optimal sonuçlar için gereklidir. Genişletilmiş takip süresi içeren ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Mesane-barsak disfonksiyonu, çocuklar, üroterapi, konstipasyon, geribildirim, TENS

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INTRODUCTION

Bladder-bowel dysfunction (BBD) refers to a set of lower urinary tract symptoms that are often accompanied by bowel complaints[1]. Lower urinary tract symptoms can manifest in many forms. They may present with symptoms such as urinary incontinence, abnormal daily urination frequency, urge to urinate, hesitancy, and straining during urination, weak urine stream, intermittent urination, and dysuria[2]. Bowel dysfunction often manifests itself in the form of primary constipation and/or fecal incontinence[2]. The prevalence of BBD in school-age children is between 9% and 21% in the literature[3,4]. The Bladder-Bowel Dysfunction Symptom Scoring system (BBDSS) is used to screen for, diagnose, and evaluate the treatment outcomes of BBD[5]. Standard urotherapy for both the patient and family involves non-pharmacologic and non-surgical management, consisting of training and behavioural management, using a bladder and bowel diary, and regular follow-up[6]. Standard urotherapy includes management of proper voiding function and demystification, maintaining appropriate and regular bladder and bowel habits, and compliance with balanced fluid intake and dietary recommendations[6,7]. In the literature, the prevalence of BBD was reported as 9.1% in a study covering 829 pediatric patients. It was understood that the probability of suffering from lower urinary tract problems was 6.8 times higher in children with complaints of constipation[4]. Standard urotherapy and proper management of constipation form the basis of BBD treatment. Pharmacotherapy and surgical treatment of lower urinary tract dysfunction should only be considered in cases that do not respond fully to first-line conservative treatment. If cases do not respond to treatment with urotherapy and constipation management, medical treatments should be initiated. In cases that do not respond to medical treatment, rehabilitation methods other than pharmacological treatments should be considered, given the close interaction between the bladder and the bowel due to their shared neural network and pelvic floor muscles[8]. These methods of rehabilitation are classified as biofeedback, pelvic floor physiotherapy, and neuromodulation[9]. This article focuses on the methods used in diagnosing and treating BBD. Considering the comfort and quality of life of children, rehabilitation methods that are useful in patients with such a common health problem can be used to shorten the treatment period, and help patients to recover quickly.

MATERIALS and METHODS

This study was conducted by retrospectively examining pediatric patients aged 5-18 years who were followed up with the diagnosis of BBD in the Ppediatric nephrology and urology clinics between 2022 and 2025. Ethical approval of the study was obtained from Non-Invasive Clinical Research Ethics Committee of Bakırçay University (approval number: 2243, dated: 07.05.2025). Patients with a Bladder-BBDSS of 13 and above were included in the study. Patients with known neurological disorders were excluded from the study. After obtaining approval from the local ethics committee, the following information was collected from patient files: age, age at presentation, complaints, presence of constipation and urinary incontinence, BBDSS, accompanying urological and nephrological anomalies, presence of infection, results of uroflowmetric evaluations, medications used, and rehabilitation methods applied during treatment.

Statistical Analysis

Descriptive statistics were used to summarize demographic data, clinical characteristics, and treatment outcomes. Continuous variables such as age and BBDSS were expressed as means with ranges or standard deviations, where appropriate. Categorical variables, including treatment modalities, presence of vesicoureteral reflux (VUR), recurrent urinary tract infections (UTIs), and relapse rates, were reported as numbers and percentages. Patients were stratified into subgroups based on baseine BBDSS levels, uroflowmetry findings, and response to their first-line treatment modalities. Treatment responses were assessed at predefined intervals (2, 6, and 9 months), and clinical improvement was defined as a reduction in BBDSS to below 13 and absence of symptom relapse. No inferential statistical tests (e.g., t-tests, chi-square tests) were applied, as the primary objective was to describe treatment patterns and outcomes rather than to statistically compare efficacies of conservative, and surgical interventions applied.

RESULTS

A total of 1846 children diagnosed with BBD were included in the study. The mean age of the participants was 104.4 months (range: 60-212.4 months). At the time of admission, the mean BBD score was 13.5±4.2 among patients who responded to conservative therapy alone (Table 1). Among the study population, 512 patients (74% male) received treatment only with osmotic-laxative drugs and urotherapy for 3 months.

All presented with urinary incontinence, and none had VUR or recurrent UTIs. This group had comparatively lower BBD scores and exhibited no relapses during the initial 6-month follow-up period (Table 2). The remaining 1334 patients had more complex clinical presentations, including recurrent UTIs (n=213), and concomitant VUR (n=38). Clinical presentations in all of these patients were consistent with either overactive bladder (OAB) or urinary incontinence. Patients diagnosed with OAB (n=412) received treatment with oxybutynin (n=267), propiverine (n=145) or , both in combination with osmotic-laxative therapy. Similarly, 922 patients presented with urinary incontinence but without OAB. Among them, 756 patients had BBDSS <20 and were treated with oxybutynin (n=542) or propiverine (n=214) in combination with an osmotic-laxative medication. None of these subgroups exhibited relapse during the first 6 months of treatment. A subgroup of 166 patients with BBDSS >20 was further analyzed. Among them, 34 patients exhibited pathological findings on uroflowmetry and were started on biofeedback therapy for 10 sessions in addition to treatment with propiverine and osmotic-laxatives. The remaining 132 patients were treated with either oxybutynin (n=87) or propiverine (n=45) plus an osmotic-laxative drug. At the end of the second month, all patients in this subgroup achieved less than 50% clinical improvement. As a result, biofeedback therapy (8 sessions) combined with propiverine and an osmotic-laxative was initiated for all 166 patients. At the end of this intervention, all patients had BBDSS <13 and showed no relapses during the initial 6-month follow-up period (Table 3). Nineteen out of 34 patients with uroflowmetry abnormalities at baseline responded to the treatment with 10-session biofeedback protocol. The remaining 17 patients required 10 additional biofeedback sessions, resulting in a 9-month treatment course. Of these, 6 patients still had persistent symptoms and were treated with transcutaneous electrical nerve stimulation (TENS) for an additional 4 months. All but one patient responded favourably to this combined treatment regimen.

Table 1. General characteristics of the study population

Variables	Values
Total number of patients	1846
Age (mean, range) (months)	104.4 (60-212.4)
BBDSS (mean ± SD)	13.5±4.2 (in 512 patients)
Female/male (%)	67/ 33

BBDSS: Bladder-Bowel Dysfunction Symptom Score

Table 2. Treatment modalities and patient subgroups

Subgroup characteristics	n	Treatments used	Relapse in the first 6 months
BBDSS ≥13, no VUR or recurrent UTI, all patients with incontinence	512	Osmotic-laxative + Urotherapy (3 months)	No
VUR (+), recurrent UTI	213 (143 male)	OAB/incontinence compatible	No
OAB	412	Oxybutynin + Osmotic-laxative (n=267), Propiverine + Osmotic-laxative (n=145)	No
Urinary incontinence (non-OAB), BBDSS <20	756	Oxybutynin + Osmotic-laxative (n=542), Propiverine + Osmotic-laxative (n=214)	No
BBDSS >20: with pathological uroflowmetry results	34 (31 female)	10 sessions biofeedback + Propiverine + Osmotic-laxative	No
BBDSS >20: without pathological uroflowmetry results	132 (96 female)	Oxybutynin/Propiverine + Osmotic-laxative	No

BBDSS: Bladder-Bowel Dysfunction Symptom Score, VUR: Vesicoureteral reflux, UTI: Urinary tract infection, OAB: Overactive bladder

Table 3. Treatment Outcomes of Patients with BBDSS >20				
Treatment groups	**n**	**Outcomes of 2-month treatment**	**Final interventions**	**Relapse**
Biofeedback + Propiverine + Osmotic-laxative (BBDSS >20)	166	<50% symptomatic improvement in all cases	Switch to propiverine +8 biofeedback sessions	No
Uroflowmetry pathology group (of above)	34	19 cases improved (BBDSS <13), 17 cases needed longer treatment	+10 biofeedback sessions maintained up to 9 months	
Extended group with persistent symptoms after 9 months	6	Persistent complaints	TENS for 4 months	Ongoing
Non-responders to all therapies	1	50% reduction in symptoms	All treatment modalities were maintained	-
BBDSS: Bladder-Bowel Dysfunction Symptom Score, TENS: Transcutaneous electrical nerve stimulation				

DISCUSSION

This study presents one of the most comprehensive clinical evaluations of BBD in a large cohort of 1846 pediatric patients and a detailed stratification based on symptom severity and treatment response was performed. A major strength of the study lies in the structured stepwise approach to therapy-ranging from conservative management to pharmacological and behavioural interventions such as biofeedback and TENS-which was tailored to each patient's clinical status and symptom burden.

In our study, the female gender was more predominant among children diagnosed with BBD. This finding is consistent with previous reports indicating a higher prevalence of BBD among girls compared to boys[10]. Anatomical, hormonal, and behavioral factors have been proposed to explain this gender disparity. The higher proportion of female patients in our cohort supports the notion that girls may be at a greater risk for developing both functional lower urinary tract symptoms and constipation, emphasizing the need for gender-specific preventive strategies. The global burden of chronic kidney disease (CKD) in children has been increasing, and voiding dysfunctions, particularly those associated with BBD, have been recognized as one of the most frequent and preventable contributors to this higher prevalence of CKD[11]. Previously experienced UTIs and untreated dysfunctional voiding during childhood not only increase the risk of CKD in later life but are also associated with increased morbidity and mortality, as well as imposing long-term economic burden on healthcare systems[12]. Consequently, early diagnosis and appropriate treatment strategies should aim not only to reduce medical complications but also to decrease public health costs in the long run. Among the modifiable risk factors, constipation is of particular clinical importance. Remarkably, resolution of constipation alone can lead to significant improvement -or even complete resolution- of urinary symptoms in many children[13]. Recurrent UTIs are often exacerbated by underlying constipation, which is strongly associated with poor dietary habits and a sedentary lifestyle[14]. Therefore, addressing nutrition and physical inactivity should be integral parts of any treatment plan. Promoting adequate hydration, a fiber-rich diet, and regular physical activity can improve both bowel and bladder health and reduce the reliance on pharmacologic interventions. In this study, children without VUR or recurrent UTIs who were treated with osmotic laxatives and urotherapy showed no relapse during the first six months. This data align with previous findings suggesting that non-invasive strategies are effective in the management of early-stage BBD[2]. Importantly, for patients with VUR and recurrent UTIs, long-term urotherapy-including timed voiding, morning and bedtime urination, generous hydration, and avoiding holding behaviour-should not be applied as a short-term treatment but must be integrated into the patient's daily life as a preventive lifestyle modification. Sustained adherence to these routines significantly reduces disease recurrence and progression[15]. In patients with more severe symptoms (BBDSS >20), especially those with pathological uroflowmetry findings, biofeedback therapy was highly effective. However, nearly half of this subgroup required extended therapy sessions or adjunctive TENS for optimal clinical improvement. This observation highlights the importance of individualized treatment timelines, which are often underemphasized in the literature[16]. Furthermore, the combination of antimuscarinic agents (oxybutynin or propiverine) with osmotic laxatives yielded consistent remission across all non-OAB incontinence

subgroups. These results underscore the advantage of addressing both bowel and bladder dysfunction concurrently- a strategy supported by multiple studies[13,15]. The most notable outcome of this study is the absence of relapse across all treatment groups during the six-month follow-up period. This favorable outcome supports the reliability of the BBDSS scoring system in stratifying disease severity and guiding targeted therapy. Moreover, it reinforces the role of early, structured, and individualized management in preventing long-term renal complications and reducing the societal and financial burden associated with untreated BBD.

As a final remark, it is essential to rule out underlying urological anomalies before initiating standard BBD protocols. Anatomic abnormalities may mimic or complicate symptoms and, if overlooked, may result in the persistence of symptoms or progression to renal impairment[13].

