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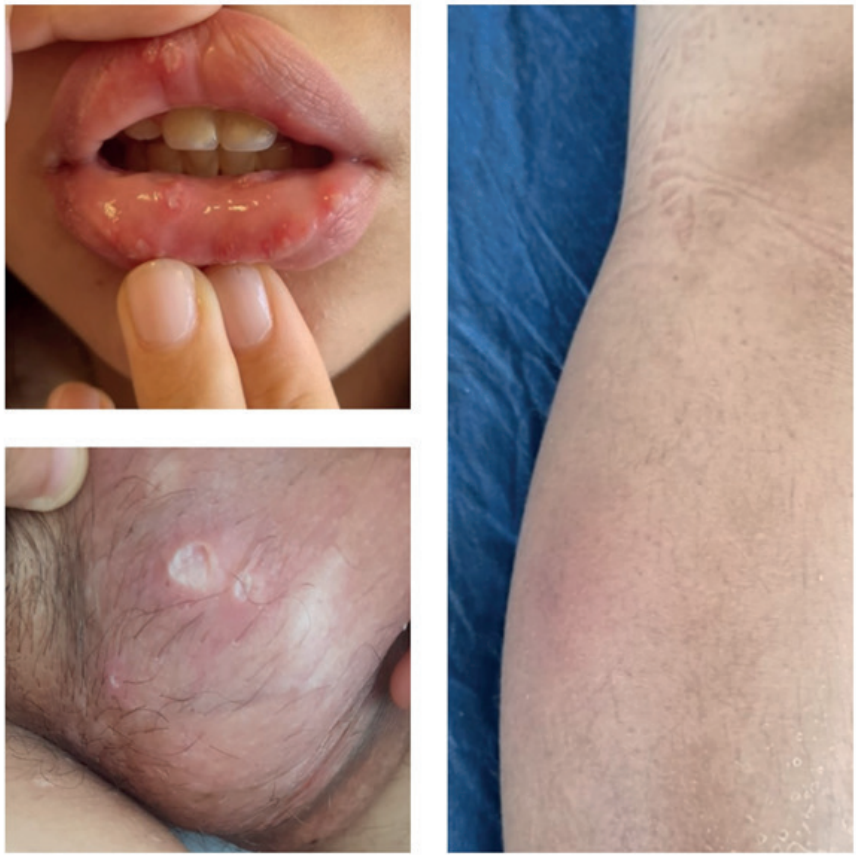

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Review

Pediatric Behçet's disease

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ABSTRACT

Behçet's disease (BD) is a vasculitis that affects vessels of any size. It is more frequent along the ancient Silk Road, extending from the Far East to the Mediterranean basin. Its etiopathogenesis is complex, and both the innate and adaptive immune systems play a role in recurrent hyperinflammation. The significant association between human leukocyte antigen B-51 and BD indicated a strong genetic background in pathogenesis. Although mucocutaneous involvement is the most common finding, it may present with a broad spectrum of clinical signs and symptoms involving the ocular, vascular, musculoskeletal, neurologic, and gastrointestinal systems. Pediatric cases may present with an incomplete clinical picture of the BD, making diagnosis difficult for the physicians. Several classification criteria have been published so far. In 2015, a classification criteria set for pediatric BD (PEDBD) was established for the first time.

The treatment strategies vary depending on the severity and type of organ involvement. The treatment should be arranged with a multidisciplinary approach according to the organs involved. Also, the possibility of developing morbidity and mortality requires early diagnosis, appropriate treatment, and close follow-up. In this review, we aimed to discuss the etiopathogenesis, clinical findings, diagnostic criteria, and treatment approach of pediatric BD based on current data.