CONCLUSION

In conclusion, this study proposes a robust and adaptable treatment framework for pediatric BBD. Future research should focus on prospective validation of this hierarchical approach, as well as long-term monitoring of renal outcomes and cost-effectiveness. Particular attention should be given to behavioral interventions, early diagnosis of constipation, and lifestyle modifications, which remain central to both the treatment and prevention of BBD.

Ethics

Ethics Committee Approval: A retrospective study was conducted in institute after the approval of Non-Invasive Clinical Research Ethics Committee the Bakırçay University, (approval number: 2243, dated: 07.05.2025).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: M.B.Ö., H.T., Ö.Ö.Ş., Concept: M.B.Ö., Ö.E., Ö.Ö.Ş., Ö.O., Design: M.B.Ö., Ö.E., Data Collection or Processing: M.B.Ö., H.T., Ö.Ö.Ş., Ö.O., Analysis or Interpretation: M.B.Ö., H.T., Ö.Ö.Ş., Ö.O., Literature Search: M.B.Ö., Ö.E., Ö.Ö.Ş., Ö.O., Writing: M.B.Ö., Ö.Ö.Ş., Ö.O.

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Original Article

Clinical Outcomes and Mortality Predictors in Patients Hospitalized in the Pediatric Intensive Care Unit due to Sepsis

Çocuk Yoğun Bakım Kliniğine Sepsis Nedeniyle Yatan Hastaların Klinik Sonuçları ve Mortalite Belirteçleri

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ABSTRACT

Objective: Sepsis is a serious disease in children and necessitates accurate mortality risk assessment. This study aims to evaluate the effectiveness of clinical findings, laboratory parameters, and scoring systems in predicting mortality and morbidity in pediatric sepsis cases in the pediatric intensive care unit (PICU).

Method: Clinical and laboratory parameters, Pediatric Index of Mortality (PIM) II, Pediatric Risk of Mortality III, Pediatric Logistic Organ Dysfunction (PELOD) and Vasoactive Inotropic Scoring (VIS) scores of 219 patients, aged between 1 month and 18 years, diagnosed with sepsis and septic shock between 2010 and 2016 were retrospectively evaluated.

Results: The mortality rate of the patients was 32.9% (72/219). The specified percentages of patients had an underlying disease (73.1%), required invasive mechanical ventilation (IMV) support (80%), and had a median hospitalization time of 11 days, while 77.2% of the patients were diagnosed with septic shock. In the multivariate logistic regression analysis, higher PIM II [odds ratio (OR): 1.027, p=0.010], PELOD OR: 1.024, p=0.001), Vasoactive-Inotropic Score (VIS) (OR: 1.016, p<0.001) scores, and lactate levels (OR: 1.143, p=0.032) were identified as significant predictors of mortality in pediatric sepsis patients. In receiver operating characteristic analysis, VIS had the highest predictive power [area under the curve: 0.820]. The partial pressure of carbon dioxide (PCO_2) significantly correlated with the length of stay in PICU (r=0.407). PIM II remarkably correlated with the duration of IMV support (r=0.516).

Conclusion: The most efficient parameters to assess mortality in pediatric sepsis were VIS, PIM II and PELOD, respectively. PCO_2 correlated with the length of stay in the PICU, and PIM II with the duration of IMV support.

Keywords: Sepsis, mortality, VIS, PIM II, PICU

ÖZ

Amaç: Sepsis çocuklarda mortalite riskinin doğru değerlendirmesini gerektiren ciddi bir hastalıktır. Bu çalışmada çocuk yoğun bakım ünitesindeki (ÇYBÜ), pediyatrik sepsis olgularında mortalite ve morbiditeyi tahmin etmede klinik bulguların, laboratuvar parametrelerinin ve puanlama sistemlerinin etkinliğini değerlendirmeyi amaçladık.

Yöntem: 2010-2016 yılları arasında sepsis ve septik şok tanısı alan, yaşları 1 ay ile 18 yıl arasında değişen 219 hastanın klinik ve laboratuvar parametreleri, Pediyatrik Mortalite İndeksi (PIM) II, Pediyatrik Mortalite Riski III, Pediyatrik Lojistik Organ Disfonksiyonu (PELOD) ve Vazoaktif İnotropik Skor (VIS) değerleri retrospektif olarak değerlendirilmiştir.

Bulgular: Mortalite oranı %32,9 (72/219) idi. Hastaların altta yatan bir hastalığı (%73,1) ve invaziv mekanik ventilasyon (İMV) desteğine (%80) ihtiyacı olup, ortalama hastanede kalış süresi 11 gündü. Hastaların %77,2'sine septik şok tanısı konuldu. Çok değişkenli lojistik regresyon analizinde, yüksek PIM II [Olasılık oranı (OR): 1,027, p=0,010], PELOD (OR: 1.024, p=0,001), VIS (OR: 1.016, p<0,001) skorları ve laktat düzeyleri (OR: 1.143, p=0,032) pediyatrik sepsis hastalarında mortalitenin önemli öngördürücü parametreleri olarak belirlendi. ROC analizinde, VIS en yüksek öngörü gücüne sahipti (eğrinin altındaki alan: 0,820). PCO_2, ÇYBÜ'de kalış süresi (r=0,407), PIM II ise İMV uygulama süresiyle önemli ölçüde ilişkiliydi (r=0,516).

Sonuç: Pediyatrik sepsiste mortaliteyi değerlendirmek için en etkili parametreler sırasıyla VIS, PIM II ve PELOD skorları idi. PCO_2, ÇYBÜ'de kalış süresi, PIM II ise İMV uygulama süresiyle ilişkiliydi.

Anahtar kelimeler: Sepsis, mortalite, VIS, PIM II, ÇYBÜ

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INTRODUCTION

Sepsis is a leading cause of morbidity and mortality among children[1]. Sepsis is a life-threatening condition caused by an aberrant response to infection that could lead to organ dysfunction[2]. Since sepsis persists as a prevalent cause of mortality and morbidity in pediatric patients, it is vital to be able to detect and categorize the severity of the disease effectively[3]. The International Pediatric Sepsis Consensus Conference previously announced the criteria of pediatric sepsis in 2005. The criteria defined sepsis as a possible or verified infection that leads to a systemic inflammatory response syndrome. Even though these standards are widely applied in day-to-day practice, this definition has limits that have been known since it was first used[4,5]. The Society of Critical Care Medicine Pediatric Sepsis Definition Task Force recently identified The Phoenix Pediatric Sepsis criteria for sepsis and septic shock in children[6]. "An infection with life-threatening organ dysfunction" is the final new definition for pediatric sepsis. This definition comprises respiratory, cardiovascular, coagulation, and neurological components of pediatric sepsis[7]. Early diagnosis of sepsis and septic shock in children and predicting the prognosis are very important; therefore, studies on this subject continue intensively[8,9].

The aim of the study was to determine clinical markers and investigate the effectiveness of standard scoring systems used in pediatric intensive care units (PICUs) in predicting mortality and morbidity in patients hospitalized due to sepsis.

MATERIALS and METHODS

Medical records of patients aged between one month and eighteen years with the established diagnosis of sepsis, who were followed up at the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between January 1, 2010, and December 31, 2016, were retrospectively evaluated. Data were collected and extracted retrospectively from medical records in compliance with the ethical principles for medical research. The conduction of the study was permitted by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Clinical Research Ethics Committee. Sepsis, septic shock, and organ failures were diagnosed according to sepsis criteria defined in 2005[4]. Demographic data, medical history, vital parameters, physical examination findings, laboratory and radiological outcomes, medications utilized, disease outcomes, and duration of stay in the PICU of the patients were critically evaluated. Assessment of disease severity and prediction of mortality risk in pediatric sepsis patients were performed based on Pediatric Index of Mortality (PIM) II, Pediatric Risk of Mortality (PRISM) III, Pediatric Logistic Organ Failure (PELOD), and Vasoactive Inotrope (VIS) Scores calculated for each patient. The PRISM III score evaluates physiological parameters collected within the first 24 hours of PICU admission, including neurological status (Glasgow Coma Scale, pupillary reactions), cardiovascular and respiratory function (blood pressure, heart rate, PaO_2/FiO_2 ratio), acid-base balance (pH, bicarbonate), and metabolic markers (glucose, potassium, creatinine) of the patients. The PIM II score is calculated at the time of PICU admission and incorporates variables such as systolic blood pressure, oxygenation status, base excess, need for mechanical ventilation, and the presence of high-risk diagnoses (e.g., cardiac arrest, severe neurological impairment). The PELOD score quantifies multi-organ dysfunction by assessing six organ systems: neurological (Glasgow Coma Scale), cardiovascular (hypotension, lactate), respiratory (PaO_2/FiO_2 ratio, ventilator dependence), hematologic (platelet count), hepatic (bilirubin), and renal (serum creatinine) functions. Higher scores in each of these systems correlate with increased disease severity and a greater risk of mortality[10-13]. VIS scoring system predicts mortality and morbidity of the patients, and is calculated by considering the following parameters in combination estimated during the first 24 hours of the patients in the PICU: dopamine dose (μg/kg/min), dobutamine dose (μg/kg/min), 100 x adrenaline dose (μg/ kg/min), 100 x noradrenaline dose (μg/kg/min), 10 x milrinone dose (μg/kg/min), and 10.000 x vasopressin dose (U/kg/min). The length of the PICU stay was calculated as the interval in days between the date of admission and discharge from the PICU. The cumulative hours required for invasive mechanical ventilation (IMV) were used to determine the duration of IMV support. Morbidity indicators encompassed the duration of IMV support and the length of stay in the PICU. Patients followed up with a diagnosis of sepsis were divided into two groups: those who died during follow-up and those who were discharged. Additionally, patients were separated into two groups as those that did and did nor require IMV support. All groups were also compared in terms of clinical, laboratory parameters, and scoring systems.

Statistical Analysis

The Statistical Package for Social Sciences version 20.0 (SPSS 20.0, IBM Corp., Armonk, NY, USA) was employed to analyze the data. The normality of continuous variables was evaluated using the Kolmogorov-Smirnov

test. In addition, graphical methods including histograms and Q-Q plots were examined. Skewness and Kurtosis values were also calculated to assess the shape of the distribution. Variables with normal distribution were presented as mean ± standard deviation, while non-normally distributed variables as median interquartile range (IQR). The chi-square or Fisher's exact test was used for the comparison of categorical data. Variables that showed statistically significant differences ($p<0.05$) were then included in a multivariate logistic regression analysis (Backward logistic regression method) to identify independent predictors of mortality. The model was adjusted for potential confounders, and multicollinearity was assessed using the Variance Inflation Factor <5 to avoid overestimation or underestimation of coefficients. Adjusted odds ratios (OR) with 95% confidence intervals were reported. Receiver Operating Characteristic (ROC) analysis was performed to measure the predictive power of mortality parameters that were found to be significant in logistic regression analysis. The area under the curve (AUC) refers to the area under the ROC curve, representing the overall ability of a model to distinguish between survivors and non-survivors (0.50-0.60: poor discrimination; 0.61-0.70: fair discrimination; 0.81-0.90: very good discrimination; 0.91-1.00: excellent discrimination). The correlation between two numerical data was calculated using the Spearman test [Spearman Correlation coefficient (r) <0.25 very weak correlation; 0.26-0.49 weak correlation; 0.50-0.69 medium correlation; 0.70-0.89 high correlation; 0.90-1.0 very high correlation] since the data did not conform to normal distribution. In all analyses, p-value of <0.05 was considered statistically significant.

RESULTS

The study population of 219 participants comprised 104 (47.5%) female, and 115 (52.5%) male patients hospitalized in the PICU with a diagnosis of sepsis. The demographic features of these patients are detailed in Table 1. The median age of the patients was 12 months (max: 204 months; min: 1 month; IQR: 6 months - 33 months). The underlying disease was present in 160 (73.1%) cases. Infection foci were detected in 123 patients (56.2%) (Table 1). Respiratory system infections were the most prevalent manifestations of sepsis. The most prevalent microorganisms that were cultivated were coagulase-negative *S. aureus* (29.5%) in blood, *E. coli* (38.2%) in urine, and *P. aeruginosa* (75%) in bronchoalveolar lavage culture media. Most (n=169; 77.2%) of the patients received the diagnosis of septic shock throughout the follow-up. IMV was applied to

Table 1. Demographic characteristics of patients with sepsis hospitalized in PICU

Characteristics	Total number of patients, n=219 (%)/ mean ± SD
Sex, n (%)	
Male	104 (47.5)
Female	115 (52.5)
Age, month	Median 12 (IQR: 6-33)
Transferred from	
Another hospital, n (%)	101 (46.1)
Emergency department, n (%)	84 (38.4)
Ward, n (%)	34 (15.5)
Hospitalized during	
Day shift, n (%)	118 (53.9)
Night shift, n (%)	101 (46.1)
Nationality, n (%)	
Turkish	207 (94.5)
Refugee patient	12 (5.5)
Parental consanguiuity, n (%)	75 (34.2)
Underlying diseases, n (%)	160 (73.1)
Neurological diseases	88 (40.3)
Endocrine/metabolic diseases, n (%)	31 (15.1)
Respiratory diseases	20(9.2)
Hematological/oncological diseases	16 (7.4)
Cardiac diseases	13 (6.0)
Gastroenterological diseases	8 (3.7)
Genetic diseases	4 (1.9)
Rheumatological diseases	2 (0.9)
Identified focus of infection, n (%)	123 (56.2)
Septic shock, n (%)	169 (77.2)
MV support, n (%)	171 (78.1)
Duration of mechanical ventilation	144 hours (1 hour to 7200 hours)
Inotropic medication use, n (%)	167 (76.2)
CRRT, n (%)	17 (7.8)
Mortality scores, median (IQR)	
PIM II	9.2 (4-22.2)
PRISM III	6 (3-13)
PELOD	1.7 (0.2-26.1)
Organ failures, n (%)	
Respiratory	172 (78.5)
Cardiovascular	158 (72.1)
Neurological	72 (32.9)
Hematological	42 (19.2)
Renal	32 (14.6)
Hepatic	20 (9.1)
Mortality, n (%)	72 (32.9)
PICU length of stay (median)	11 (1 to 311 days)

MV: Mechanical ventilation, CRRT: Continuous Renal Replacement Therapy, PIM: Pediatric Index of Mortality, PRISM: Pediatric Risk of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, PICU: Pediatric Intensive Care Unit, IQR: Interquartile range

171 (78.1%) cases. The median value of the duration of IMV support was 144 hours (IQR: 72-360 hours) (max.: 7200-min.: 1 hour). At least one inotropic treatment was started in 167 patients (76.2%). Seventeen patients (7.8%) received dialysis treatment including hemodiafiltration (n=16), and peritoneal dialysis (n=1). The most common organ failures were respiratory (n=172; 78.5%) and cardiovascular (n=158; 72.1%) system failures.

Seventy-two (32.9%) patients did not survive. The median intensive care unit stay was 11 days (max.: 311 days-min.: 1 day), and the median hospital stay was 23 days (max.: 327 days-min.: 1 day).

There was no significant relationship between mortality and age, body weight, gender, refugee status of the patients, the presence of an underlying disease, and being admitted to the intensive care unit outside working hours (p>0.05). However, the survival rate was higher among those admitted to the emergency department (p=0.017). Survival was also significantly higher in patients with an infection focus (p<0.001), although no significant relationship was found between positive culture results and survival rates (p= 0.158) (Table 2). A significant association was observed between mortality, the necessity for IMV support and high scores obtained (p<0.05). Nevertheless, there was no statistically significant association between the necessity for a blood transfusion and survival (p>0.05). Mortality was found to be significantly higher in those with low Glasgow Coma Scores, bradypnea, low mean arterial pressure, hypothermia, low oxygen saturation and high FiO_2 requirement (p<0.05) (Table 3). An analysis of laboratory data revealed that deceased patients exhibited a higher prevalence of several adverse medical conditions, and laboratory parameters compared to those who survived including anemia, thrombocytopenia, hypocalcemia, elevated levels of lactate dehydrogenase, troponin, international normalized ratio (INR), prothrombin time, activated partial thromboplastin time (aPTT), and D-dimer, along with low levels of fibrinogen. Additionally, the deceased patients showed lower pH and HCO_3 values, along with increased lactate levels and base deficit. All these findings were statistically significant (p<0.05) (Table 4). In the logistic regression analysis, higher PIM II, PELOD, and VIS scores, and higher lactate levels were identified as significant predictors of mortality (p<0.05). The significant parameters identified in the logistic regression analysis were evaluated using ROC analysis. The parameters with the highest predictive power for mortality were PIM II, PELOD, and VIS scores (Table 5, Figure 1).

The pCO_2 value showed the strongest correlation with the duration of PICU stay (r=0.407), while the PIM II score indicated the highest correlation with the length of stay on IMV support (r=0.516) (Table 6). The relationships between the duration of patient's stay on IMV support and intensive care, the presence of chronic disease, his/her refugee status, and living place were examined. It was found that only patients with underlying chronic diseases were monitored longer on IMV (p=0.003) and stayed longer in PICU (p<0.001).

DISCUSSION

In this study, we examined the predictive markers of mortality for 219 patients diagnosed with sepsis.

Table 2. Relationships between demographic data, baseline characteristics of patients and survival

Parameters median (IQR) or n (%)	Non-survivors (n=72)	Survivors (n=147)	p-value
Age, months, median (range)	11.5 (5-36)	12 (5-36)	0.365
Body weight (kg) median (range)	8 (5-16)	8 (5.5-12)	0.834
Sex, n (%) Female Male	 36 (50) 36 (50)	 68 (46.3) 79 (53.7)	 0.602
Refugee patient, n (%)	5 (6.9)	7 (4.8)	0.535
Presence of an underlying disease, n (%)	45 (71.4)	81 (66.4)	0.486
Admission during night shift, n (%)	67 (45.6)	34 (47.2)	0.819
Transferred from Emergency department, n (%) Ward, n (%) Another hospital, n (%)	18 (25) 40 (55.6) 14 (19.4)	66 (44.9) 61 (41.5) 14 (19.4)	 **0.017***
Identified focus of infection, n (%)	28 (38.9)	95 (64.6)	**<0.001**
Positive culture results, n (%)	30 (41.7)	47 (32)	**0.158**

*Statistical significance due to pediatric emergency department admissions. IQR: Interquartile range

Worldwide cooperative cross-sectional research carried out in 2013 determined that 8.2% of the children under the age of 18 were treated for severe sepsis in intensive care units (ICUs) with a corresponding hospital mortality rate of 25%. The research revealed no substantial difference in the incidence of sepsis between industrialized and developing countries[14,15]. In our study, 72 out of 219 patients exited, with an associated mortality rate of 32.9%. This high mortality rate could be attributed to the significant age distribution in infancy, a large percentage of underlying illnesses (73.1%), and majority-almost two-thirds - of the patients suffering from septic shock. Furthermore, the fact that nearly 80% of our patients needed IMV support and stayed in the PICU for a median duration of 11 days indicates that they were suffering from severe sepsis.

Table 3. Comparisons of clinical features between non-survivors and survivors

Clinical parameters median (IQR) or n (%)		**Non-survivors (n=72)**	**Survivors (n=147)**	**p-value**
Vital signs				
GCS scores, median (IQR)		8 (4-12)	13 (10-15)	**<0.001**
Pulse rate, n (%)	Normal	3 (4.2)	9 (6.1)	0.067
	Tachycardia	65 (90.3)	137 (93.2)	
	Bradycardia	4 (5.6)	1 (0.7)	
Respiratory rate, n (%)	Normal	9 (12.5)	18 (12.2)	**0.028***
	Tachypnea	58 (80.6)	128 (87.1)	
	Bradypnea	5 (6.9)	1 (0.7)	
Blood pressure, n (%)	Normal	29 (40.3)	82 (55.8)	0.089
	Hypotension	40 (55.6)	59 (40.1)	
	Hypertension	3 (4.2)	6 (4.1)	
Mean arterial pressure, n (%)	Normal	51 (70.8)	134 (91.2)	**<0.001****
	Low	20 (27.8)	11 (7.5)	
	High	1 (1.4)	2 (1.4)	
Body temperature, n (%)	Normal	7 (9.7)	23 (15.6)	**<0.001*****
	Hyperthermia	39 (54.2)	107 (72.8)	
	Hypothermia	26 (36.1)	17 (11.6)	
Oxygen saturation, median (range)		88 (78-95)	92 (86-98)	**0.003**
FiO_2 support, median (range)		80 (60-100)	50 (40-60)	**<0.001**
Organ failure, n (%)	Respiratory	69 (95.8)	103 (70.1)	**<0.001**
	Cardiovascular	64 (88.9)	94 (63.9)	**<0.001**
	Neurological	46 (63.9)	26 (17.7)	**<0.001**
	Renal	15 (20.8)	17 (11.6)	**0.068**
	Hepatic	13 (18.1)	7 (4.8)	**<0.001**
	Hematological	28 (38.9)	14 (9.5)	**<0.001**
Scoring systems, n (%)	PIM II	19.8 (9.2-65.6)	6.9 (2.4-12.7)	**<0.001**
	PRISM III	14 (6.2-22.7)	5 (3-9)	**<0.001**
	PELOD	29 (2-87.7)	1.3 (0.1-16.2)	**<0.001**
	VIS	95 (33.7-120)	10 (0-25)	**<0.001**
IMV Support, n (%)		71 (98,6)	100 (68)	**<0.001**
RBC transfusion, n (%)		61 (84,7)	117 (79.6)	**0.361**

Statistical significance due to *bradypnea, **low arterial pressure, ***hypothermia. IQR: Interquartile range, GCS: Glasgow Coma Scale, FiO_2: Fraction of inspired oxygen, PIM: Pediatric Index of Mortality, PRISM: Pediatric Risk of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, VIS: Vasoactive Inotropic Scoring, RBC: Red blood cell

Leukocytosis, anemia, thrombocytopenia, and endothelial activation are some of the hematologic alterations that can be brought on by severe sepsis[16]. A study conducted on 1073 patients to develop a new mortality scoring system of meningococcal sepsis, thrombocytopenia, aPTT, and INR elevation were shown to be among the most significant parameters in terms of predicting mortality[17]. It has been previously demonstrated D-dimer levels increase at an early stage of the disease in individuals with severe sepsis and disseminated intravascular coagulation[18]. According to our findings, anemia, thrombocytopenia, and coagulopathy were more commonly found in deceased individuals. None of these factors showed statistical significance when analyzed with logistic regression. The latest diagnostic tool, the Phoenix Sepsis Score, incorporates criteria such as thrombocytopenia, elevated INR, D-Dimer, and decreased fibrinogen levels.