Keywords: Behçet's disease, pediatric

INTRODUCTION

Behçet's disease (BD) is a vasculitis with systemic inflammation that can affect arteries and veins of all sizes.[1] The most common clinical findings are oral and genital aphthae, skin involvement, arthritis, uveitis, and thrombophlebitis. It is known that mucocutaneous involvement is more common, especially in pediatric cases.[2] The distribution of BD in the world coincides with the historical Silk Road (area between the Mediterranean region and the Far East). The disease often occurs in young adulthood between the ages of 20 and 40; however, about one-fifth of patients have a pediatric-onset BD.[3,4] Pediatric BD differs from adult-onset BD in terms of clinical findings, treatment approach, and outcome. Considering that BD can involve many organ systems, the treatment approach should be planned with a multidisciplinary perspective for the affected organ system.[5,6]

Epidemiology

The frequency of BD varies from country to country, and Turkey has the highest prevalence in the world with 20-420/100000.[7,8] Then, the countries with the highest prevalence are the Middle Eastern countries and Saudi Arabia. The frequency was 15.9/100000 in Italy, 5.2/100000 in the USA, and 0.9/10000 in the UK.[9] The actual prevalence of BD in children is not yet known. The pediatric BD prevalence in the United Kingdom and the

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Republic of Ireland has been reported as 4.2 per million.[10] The majority of pediatric BD cases presented in the literature have been reported from Iran, Turkey, Italy, France, and England.[2,11-16]

Etiopathogenesis

Although the etiopathogenesis of BD has not been clearly clarified, it is noteworthy that it has common features of autoimmune and autoinflammatory diseases. As in autoimmune diseases, immunosuppressive agents are helpful in the treatment, autoantigen and antigen-specific T cells play a role in the pathogenesis. It resembles autoinflammatory diseases with its course with inflammatory attacks and increased neutrophil activity and interleukin 1B (IL-1B) activity during exacerbations.[17,18] Also, the absence of autoantibodies implicated in the pathogenesis of BD suggests that BD may have an autoinflammatory nature.

The disease occurs in genetically predisposed individuals, triggered by environmental factors such as infection.[19,20] Herpes simplex virus -1 (HSV-1) and streptococcus species are infectious agents clearly associated with BD.[21] Professor Hulusi Behçet is the first author to describe the relationship between BD and infectious diseases.[22] Similarities were found between Streptococcus sanguinis, a subspecies of Streptococcus species, and human proteins such as heat-shock protein.[21] Antibodies against S. sangius and S. pyogenes were higher in patients with BD compared to the control group.[23] Moreover, the first symptoms observed in the oral mucosa in most of the patients suggested to the researchers that the oral microbial flora may play a role in the pathogenesis.[24] Recent studies have shown that gut microbiota content also plays a role in the pathogenesis of BD.[25,26]

Clustering of BD, especially in a certain geography, suggests the importance of genetic features in pathogenesis. Human leukocyte antigen (HLA) B-51, located in MHC class I, is the gene region with the most evidence for the disease.[27] Genome-wide association studies (GWAS) found that polymorphisms observed in non-HLA genes were also higher in individuals with BD.[28,29] Endoplasmic reticulum aminopeptidase 1 (ERAP1) genetic variation is one of the loci associated with BD. In addition to BD, ERAP-1 has also been shown to be associated with psoriasis and ankylosing spondylitis.[30,31] ERAP-1 polymorphism affects T-cell and natural killer cell identification.[32-35] Single nucleotide polymorphisms of interleukin 10 (IL-10) and IL-23/IL-12RB2 gene were also associated with BD in Turkish and Japanese patients.[18,36] Other genetic causes known to be associated with BD include STAT4 gene expression, which is associated with IL-17 production, and changes in the promoter region of tumor necrosis factor.[18,37]

Clinical features

Although the distribution of clinical findings varies from country to country, mucocutaneous involvement is the most common finding in pediatric BD patients.[1] Recurrent oral aphthous stomatitis is observed in almost all patients (Figure 1).[15,20,38,39] It is typically characterized by painful ulcers on the lips, tongue, and palate, and the lesions usually heal within 3-10 days. Sometimes, healing may take weeks, but scarring is not observed. While oral aphthous stomatitis was mandatory in the diagnostic criteria of BD until 2014, this requirement has been removed with the criteria of The International Criteria for Behçet's Disease (ICBD) set in 2014.[40] According to the consensus classification criteria of pediatric Behçet's disease (PEDBD), oral aphthae are accepted as diagnostic criteria if at least three attacks per year.[15] Oral ulcers can be triggered by infections, stress, fatigue, and certain foods such as eggplants, nuts, tomatoes, and hot peppers.[41]

The frequency of genital ulcers ranges from 33% to 82% in various case series (Figure 1).[42] In the results of a 10-year single-center case experience study in Turkey, the frequency of genital ulcers was 56%.[42] Genital aphthous lesions are observed more