Table 4. Laboratory findings in non-survivors and survivors

Laboratory parameters		**Non-survivors (n=72)**	**Survivors (n=147)**	**p-value**
White blood cell count, n (%)	Normal	26 (31.1)	62 (42.2)	0.401
	Leukocytosis	29 (40.3)	61 (41.5)	
	Leukopenia	17 (23.6)	24 (16.3)	
Anemia, n (%)		54 (75)	76 (51.7)	**0.001**
Neutrophil count, median (IQR)		6200 (4100-10300)	14400 (8000-39800)	0.193
Lymphocyte count, median (IQR)		4900 (4100-7400)	1900 (1150-12900)	0.935
Thrombocytopenia, n (%)		34 (47.2)	29 (19.7)	**<0.001**
Eosinophil count, median (IQR)		200 (150-5350)	100 (50-3000)	0.772
RDW, median (IQR)		21 (14.5-24.2)	17.2 (15.5-19.3)	0.573
MPV, median (IQR)		8.9 (7.5-9.5)	8.2 (7.5-10.8)	0.567
CRP, median (IQR)		6.2 (1.1-21.2)	11.2 (5.4-23.3)	0.712
Procalcitonin, median (IQR)		6.9 (0.3-42)	10.5 (2.3-45.2)	0.216
Glucose, median (IQR)		58 (30-77)	98 (83-182)	0.072
Urea, median (IQR)		45 (14-49)	26 (14-35)	0.176
Creatinine, median (IQR)		0.4 (0.4-0.8)	0.5 (0.4-0.8)	0.120
Sodium, median (IQR)		140 (137-146)	134 (133-139)	0.532
Potassium, median (IQR)		4.3 (3.8-6.5)	3.9 (3.7-4.5)	0.405
Calcium, median (IQR)		7.4 (7-8)	8.6 (8.3-9.3)	**0.004**
Alanine transaminase, median (IQR)		41 (17-559)	19 (15-91)	0.325
Albumin, median (IQR)		2.6 (2.4-2.9)	3.1 (2.9-3.5)	**<0.001**
Lactate dehydrogenase, median (IQR)		821 (377-5685)	336 (292-533)	**<0.001**
Troponin, median (IQR)		0.2 (0-7.1)	0.03 (0.01-0.05)	**0.001**
INR, median (IQR)		2 (1.2-5)	1.2 (1.2-1.3)	**0.010**
Prothrombin time, median (IQR)		23.3 (15.4-47.7)	15.7 (15.2-16.2)	**0.024**
aPTZ, median (IQR)		43.3 (22-54.6)	36.8 (32.1-42.8)	**0.012**
D-dimer, median (IQR)		5000 (2352-5000)	1535 (682-3823)	**0.010**
Fibrinogen, median (IQR)		285 (115-385)	414 (293-368)	**0.045**
pH, median (IQR)		7.17 (7.10-7.30)	7.43 (7.32-7.49)	**0.001**
pCO_2, median (IQR)		47 (38-55)	29 (29-48)	0.846
HCO_3, median (IQR)		17 (13-19)	22 (19-29)	**<0.001**
Lactate, median (IQR)		2.1 (1.4-5.7)	1.2 (0.9-1.6)	**0.013**
Base excess, median (IQR)		-8.3 (-13.8 - -5.8)	-3.4 (-6.4 + 5)	**<0.001**

IQR: Interquartile range, RDW: Red cell distribution width, MPV: Mean platelet volume, CRP: C-reactive protein, aPTZ: Activated partial thromboplastin time, pCO_2: Carbon dioxide partial pressure, INR: International normalized ratio

Table 5. Logistic regression analysis of statistically significant parameters and analysis of prognostic factors by ROC analysis for sepsis-related mortality in the PICU

	Logistic regression analysis of the statistically significant parameters for sepsis-related mortality in the PICU			Analysis of prognostic factors by ROC analysis for sepsis-related mortality
Parameters	**p-value**	**Odds ratio**	**95% confidence, interval**	**AUC**
PIM II	**0.010**	1.027	1.006-1.048	0.797
PELOD	**0.001**	1.024	1.010-1.038	0.794
VIS	**<0.001**	1.016	1.009-1.024	0.820
Lactate	**0.032**	1.143	1.011-1.292	0.636

PICU: Pediatric Intensive Care Unit, AUC: Area under the curve, PIM: Pediatric Index of Mortality, PRISM: Pediatric Risk of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, VIS: Vasoactive Inotropic Scoring

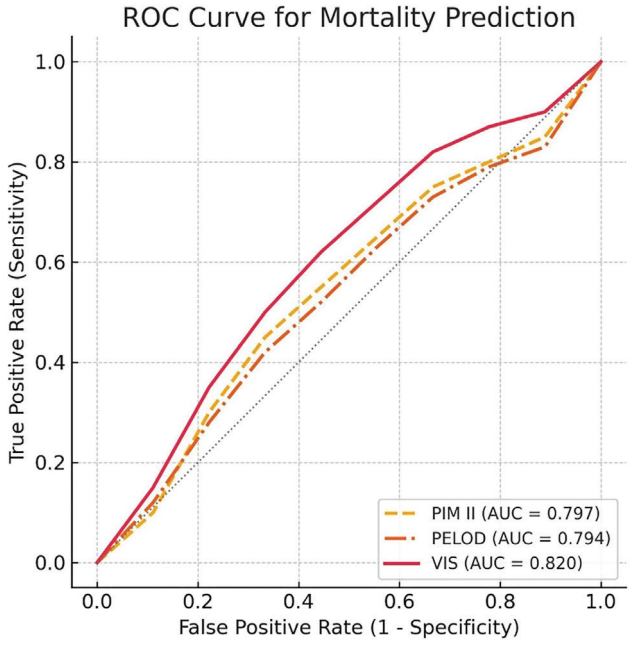

Figure 1. Receiver Operating Characteristics (ROC) curve for mortality prediction in PICU

PICU: Pediatric Intensive Care Unit, PIM: Pediatric Index of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, VIS: Vasoactive Inotropic Scoring, AUC: Area under the curve

However, our findings did not validate this score, as the Phoenix Sepsis Score is designed for diagnosis rather than predicting mortality.

Hyperlactatemia seen in the critically ill patient group diagnosed with sepsis and septic shock, is a product of anaerobic metabolism that develops secondary to inadequate oxygen distribution, resulting in cellular stress. The study conducted on 87 patients diagnosed with septic shock reported that the serum lactate levels of patients who died in the first 24 hours of admission were higher than those who died after the 24th hour with a notable reduction in the serum lactate levels in the first 24 hours of admission in surviving patients and that the longevity of lactic acidosis was the reliable indicator of non-survival[19]. According to a recent study, specifically, a lactate level of ≥4.95 mmol/L upon admission was associated with 32.5 times greater odds of developing severe outcomes, including mortality or the requirement for assisted ventilation[20]. In our logistic regression analysis, elevated lactate levels were found to be a significant predictor of mortality in pediatric sepsis patients (OR: 1.143). This OR indicates that for each unit increase in lactate levels, the odds of mortality increase by approximately 14.3%. The blood lactate AUC indicated that higher lactate levels had a fair but limited ability to discriminate between survivors and non-survivors. This finding aligns with previous studies demonstrating the prognostic value of lactate as a marker of tissue hypoxia, impaired oxygen delivery, and metabolic dysfunction in critically ill patients.

In our study, approximately 2/3 of the patients were started on at least one inotropic treatment, and most frequently dopamine was used. The estimated vasoactive inotropic score was considerably elevated in the deceased patients. In the ROC analysis, the AUC values for PIM II, PELOD, and VIS were 0.797, 0.794, and 0.820, respectively, indicating good discriminative ability in predicting mortality in pediatric sepsis patients. The VIS score demonstrated the highest predictive performance (AUC =0.820), suggesting that requirements for vasoactive support play a crucial role in mortality risk stratification. The PIM II (AUC =0.797) and PELOD (AUC =0.794) scores also showed good discrimination, reflecting the impact of multi-organ dysfunction and physiological derangement on patient outcomes. While all three scoring systems exhibited reliable predictive

Table 6. Correlations between the length of stay in the pediatric intensive care unit and the duration of mechanical ventilation support

	The length of stay in the pediatric intensive care unit		The duration of mechanical ventilation support	
Parameters	**p**	**r**	**p**	**r**
PIM II	**<0.001**	0.345	**<0.001**	0.516
PRISM III	-	-	**0.001**	0.265
PELOD	**<0.001**	0.352	**<0.001**	0.354
GCS	**0.023**	-0.224	**0.010**	-0.253
Oxygen saturation	**<0.001**	-0.337	**0.002**	-0.259
Hemoglobin	**0.008**	0.216	**-**	-
Glucose	**0.003**	0.246	**0.002**	0.259
pH	**0.015**	-0.200	**-**	-
pCO2	**<0.001**	0.407	**<0.001**	0.301
HCO3	**0.001**	0.268	**0.009**	0.215
Base excess	**0.011**	0.210	**-**	-
VIS	**0.001**	0.269	**<0.001**	0.358

GCS: Glasgow Coma Scale, PIM: Pediatric Index of Mortality, PRISM: Pediatric Risk of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, VIS: Vasoactive Inotropic Scoring

values, the superior performance of VIS highlights the importance of hemodynamic instability in the prognosis of patients with sepsis. According to the results of ROC analysis, the vasoactive inotropic score was the most efficient parameter in predicting mortality in our patient group. This finding is consistent with literature; many studies show that VIS correlates with high mortality[21,22].

Patients admitted from the emergency department had a significantly higher survival rate in our study. This may reflect earlier recognition of pediatric sepsis symptoms and timely initiation of interventions such as fluid resuscitation, antibiotherapy, and airway management. The presence of pediatric emergency physicians familiar with sepsis protocols may contribute to this improved outcome, as supported by previous studies emphasizing early diagnosis and management in emergency settings. Multiple organ failure developing based on sepsis causes a significant increase in patient mortality rates. PELOD is a scoring system that assesses the impact of organ dysfunctions in the PICU and correlates with mortality rates in research studies[23,24]. The PELOD score, which evaluates the severity of organ failures, was also found to have a mortality predictive power similar to the PIM II score in our study.

Our study supports the Phoenix Sepsis Score, which has been recently formulated with data acquired from more than 3 million pediatric patients worldwide. Phoenix Sepsis Score applies the definition of infection with life-threatening organ dysfunction, including the respiratory, cardiovascular, coagulation, and neurological systems. Cardiovascular dysfunction is based on hypotension, elevation of lactate, and the need for vasoactive medication[6,7]. The VIS score, related to the need for vasoactive medication, which is emphasized in determining these very new criteria, is the most significant criterion in our study. The four-organ failure and elevation of lactate mentioned were also found to be significant in our study.

In our study, PCO_2 correlated with the length of stay in the PICU. PIM II scores correlated with the duration of IMV support. A longitudinal study including over 10,000 patients established a comparison model for length of stay in the PICU, identifying mechanical ventilation as one of the four primary determinants among the therapeutic modalities[25]. Furthermore, a recent investigation of patients with bronchiolitis hospitalized in the PICU demonstrated a correlation between the length of stay and pH, pCO_2, and bicarbonate levels[26]. In a study of 536 patients, the parameters with the highest mortality prediction were identified as the prolonged duration of MV support, the presence of MODS, and the PIM II score. However, the correlation between PIM II and the duration of MV support was not specified[27].

Study Limitations

Our study has some limitations. The primary limitation of the current study is that it was conducted at a single center and utilized a retrospective design. Furthermore,

we were unable to apply the Phoenix Sepsis Score, which has been recently established, to our patients. However, there is a good agreement between these very new diagnostic criteria and our results. We think that additional large-scale prospective and multicenter studies are required to substantiate our findings.

CONCLUSION

In our study, the most reliable parameters to estimate mortality in children with sepsis and septic shock were VIS, PIM II and PELOD, respectively. The initial PCO_2 value showed the highest correlation with the PICU length of stay, and PIM II showed the highest correlation with the duration of IMV support.

Ethics

Ethics Committee Approval: The study approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinical Research Ethics Committee (approval number: 15, dated: 26.06.2016).

Informed Consent: Retrospective study.

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Footnotes

Author Contributions

Concept: E.U., A.B.A., Design: E.U., A.B.A., M.A., Data Collection or Processing: E.U., F.K., Ü.A., G.Ö., N.Z., F.D., Analysis or Interpretation: A.B.A., M.A., F.K., G.Ö., Literature Search: E.U., F.K., Ü.A., N.Z., F.D. Writing: E.U., A.B.A., M.A.

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Case Report

A Case of Sanfilippo Syndrome Type C and Wolfram Syndrome Type 1 and the Role of Next-Generation Sequencing in Diagnosis

Tip C Sanfilippo Sendromu ve Tip 1 Wolfram Sendromu Birlikteliği Gösteren Bir Olgu ve Tanıda Yeni Nesil Dizilemenin Rolü

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ABSTRACT

Mucopolysaccharidosis IIIC (MPS IIIC) and Wolfram syndrome type 1 (WS1) are rarely seen autosomal recessive disorders with overlapping clinical features. This case report aims to highlight the role of next-generation sequencing (NGS) in diagnosing complex phenotypes and the necessity of considering multiple genetic disorders, particularly in consanguineous populations. We present a 15-year-old male who priorly received the diagnosis of WS1, and currently exhibited dysmorphic features, intellectual disability, developmental delay, diabetes mellitus, diabetes insipidus, optic atrophy, and seizures. Clinical exome sequencing identified homozygous pathogenic variants in both *WFS1* and *HGSNAT* genes. While confirming WS1, these findings also implicated MPS IIIC as the underlying cause of symptoms unexplained by WS1. This is the first reported case of concurrent MPS IIIC and WS1. The findings underscore the critical role of NGS in diagnosing complex genetic conditions and emphasize the importance of comprehensive genetic evaluation, especially in cases with unexplained clinical variability.

Keywords: *HGSNAT*, *WFS1*, Sanfilippo syndrome type C, Wolfram syndrome type 1, next-generation sequencing

ÖZ

Mukopolisakkaridoz IIIC (MPS IIIC) ve Wolfram sendromu tip 1 (WS1), fenotipik benzerlikler gösteren nadir otozomal resesif hastalıklardır. *HGSNAT* patojenik varyantlarından kaynaklanan MPS IIIC, heparan sülfat birikimine ve ilerleyici nörodejenerasyona yol açarak davranış bozuklukları, gelişimsel gerilik ve motor disfonksiyonla kendini gösterir. *WFS1* patojenik varyantlarının neden olduğu WS1 ise, diabetes insipidus, diabetes mellitus, optik atrofi, işitme kaybı ve nörodejenerasyon ile karakterizedir. Bu çalışmada, WS1 tanısı bulunan 15 yaşında bir olgu sunulmaktadır. Olgu, dismorfik yüz özellikleri, entelektüel yetersizlik, gelişimsel gerilik, diabetes mellitus, diabetes insipidus, optik atrofi ve nöbetlerle başvurmuştur. Klinik ekzom dizilemeyle, *WFS1* ve *HGSNAT* genlerinde homozigot patojenik varyantlar saptanmış, WS1 tanısı doğrulanırken WS1 ile açıklanamayan bulguların MPS IIIC ile ilişkili olduğu ortaya koyulmuştur. Bu çalışmada sunulan olgu, MPS IIIC ve WS1'in eş zamanlı teşhis edildiği ilk olgu olup, yeni nesil dizilemenin karmaşık fenotiplerin belirlenmesindeki önemini ve özellikle akraba evliliği yüksek popülasyonlarda birden fazla genetik hastalığın değerlendirilmesi gerekliliğini vurgulamaktadır.

Anahtar kelimeler: *HGSNAT*, *WFS1*, tip C Sanfilippo sendromu, tip 1 Wolfram sendromu, Yeni Nesil Dizileme

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INTRODUCTION

Sanfilippo syndrome is primarily characterized by early-onset, severe, and progressive degeneration of the central nervous system, with subtype-specific variations. Clinical features include cortical atrophy, progressive dementia, motor dysfunction, hyperactivity, learning disabilities, aggressive behavior, sleep disturbances, and profound intellectual impairment[1]. This syndrome is linked to deficiencies in four distinct enzymes responsible for the lysosomal degradation of heparan sulfate and is classified into four genetic subtypes. Type C Sanfilippo syndrome results from biallelic pathogenic variants in the *HGSNAT* gene, leading to a deficiency of the enzyme heparan α-glucosaminide N-acetyltransferase, a lysosomal membrane protein. This deficiency causes the accumulation of heparan sulfate and subsequent cellular dysfunction[2].

Wolfram syndrome type 1 is an autosomal recessive disorder caused by pathogenic variants in the *WFS1* gene. It is characterized by diabetes mellitus (DM), optic atrophy, hearing loss, and neurodegenerative symptoms. *WFS1* encodes Wolframin, a transmembrane protein localized in the endoplasmic reticulum (ER). Wolframin plays critical roles in maintaining ER homeostasis, regulating intracellular calcium levels, and ensuring the proper folding of secretory proteins. A deficiency in Wolframin leads to cell death through ER stress and reduced insulin secretion, particularly affecting pancreatic beta cells[3,4].

The coexistence of two or more syndromes in a single individual is extremely rare. Advances in next-generation sequencing (NGS) technologies have facilitated the simultaneous diagnosis of multiple monogenic disorders by elucidating their genetic basis. In this study, we report a case initially followed with a clinical diagnosis of Wolfram syndrome. However, due to the presence of additional findings suggestive of a comorbid condition, a clinical exome panel was analyzed for other potential diseases which identified a homozygous pathogenic variant in the *HGSNAT* gene, in addition to the *WFS1* gene variant. To the best of our knowledge, this is the first documented case in the literature in which these two syndromes coexisted. This case report aims both to highlight the diagnostic challenges associated with the co-occurrence of rare syndromes and to underscore the critical role of genetic analysis in such cases.

CASE REPORT

A 15-year-old male, the third child of a consanguineous marriage (1.5-degree cousins) was referred to our clinic due to dysmorphic features, neuromotor developmental delay, moderate intellectual disability, DM, diabetes insipidus, and bilateral optic atrophy (Figure 1).

At 18 months of age, he was admitted to the hospital with an upper respiratory tract infection, where incidental hyperglycemia was detected. Further investigations revealed negative diabetes autoantibodies, and he was subsequently diagnosed with DM.

His developmental milestones were delayed, with head control achieved at 6 months, sat without support at 12 months, and walked without assistance at 18 months. Although he initially developed meaningful speech at 12 months, language regression was observed after onset of his DM. Currently, he utters nonsensical words and is unable to form complete sentences.

At age 14, an electroencephalogram revealed mild epileptic abnormalities, and magnetic resonance imaging showed increased signal intensity in the peritrigonal white matter, suggestive of prior hypoxic-ischemic injury, along with prominence of the mega cisterna magna and the occipital horns of both lateral ventricles. Fundoscopic examination confirmed bilateral optic atrophy. A visual evoked potential test indicated an absence of significant responses in the bilateral anterior visual pathways.

Whole abdominal ultrasonography showed stage 0-1 liver parenchymal echogenicity, results of hearing tests and echocardiography were unremarkable. The patient's current medications include levetiracetam, desmopressin, insulin, and melatonin.

His physical examination revealed short stature (<3rd percentile, -5.8 standard deviation score), coarse facial features, hard and dry hair, thick eyebrows, synophrys, upslanting palpebral fissures, epicanthus, long eyelashes, a depressed nasal root, macrotia, thickening of the helices, anteverted nostrils, and hypertrichosis. The patient has difficulty walking and is not independently mobile. For the past year, he has been consuming only liquid foods due to dysphagia. He has poor social interactions and academic performance, along with irritability and sleep disturbances. The patient has received four years of special education to improve his speech, cognitive development, and social skills.

His older brother, diagnosed with Wolfram syndrome type 1, exhibited symptoms of DM, diabetes insipidus, and optic atrophy but had normal motor and cognitive development.

Informed consent was obtained from the patient's parents for genetic testing and the publication of test results and clinical findings. Exome sequencing was performed on leukocyte-derived genomic DNA using the SOPHIA™ Genetics Clinical Exome Solution V2 Kit, covering 4490 genes. Sequencing was conducted on the Illumina NextSeq platform, and data analysis was performed using the SOPHIA™ DDM V4 analysis platform. Variant annotation was based on the GRCh37/hg19 human genome reference.

Identified variants were filtered according to a 1% allele frequency threshold using population databases such as dbSNP142, Human Reference Genome, 1000 Genomes Project, OMIM database, and an internal database of exomes from 3,206 individuals of

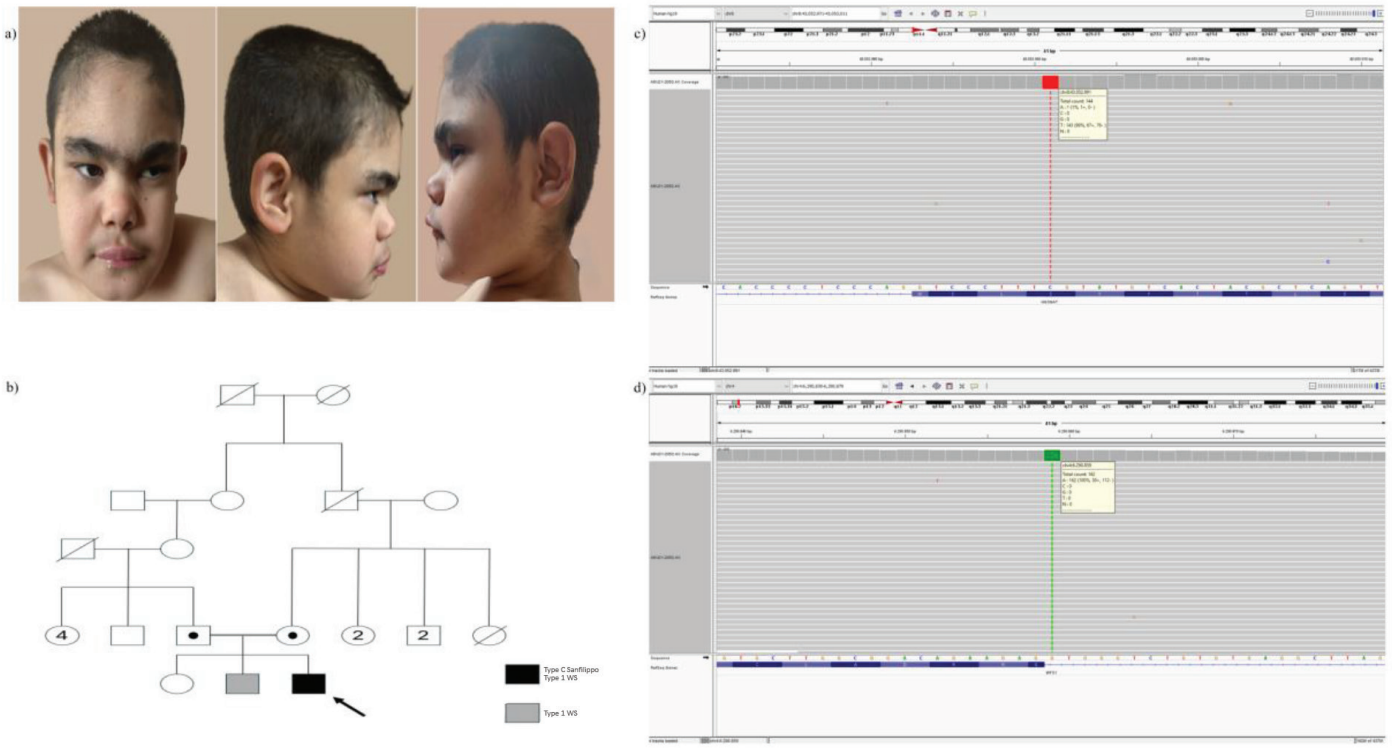

Figure 1. a) Dismorphic features of the proband. b) Proband's pedigree. c) *HGSNAT* NM_152419.2:c.1622C>T p.(Ser541Leu). d) WFS1 NM_001145853.1:c.460+1G>A

Turkish ethnicity. Sequence variant classification followed the guidelines set by the American College of Medical Genetics and Genomics.

RESULTS

As a result of NGS analysis, *HGSNAT* NM_152419.2:c.1622C>T; p.(Ser541Leu) and *WFS1* NM_001145853.1:c.460+1G>A variants were identified in homozygous form in our case (Figure 1c and d). Segregation analysis using Sanger sequencing method revealed that both parents were heterozygous carriers of these variants.

DISCUSSION

This case report highlights the coexistence of Sanfilippo syndrome type C and Wolfram syndrome type 1, two distinct autosomal recessive disorders. With the expanding use of NGS, the simultaneous identification of multiple hereditary diseases has become more feasible, offering a rapid and cost-effective diagnostic approach for complex phenotypes.