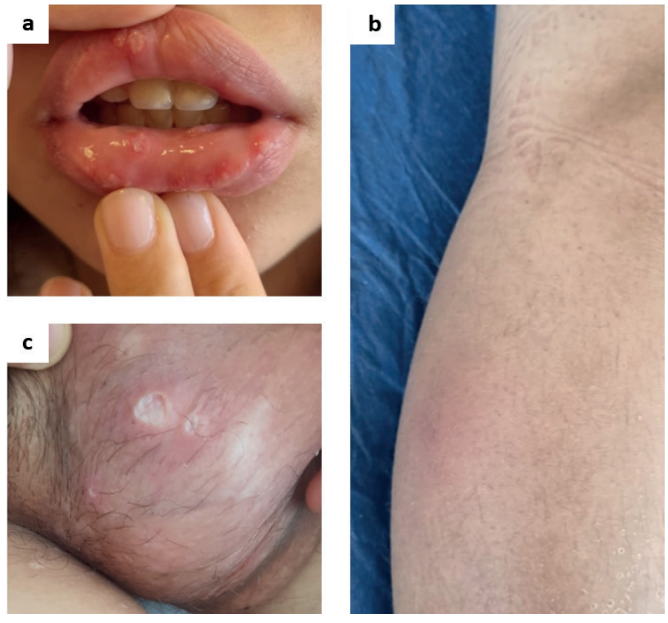

Figure 1. Some of the clinical features of Behçet's disease; Painful non-scaring recurrent oral aphthous lesions on the lips, tongue, and palate, usually healing within 3-10 days (Figure 1a), red, tender nodules called erythema nodosum, usually occur on the legs (Figure 1b), painful and deeper genital aphthous lesions, healing with scarring, and usually located in the labia major and minor in girls, and the scrotum in boys (Figure 1c).

often in girls; they are located in the labia major and minor in girls and in the scrotum in boys. Rarely, the perineal and perianal regions may be involved. Unlike oral aphthous lesions, genital ulcers are deeper, irregular, and heal with scarring.[43]

The most common skin lesions include pseudofolliculitis, papulopustular, erythema nodosum, skin rash, and acne (Figure 1). The frequency of skin involvement varies between 39% and 85% from country to country.[44] Although not specific for BD, pathergy positivity can be seen in 14.5% to 57% of patients.[11,45,46] The application of the test is the intradermal puncture of an avascular area on the anterior surface of the forearm with a sterile needle. An indurated erythematous papule or pustule that occurs after 48 hours is considered positive for the test.[47] The main underlying mechanism is the nonspecific hypersensitivity reaction to trauma.

After mucocutaneous lesions, the most frequently involved organ is the eye.[11,48] Eye involvement occurs approximately 2-3 years after the onset of BD, but it is observed simultaneously with the diagnosis in about 10%-20% of cases. Common eye symptoms include blurred vision, photophobia, redness, epiphora, and periorbital pain; eye manifestations include anterior uveitis, posterior uveitis, panuveitis, and retinal vasculitis. Bilateral eye involvement is more common; males have an increased risk for eye involvement compared to females.[49,50] While anterior uveitis is prominent in the younger age group, the incidence of panuveitis increases with older age.[51] It progresses with recurrent attacks in more than half of pediatric BD patients.[52] Vision loss may develop due to recurrent attacks and secondary complications (such as cataract, posterior synechiae, macular edema, and maculopathy).[50-52] Ocular involvement in BD is one of the most important causes of morbidity.

Musculoskeletal complaints are present in 20% to 63% of pediatric BD patients.[12,41,42] Peripheral joints such as the knee, ankle, elbow, and wrist are more affected than axial joints. Joint involvement is non-erosive and non-destructive.

Although neurological involvement is less common in pediatric patients (3.6%-30%) than in adults, it occurs especially during puberty.[48] Neurological manifestations can be grouped into two categories: parenchymal form and non-parenchymal vascular form. The non-parenchymal vascular form is more common in children, and cerebral venous sinus thrombosis is reported as the most frequent central nervous system manifestation.[53] The parenchymal lesions are mainly located at the mesodiencephalic junction and the brainstem.[54] Of note, neurological manifestations may present as encephalomyelitis or aseptic meningitis.