The *HGSNAT* c.1622C>T variant leads to misfolding of the heparan α-glucosaminide N-acetyltransferase enzyme, disrupting lysosomal targeting and enzymatic activity, ultimately resulting in cognitive decline[1,2,5-7]. Studies on *HGSNAT* variants have shown that misfolding-induced glycosylation defects, leading to intracellular retention and loss of function[5]. Glucosamine treatment has been suggested to partially restore enzymatic activity in some missense variants, including S541L[5].

The *WFS1* c.460+1G>A variant disrupts splicing, leading to a truncated or absent wolframin protein[8,9]. Deficiency of Wolframin protein impairs protein folding and calcium homeostasis, triggering ER stress, defective insulin secretion, and neuronal apoptosis[3,4]. The absence of diabetes autoantibodies in this case suggests diabetes is more consistently associated with Wolfram syndrome rather than classical type 1 diabetes.

A study of 24,164 cases with type 1 diabetes and 50 cases with Wolfram syndrome found that diabetes was the initial presentation in Wolfram syndrome, manifesting with optic atrophy, motor retardation, and dysphagia among the most common neurodegenerative findings. The study further reported that hearing loss and neurological/psychiatric symptoms are less frequently observed in patients with Wolfram syndrome-associated

diabetes when glycemic control is maintained (HbA1c ≤7.5)[10]. In our study, neurocognitive decline was not observed in the patient's older brother, who was diagnosed with WS1, and this was attributed to his strict glycemic control (HbA1c ≤7.5). However, in our patient, as the HbA1c level could not be kept under control as effectively as in his brother.

Hyperactivity, cognitive impairment, speech delay, and epilepsy are common in patients carrying a variant in the *HGSNAT* gene, while macrocephaly, hepatomegaly, and dysostosis multiplex are seen in more severe cases[7]. Our patient exhibited developmental and neurological symptoms but lacked several common *HGSNAT*-associated features, such as macrocephaly, sphincter control problems, recurrent infections, hepatomegaly, dysostosis multiplex, and diarrhea. Epilepsy was diagnosed approximately two years after the patient's initial presentation. Furthermore, less common findings, including hypoacusis, inguinal and umbilical hernias, and mitral insufficiency, were not observed in our case. Both Wolfram syndrome and MPS IIIC may induce neurological impairments. Literature suggests that Wolfram syndrome commonly presents with optic atrophy and hearing impairment, while MPS IIIC is associated with neurocognitive decline, hyperactivity, and speech regression. The coexistence of both disorders complicates the attribution of specific neurological findings. The fact that the same *WFS1* variant was homozygous in the patient's older brother, who had not neurological symptoms suggests that the neurological manifestations in our patient may be associated with Sanfilippo syndrome. However, there is a difference in the clinical management of Wolfram syndrome-associated diabetes between the two siblings, and it is thought that poor glycemic control in our patient may have contributed to the development of neurological findings. Naturally, individuals carrying the same variant may exhibit phenotypic variability. Therefore, further histopathological, and genetic studies on different tissues are necessary to clearly determine the underlying cause of the neurological findings.

In a study published by Çelmeli et al.[11] DM, progressing to partial central diabetes insipidus, sensorineural hearing loss, optic atrophy and bladder dysfunction have been reported in three Turkish children with *WFS1* variants. However, our case had not hearing impairment and urinary tract anomalies. Other homozygous *WFS1* cases have shown diverse urological findings[8,9,12]. Although neurogenic bladder dysfunction is frequently associated with Wolfram syndrome due to brainstem involvement[13], our patient did not manifest any signs and symptoms of remarkable bladder dysfunction. Intellectual disability of the patient may have limited the assessment of subtle urological symptoms, necessitating further urodynamic studies.

This case underscores the diagnostic challenges in distinguishing overlapping phenotypes in rare genetic syndromes. Our findings emphasize the role of NGS in identifying coexisting disorders and highlight the need for multidisciplinary approaches in evaluating complex clinical presentations.

CONCLUSIONS

This case represents the first reported coexistence of Sanfilippo syndrome type C and Wolfram syndrome type 1, emphasizing the diagnostic challenges associated with overlapping of rare genetic disorders. Our findings underscore the importance of genetic testing in cases with atypical presentations and suggest that a multidisciplinary approach is essential for optimal patient management.

Ethics

Informed Consent: Written informed consent was obtained from the parents of the child.

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Footnotes

Author Contributions

Concept: G.B., A.T., Design: Z.M.Y., G.B., A.T., Data Collection or Processing: A.M.E, Analysis or Interpretation: R.S., A.M.E., Literature Search: Z.M.Y., R.S., Writing: Z.M.Y., R.S.

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Case Report

Necrotizing Enterocolitis Due to Respiratory Syncytial Virus in a Newborn Baby

Yenidoğan Bebekte Respiratuvar Sinsitiyal Virüse Bağlı Nekrotizan Enterokolit

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ABSTRACT

Although rare, respiratory syncytial virus (RSV) infections can cause life-threatening extrapulmonary complications in otherwise healthy neonates. In this report, we describe a term infant who was admitted to the neonatal intensive care unit with transient tachypnea of the newborn but developed respiratory failure due to RSV bronchiolitis on follow-up which was complicated with necrotizing enterocolitis (NEC) and intestinal perforation. We want to draw attention to the development of NEC in a previously healthy term newborn infant with severe RSV disease, even in the absence of traditional risk factors. We hypothesize that the dysregulated pro-inflammatory response associated with severe RSV disease may alter intestinal blood flow and normal healthy microbial flora compromising mucosal epithelial cell barrier against bacterial translocation. Enteral feeding intolerance and septic ileus may represent important clinical outcomes in these patients.

Keywords: Respiratory syncytial viruses, necrotizing enterocolitis, bronchiolitis

ÖZ

Her ne kadar nadir olsa da, solunum sinsityal virüsü (RSV) enfeksiyonları, sağlıklı yenidoğanlarda yaşamı tehdit edebilecek akciğer dışı komplikasyonlara neden olabilir. Bu olguda, doğumdan sonra geçici takipne (TTN) tanısıyla yenidoğan yoğun bakım ünitesine (YYBÜ) yatırılan, ancak takip sürecinde RSV bronşiolitine bağlı solunum yetmezliği gelişen ve bu durumun nekrotizan enterokolit (NEK) ile bağırsak perforasyonu gibi komplikasyonlara yol açtığı bir zamanında doğmuş yenidoğan olgu sunulmuştur. Bu olgu ile, geleneksel risk faktörleri olmaksızın, daha önce tamamen sağlıklı olan zamanında doğmuş bir yenidoğanda ciddi RSV hastalığı sonrasında NEK gelişebileceğine dikkat çekmek istiyoruz. Hipotezimize göre, ciddi RSV hastalığı ile ilişkili düzensizleşmiş pro-enflamatuvar yanıt, bağırsak kan akımını ve sağlıklı mikrobiyotayı değiştirebilir; bu da mukozal epitel hücre bariyerinin bakteriyel translokasyona karşı direncini zayıflatabilir. Bu hastalarda enteral beslenme intoleransı ve septik ileus, önemli klinik sonuçlar olarak ortaya çıkabilir.

Anahtar kelimeler: Solunum sinsityal virüsleri, nekrotizan enterokolit, bronşiolit

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INTRODUCTION

Respiratory syncytial virus (RSV) is the leading infectious agent causing lower respiratory tract infections (LRTIs) and hospitalizations in infants, particularly those under one year of age[1]. The global RSV hospitalization rate for children under five years of age is 0.4% per year, highest among infants under six months (2%) and preterm infants under one year (6%)[2]. While RSV bronchiolitis is usually self-limiting, severe cases are more common in high-risk groups, including preterm infants, those with chronic lung or heart disease, immunodeficiencies, or daycare exposure[3]. Predicting the risk of serious complications of RSV infection is challenging. Gastrointestinal (GI) complications are rare, and necrotizing enterocolitis (NEC) has only been reported in a few cases[4]. NEC primarily affects preterm infants due to their immature intestines, but its pathogenesis in term infants is often linked to poor mesenteric oxygenation and underlying conditions like perinatal asphyxia, congenital heart disease, or sepsis. NEC in healthy term infants without risk factors is exceptionally rare[5]. This report presents a term newborn who developed NEC due to RSV-related late-onset nosocomial sepsis. Recognizing this rare but

severe complication with manifestations distinct from typical RSV respiratory symptoms can help clinicians identify at-risk infants at an early stage of the disease, enhance clinical suspicion, and initiate timely, life-saving interventions.

CASE REPORT

A male infant, born from a gravida 3, para 1 29-year-old mother via C-section at 38^{+1} weeks gestation, weighing 3035 g showed signs and symptoms of respiratory distress requiring nasal application of continuous positive airway pressure (nCPAP) after the initial postnatal stabilization steps in the delivery room. He was then transferred to the neonatal intensive care unit (NICU) for advanced respiratory support with the diagnosis of transient tachypnea of the newborn (TTN). Apgar scores at the first and fifth postnatal minutes were 9 and 10 points, respectively. He was provided with non-invasive ventilation support via nasal application of intermittent positive pressure ventilation (nIPPV). Initial physical examination revealed symptoms and signs of tachypnea, tachycardia, grunting, and intercostal retractions. The peripheral oxygen saturation (SpO_2) was between 90% and 95% under 25% oxygen support. Arterial blood gas analysis, chest X-ray and transfontanel ultrasound were normal. Cardiac echocardiogram revealed a small perimembranous inlet ventricular septal defect with a mild-moderate shunt and secundum atrial septal defect (ASDII) which did not cause any hemodynamic instability. Normal chest X-ray, complete blood count ,peripheral blood smear findings, as well as negative acute phase reactants and blood culture ruled out presence of early-onset neonatal sepsis and congenital pneumonia.

After application of non-invasive mechanical ventilation support for one day, the infant was transitioned to room air. His nutritional support was provided with total parenteral nutrition (TPN) on the first day of life. On day 2, minimal enteral feeding with a volume of 20 mL/kg was started with breast milk and increased gradually, reaching full feeds by day 3. From postnatal day 2, he was brought to his mother who provided kangaroo care for her infant

On postnatal day 6, the infant developed lethargy, feeding intolerance with emesis and abdominal distension, tachypnea, and grunting. Laboratory tests for late-onset nosocomial neonatal sepsis revealed leukocytosis, thrombocytopenia, elevated C-reactive protein and procalcitonin. Blood gas analysis was compatible with respiratory acidosis. Chest X-ray findings included prominent bilateral bronchovascular markings, air trapping, and patchy densities in the right lung. Abdominal X-ray showed an abnormal gas pattern with dilated and edematous bowel loops, consistent with septic ileus. However, there were no signs of pneumatosis intestinalis, portal venous gas, or spontaneous intestinal perforation. Oral feeding was discontinued, and TPN as well as empiric combination antibiotherapy with broad-spectrum antibacterials (vancomycin + meropenem) was initiated after taking blood, urine and cerebrospinal fluid cultures. Gastric decompression using intermittent nasogastric suction was performed. Non-invasive ventilation support was provided with nIPPV. Abdominal ultrasound revealed free fluid between the bowel loops, bowel wall thickening and edema with increased echogenicity. The infant was started on pentoxifylline and intravenous immunoglobulin as adjunctive therapies for sepsis. A nasopharyngeal swab was sent for differential diagnosis of respiratory viruses including severe acute respiratory syndrome-coronavirus-2 after learning that his mother had mild symptoms like runny nose and sore throat suggestive of acute upper respiratory tract infection during her visit to the NICU. The polymerase chain reaction (PCR) test was found to be positive for RSV. The stool PCR test for enteric pathogens as well as blood, urine and cerebrospinal fluid cultures were all negative. On follow-up, the infant developed mixed acidosis and circulatory compromise requiring vasopressor support, endotracheal intubation, and invasive mechanical ventilation. Replacement therapy with appropriate blood products was administered for the management of anemia and thrombocytopenia. On postnatal 8^{th} day, abdominal distension worsened significantly, and additional physical signs suggesting further clinical deterioration such as abdominal wall erythema, crepitus, and induration were observed. The diagnosis of bowel perforation was confirmed by the abdominal radiography that revealed free air under the diaphragm consistent with the diagnosis of pneumoperitoneum. Due to intestinal perforation, the infant underwent exploratory laparotomy with resection of the affected intestinal region and end-to-end anastomosis without the need for ileostomy or colostomy. Postoperatively, he received ongoing medical management, including supportive care and antibiotherapy.

Intraoperative findings revealed a segmental necrosis and perforation of the distal ileum. Approximately 5 cm of the affected bowel was resected, followed by a primary end-to-end anastomosis. Any signs of diffuse peritonitis, abscess or additional pathology were not observed in the remaining bowel segments. A pelvic drain was

placed at the conclusion of the surgery. Post-operative care included continued TPN and antibiotherapy. On post-operative day 5, a contrast enema was performed to assess anastomotic integrity and rule out stricture and any post-operative complications were not observed. Enteral feeding was initiated on postoperative day 10 at a dose of 10-20 mL/kg TPN and its dose was gradually increased based on the patient's tolerance. By postoperative day 17, full enteral feeding was achieved. The infant was discharged in good health on postnatal day 30.

Written informed consent was obtained from the infant's parents for publication of this case report.

DISCUSSION

NEC is one of the most common GI emergencies with devastating results in the newborn. Most cases occur in very low birth weight (VLBW) preterm infants (birth weight <1500 g) born at <32 weeks of gestation, however approximately 10% of cases occur in term infants[5]. Term infants who develop NEC typically have preexisting illnesses such as perinatal asphyxia, intrauterine growth restriction, congenital heart disease, sepsis, hypotension, gestational diabetes, polycythemia, history of blood transfusions, or maternal drug use[5]. The case we present here is a full-term male infant who did not have any of the traditional risk factors for NEC. The infant was delivered via C-section, with high Apgar scores and without any need for resuscitation. He was admitted to the NICU for TTN. Non-invasive ventilation was used briefly at minimal settings for 24 hours, after which he was transitioned to room air. No signs of congenital pneumonia or early-onset neonatal sepsis were observed. He exclusively received breast milk, which is known to reduce NEC risk by promoting gut health through its prebiotic and probiotic components. Enteral feeds were introduced minimally on day one and gradually increased to full feeds.

RSV infections in infants usually present as upper respiratory symptoms progressing to bronchiolitis. Extrapulmonary manifestations of RSV are quite uncommon[4]. Severe cases, particularly affecting preterm or immunocompromised infants, may cause apnea, respiratory failure, myocarditis, arrhythmias, encephalopathy, seizures, jaundice, or GI complications like gastroenteritis. However, RSV-related NEC is exceptionally rare[6]. Although NEC is most frequently seen in preterm infants, there are only a few reported cases linking RSV to NEC in term neonates. For instance, Eisenhut[4] described extrapulmonary complications of RSV, including NEC, but most cases occurred in premature infants[4]. Lambert et al.[5] and Abbo et al.[7] also reviewed cases of NEC in full-term neonates, yet a causal relationship between their cases with NEC, and RSV was not explicitly confirmed.

Arias et al.[8], described 4 previously healthy, term and late-preterm infants in all hospitalized with respiratory failure due to RSV bronchiolitis and developed NEC on follow-up. This article is striking in terms of demonstrating the devastating results of RSV. Indeed, although 3 infants presented in this article were discharged from the hospital without further complications; 1 infant died of septic shock. These findings underscore the importance of recognizing RSV as a potential but underreported trigger for NEC in term infants.

One hypothesis linking RSV to NEC suggests that an immature immune system, especially in premature infants, struggles to control viral replication, leading to development of severe disease[9]. This case is notable because the infant was full-term and previously healthy yet developed a severe RSV infection triggering a systemic inflammatory response. Since he showed signs and symptoms of severe sepsis such as mixed acidosis, hypotension, bicytopenia, and coagulopathy soon after the onset of the diseas, he likely had a high viral load. Pro-inflammatory mediators have the potential to damage protective barriers in the gut, alter intestinal blood flow, and reduce the expression of tight junctions, leading to increased gut permeability and bacterial translocation[10]. RSV infection in our patient likely caused immune dysregulation and excessive pro-inflammatory cytokine production, compromising gut barrier integrity and promoting bacterial translocation. These mediators further aggravated intestinal injury, leading to bowel necrosis and perforation.

Another potential mechanism is RSV-induced hypoxia and hypoperfusion[11]. Although the infant was initially managed with non-invasive ventilation, he later required intubation due to mixed acidosis and hypotension. Although his blood gas analysis measurements were within normal range. and SpO_2 targets were reached with minimal ventilator settings, he might have experienced a transient hypoxic phase potentially impairing the integrity of the intestinal mucosal barrier and promoting perforation.

It has been demonstrated that the lung-gut microbiota axis plays an important role in the development, regulation, and maintenance of healthy immune responses. In their review, Marsland et al.[12] have

suggested the presence of a "vital cross-talk" between the mucosal tissues of our body by exemplifying intestinal complications developed during respiratory disease and vice versa[12]. Some respiratory viral infections like influenza are shown to accompany intestinal symptoms in the course of the disease due to alterations in intestinal microenvironment and induction of intestinal immune injury through microbiota-mediated inflammatory processes[13]. In our case, RSV may have caused intestinal mucosal injury via similar pathways resulting in intestinal perforation. Animal studies and *in vitro* models provide mechanistic support for this hypothesis. For example, Chiba et al.[14] demonstrated that RSV infection in mice alters the composition of gut microbiota and aggravates systemic inflammation, increasing intestinal permeability. Similarly, Groves et al.[15] reported that RSV can induce toll-like receptor signaling and cytokine dysregulation in intestinal epithelial cells, compromising mucosal integrity. These findings support the notion that RSV-induced dysbiosis and immune activation may contribute to NEC pathogenesis, even in the absence of traditional risk factors.

Our patient was a full-term healthy infant with no other comorbidities except mild TTN. All standard delivery room and neonatal intensive care interventions were appropriately applied, including non-invasive ventilation, early kangaroo care, and exclusive breastfeeding. Empiric antibiotherapy was avoided. Despite these optimal disease management strategies, high viral load with RSV led to an induction of exaggerated inflammatory response that ultimately resulted in intestinal perforation. In conclusion, severe RSV disease in newborns can result in NEC, even in the absence of traditional risk factors. Clinicians should consider the possibility of NEC in infants who develop feeding intolerance and abdominal distension during RSV infection and take appropriate precautions.

Given the potential for RSV to cause severe complications such as NEC even in term infants, implementation of preventive strategies carries crucial importance. In addition to maternal immunization during pregnancy, which facilitates the transplacental transfer of RSV-specific antibodies, the use of long-acting monoclonal antibodies like nirsevimab directly in newborns has also shown promise in protecting against severe RSV disease. The Centers for Disease Control and Prevention recommends RSV vaccination during 32-36 weeks of gestation and also supports the use of nirsevimab in infants born during or entering their first RSV season. These complementary approaches hold promise in mitigating not only common respiratory symptoms but also rare and life-threatening complications such as NEC in term neonates.

Ethics

Informed Consent: Written informed consent was obtained from the infant's parents for publication of this case report.

Footnotes

Author Contributions

Surgical and Medical Practices: M.B.Ö., Ö.O., Concept: M.B.Ö., D.E., Ö.O., Study Design: M.B.Ö., D.E., Ö.O., Data Collection or Processing: M.B.Ö., Ö.O., Analysis or Interpretation: M.B.Ö., D.E., Ö.O., Literature Search: M.B.Ö., D.E., Ö.O., Writing: M.B.Ö., Ö.O.

Conflict of Interest: The authors have no conflict of interest to declare.

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Case Report

A Rare Case of Cystic Hygroma and Familial Nystagmus in a Newborn with *SHOC2* Gene Mutation

SHOC2 Gen Mutasyonu ile İlişkili Kistik Higroma ve Ailevi Nistagmus: Nadir Bir Olgu Sunumu

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ABSTRACT

Cystic hygroma (CH) is a lymphatic malformation commonly associated with various genetic disorders, including RASopathies-syndromes caused by mutations in the RAS-MAPK signaling pathway. We present a neonate referred to our center due to CH and dysmorphic facial features. During follow-up, interventricular septal hypertrophy and nystagmus were identified. Molecular analysis revealed a pathogenic c.4A>G (p.Ser2Gly) variant in the *SHOC2* gene. This mutation is associated with a rare subtype of RASopathies known as Noonan-like syndrome with loose anagen hair. Although four additional male relatives also exhibited nystagmus, sequencing of the *FRMD7* gene and whole-exome analysis did not reveal any other pathogenic variants associated with nystagmus, highlighting the clinical complexity of the case. This report emphasizes the importance of considering the possibility of dual diagnoses in cases presenting with complex clinical features. It also underscores the value of prioritizing multigene panel testing in patients with overlapping phenotypes among RASopathy subgroups, where phenotypic distinctions remain unclear.

Keywords: SHOC2, cystic hygroma, Noonan-like Syndrome with loose anagen hair, Ser2Gly

ÖZ

Kistik higroma (KH), genellikle RAS-MAPK sinyal yolundaki mutasyonlardan kaynaklanan sendromlar olan RASopatiler de dahil olmak üzere çeşitli genetik bozukluklarla ilişkilendirilen bir lenfatik malformasyondur. Yenidoğan döneminde KH ve dismorfik yüz görünümü nedeniyle tarafımıza yönlendirilen olguda, takip sürecinde interventriküler septal hipertrofi ve nistagmus saptanmış; moleküler analiz sonucunda *SHOC2* geninde patojenik c.4A>G (p.Ser2Gly) varyantı belirlenmiştir. Bu mutasyon, RASopatilerin nadir bir alt tipi olan gevşek anagen saçlı Noonan benzeri sendrom ile ilişkilidir. Olgumuz dışında ailede dört erkek bireyde nistagmus saptanmasına rağmen, *FRMD7* gen dizi analizi ve tüm ekzom dizilemesi sonucunda nistagmusla ilişkili ek patojenik varyant saptamamış ve bu durum olgunun klinik karmaşıklığını ortaya koymuştur. Bu rapor, karmaşık klinik tablolar sergileyen olgularda çift tanı olasılığının dikkate alınmasının önemini vurgulamakta ve RASopati alt grupları arasında fenotipik özelliklerin henüz net bir şekilde ayrışmadığı hastalarda multigen panel testlerinin öncelikli olarak değerlendirilmesini önermektedir.

Anahtar kelimeler: SHOC2, kistik higroma, gevşek anagen saçlı Noonan benzeri sendrom, Ser2Gly

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INTRODUCTION

Cystic hygroma (CH), is a vascular/lymphatic malformation defined by dilated lymphatic ducts resulting from inadequate communication between the lymphatic and venous systems. It can occur anywhere in the body but tend to occur mainly in the neck and axilla. It has an incidence of approximately 1 in 1,000 to 6,000 live births and 1 in 750 miscarriages[1]. CH can occur as an isolated entity, or in association with fetal structural anomalies. They have been found to be associated with

certain conditions, such as chromosomal aneuploidies, hydrops fetalis, intrauterine death or other genetic disorders[2].

RAS-MAPK signaling pathway-related disorders should be considered when prenatal ultrasonography reveals findings such as increased nuchal translucency or CH. Noonan syndrome [(NS), OMIM 163950] is the most frequently seen RASopathy. However, NS is genetically heterogeneous, with over ten genes (such as *PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1,* and *CBL*) linked to this condition or closely related disorders, including LEOPARD syndrome [(LS); OMIM 151100] and Noonan-like syndrome with loose anagen hair [(NS/LAH), OMIM 607721][3]. NS/LAH syndrome, a rare type of RASopathy, shares features reminiscent of NS and is characterized by a distinct pattern of ectodermal anomalies[4]. This condition is primarily caused by mutations in the *SHOC2* gene which encodes a protein composed mainly of leucine-rich repeats (LRRs), organized in a sequence that forms a domain crucial for protein-protein interactions[5].

To date, approximately ten pathogenic or likely pathogenic variants of the *SHOC2* gene have been identified. Notably, among these variants, a recurrent activating mutation in *SHOC2* gene, ie. p.Ser2Gly, has been commonly observed in NS/LAH patients[6]. Herein, we have presented a case of a patient with excessive loose neck skin tissue and familial nystagmus, who was prenatally diagnosed with CH and found to have a mutant variant of *SHOC2* gene.

CASE REPORT

A newborn was referred to our genetic department due to her dysmorphic features. She was born via cesarean section at 35 weeks of gestation, with a birth weight of 3950 gr (2.78 SDS). She was the fourth child of healthy, consanguineous parents. During antenatal follow-up, CH was detected at 13 weeks of gestation, and chorionic villus sampling did not reveal any numerical anomalies on karyotype analysis. Additionally, polyhydramnios was noted at 34 weeks of gestation. The patient had APGAR scores of 6 and 7 at the postnatal first and fifth minutes, respectively, and was intubated for 2 days due to respiratory distress. On physical examination, her height was 49 cm (0.93 SDS), and her head circumference was 33 cm (0.44 SDS). Dysmorphic facial features included a coarse face, hypertelorism, downslanting palpebral fissures, low-set ears with prominent ear lobes, flattened and wide nasal root, long philtrum and microretrognathia. She also presented with a flat occiput, deep palmar creases, short neck and excessively loose neck skin tissue [Figure 1. (A, H)].

Ocular examination was unremarkable, and a hearing test indicated bilaterally normal hearing acuity. Abdominal and transfontanel ultrasonography (TFUS) showed no abnormalities. Echocardiography revealed a thin patent ductus arteriosus (PDA) and patent foramen ovale (PFO). Results of karyotype analysis performed to exclude sex chromosome abnormalities, were unremarkable. Based on her physical manifestations, a disorder related to the RAS-MAPK signaling pathway was considered. We conducted a targeted gene panel for RASopathies and a pathogenic mutation in the *SHOC2* gene, c.4A>G;p.Ser2Gly, was detected (Figure 1. J). Segregation analysis showed that both parents had wild type sequence.

She achieved head control at 3 months of age, and began sitting with support by six months. At 8 months of age, her weight was 6.4 kg (-1.8 SDS), her height was 65 cm (-1.4 SDS), and her head circumference was 43.5 cm (-0.17 SDS). Due to her relative macrocephaly, a repeat TFUS was performed, which showed enlargement of the lateral, third, and fourth ventricles. Cranial magnetic resonance imaging revealed no abnormalities other than a mildly enlarged ventricular system. Subsequently, echocardiography was repeated and interventricular septal hypertrophy was detected. The patient also presented with eczema, sparse hair, sparse eyebrows (Figure 1. C, F) and nystagmus. Her family history revealed that four other family members had also nystagmus (Figure 1. I). Since, all affected family members with nystagmus were male except our patient, we initially performed sequence analysis for *FRMD7* gene. However, no pathogenic variants of FRMD7 were identified. We then performed whole exome sequencing (WES) to explore other potential genetic causes of nystagmus , but this test also failed to identify any relevant gene variants.

DISCUSSION

In this study, we reported a patient presenting with familial nystagmus and excessive loose neck skin tissue, distinctive facial features, attributed to *SHOC2* gene mutation, a rare cause of RASopathy. Ensuring the integrity of RAS-MAPK signaling pathway, in which *SHOC2* gene plays a role, is essential for maintaining both early and late developmental processes, including organ formation, morphological determination, synaptic plasticity, and growth[5].

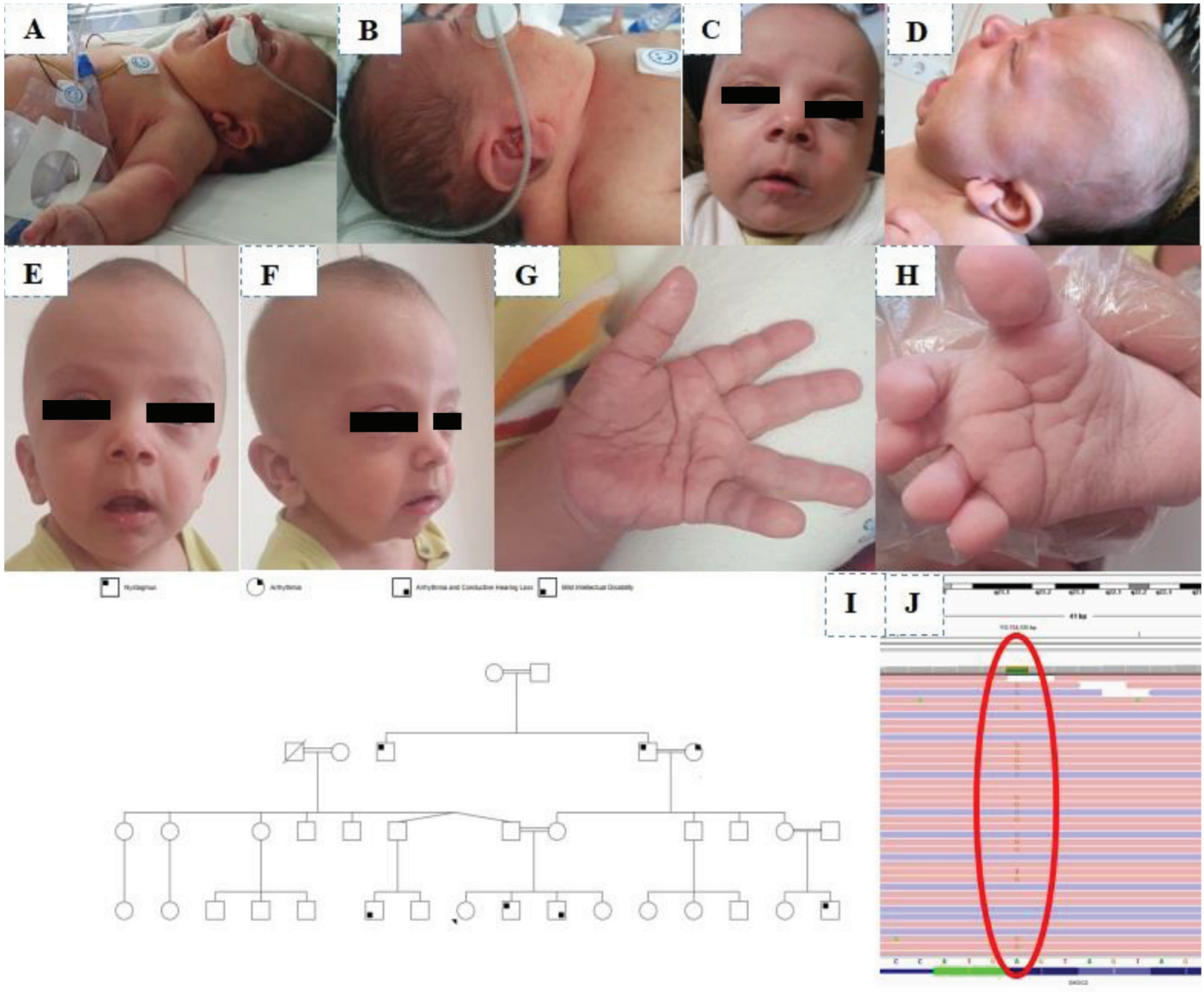

Figure 1. The main characteristic facial features of the patient, the patient's pedigree, and an IGV image of the genomic region corresponding to the *SHOC2* gene (c.4A>G; p.Ser2Gly) are shown. A photograph of the patient on the second day demonstrates low-set ears with prominent earlobes, a short neck, and excessive loose skin tissue around the neck **(A, B)**. Photographs of the patient at the fifth months **(C, D)** and eleventh months **(D, E)** of age show sparse hair, sparse eyebrows, hypertelorism, down-slanting palpebral fissures, low-set ears with prominent earlobes, a flattened and wide nasal root, a long philtrum, microretrognathia, and a short neck. Deep palmar and plantar creases are also visible **(F, G)**. The pedigree of the patient and family members with nystagmus are shown **(I)**. An IGV image of the genomic region corresponding to the *SHOC2* gene (c.4A>G; p.Ser2Gly) is provided **(J)**

IGV: Integrative genomics viewer

Mutations in *PTPN11* coding gene are identified in 2% of fetuses with increased nuchal translucency and in 16% of those with CH. Additionally, *de novo* mutations in *PTPN11*, *KRAS*, or *RAF1* genes were detected in 17.3% of fetuses with a normal karyotype and abnormal prenatal ultrasound findings such as increased nuchal translucency, hydrothorax, polyhydramnios, CH, cardiac anomalies, hydrops fetalis, and ascites[7]. In our patient, prenatal assessments revealed CH and polyhydramnios. Postnatally, the patient exhibited dysmorphic facial features including coarse facial findings, hypertelorism, downslanting-palpebral fissures, low-set ears with prominent ear lobes, flattened and wide nasal root and a webbed neck compatible with the diagnosis of NS.

A targeted gene panel for RASopathy-related disorders identified a pathogenic *SHOC2* gene variant (c.4A>G; p.Ser2Gly), which is commonly observed in NS/LAH patients. Clarifying ectodermal findings associated with SHOC2 mutations in the neonatal period remains challenging. Given the clinical overlap and molecular heterogeneity in RASopathy patients, we recommend the use of multigene panels for the establishment of a faster and more accurate diagnosis when phenotypic features suggest NS.

Structural cardiac anomalies and hypertrophic cardiomyopathy have been frequently reported in cases with RASopathies. Most patients with NS/LAH have congenital heart defects, particularly mitral valve dysplasia and septal defects[5,8]. An initial echocardiography of our patient revealed the presence of a PFO and a thin PDA. Follow-up echocardiography showed closure of both the PFO and PDA, but also identified thickening of the interventricular septum. This finding underscores the importance of regular and periodic systemic evaluation in such cases, with particular attention to monitoring for the likely presence of hypertrophic cardiomyopathy and its potential complications.

Emerging evidence suggests that patients with NS may present with a wide spectrum of ocular manifestations. However, refractive errors are the most prevalent ocular abnormalities in patients with NS. In a recent study, nystagmus was observed in 16 out of 105 patients, with 2 of these patients carrying a SHOC2 mutation[9]. In our study, both the patient and many of her family members exhibited nystagmus. Given the family history, the nystagmus observed in this case was considered more likely to be associated with a different etiology than the SHOC2 mutation.

Unfortunately, FRMD7 sequence analysis and WES analysis did not identify any likely pathogenic/pathogenic variant that could be linked to the nystagmus. Therefore, follow-up reanalysis of the patients WES data and further molecular studies for the affected family members were planned.

CONCLUSION

In conclusion, abnormalities of the lymphatic system, including CH and lymphedema, in conjunction with hypertrophic cardiomyopathy, should prompt consideration of a RASopathy. During the neonatal period, due to the absence of distinctive phenotypic features across RASopathy subgroups, the use of a targeted gene panel analysis should be prioritized as the primary diagnostic tool. Moreover, although concomitant findings such as nystagmus have been reported in association with RASopathies, it is imperative to thoroughly ascertain whether similar clinical manifestations are present in family members to avert the potential oversight of a dual diagnosis.

Ethics

Informed Consent: Written consent was obtained from the patients' parents for the use of their medical data and photographs.

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Footnotes

Author Contributions

Surgical and Medical Practices: S.S., C.A., Concept: C.Y.U., S.G., Design: F.H., S.G., Ö.G.B., Data Collection or Processing: S.S., S.G., C.A., Analysis or Interpretation: F.H., C.Y.U.,Ö.G.B., Literature Search: F.H., C.A., C.Y.U., Ö.G.B., Writing: S.S.

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