Vascular involvement affects vessels of any size, and the frequency of involvement varies between 5 and 20% in children with BD.[55] Venous thrombosis of the lower extremities is the most common vascular manifestation of BD but can be seen in other sites such as the portal vein and the suprahepatic vein.[55,56] Stenosis, occlusions, or especially aneurysms can be seen in the arterial system.

Gastrointestinal findings are more common in children than adults.[57] Gastrointestinal system involvement should be suspected in BD patients with complaints such as diarrhea, gastrointestinal bleeding, and abdominal pain, and it should be differentiated from inflammatory bowel disease. Rare manifestations such as cardiac complications and renal involvement have also been reported.[58,59]

BD may present a broad spectrum of clinical signs and symptoms involving multiple systems. Of note, pediatric cases may present with an incomplete clinical picture of the BD, and it may take time for the typical phenotype to develop. Therefore, it is important to maintain a high clinical index of suspicion for diagnosis.

Classification criteria

The heterogeneity of the disease makes it difficult to define a diagnosis or classification set for BD. Many efforts have been made to develop more precise diagnostic and/or classification criteria in adults, and many criteria have been proposed (Table 1). The most widely used criterion is the International Study Group (ISG) criteria proposed in 1990.[60] In 2014, the International Criteria for BD (ICBD) was published by a team from 27 countries, which was found to be more sensitive than the ISG criteria.[40] Vascular and neurological findings are included in the ICBD criteria. The PEDBD criteria, the first pediatric criteria, is based on a large cohort of BD patients, including European and non-European countries (Table 1).[15] Batu et al. evaluated the performances of PEDBD and ISG criteria in children with BD and found that PEDBD criteria showed better sensitivity than ISG criteria (52.9% vs. 73.5%).[61] However, expert opinion remains the gold standard for diagnosis.

Treatment

Our knowledge of treatment is largely based on the experience of adults due to the lack of controlled studies in pediatric BD. The goal of treatment is to reduce inflammatory flares and relapses and prevent irreversible tissue damage. The treatment strategies vary depending on the severity and type of organ involvement. Topical corticosteroids and colchicine are widely used for mucocutaneous manifestations. Colchicine use was associated with a reduced incidence of genital ulcers, erythema

Table 1. The most widely used classification criteria in adults and pediatric BD patients

Pediatric Behçet's Disease Criteria[15] (Three of the following criteria are required to classify a child to have BD)		**International Study Group (ISG) criteria**[60]	**International Criteria for BD (ICBD)** (scoring 4 points required)[40]
Recurrent oral aphthosis	At least 3/year	**Recurrent oral ulceration** **Plus, two of the following signs** Recurrent genital ulcer Eye lesions Skin lesions Pathergy test	Oral aphthosis (2 points) Genital aphthosis (2 points) Ocular lesions (2 points) Skin lesions (1 point) Neurological manifestations (1 point) Vascular manifestations (1 point) Positive pathergy test (1 point)
Genital ulceration	Typically with a scar		
Skin features	Acneiform lesions, necrotic folliculitis, erythema nodosum		
Ocular involvement	Anterior and/or posterior uveitis, retinal vasculitis		
Neurological signs	With the exception of headache		
Vascular involvement	Venous thrombosis, arterial thrombosis, arterial aneurysm		

nodosum, and arthritis.[62-64] Short-term systemic corticosteroids, avoiding long-term use, may also help severe ulcer healing. In addition, immunosuppressive agents such as azathioprine or tumor necrosis factor-alpha inhibitors (TNFis) can be used in patients with mucocutaneous manifestations who do not respond to colchicine treatment.[55,65] In a randomized controlled study, apremilast, a phosphodiesterase four inhibitor, was also effective in reducing BD-associated oral ulcers.[66]

Collaboration with an ophthalmologist is essential for close follow-up, as uveitis can cause permanent vision damage. Azathioprine is widely used in children with ocular BD.[63] TNFis also have been reported to show a significant effect in patients with a poor response to conventional immunosuppressants.[41,67] In the European League Against Rheumatism (EULAR) recommendations, for posterior segment involvement of ocular BD, the use of azathioprine, cyclosporine-A, interferon-alpha (IFN-α), or TNFis are stated, whereas high-dose glucocorticoids, infliximab, or IFN-α was recommended for sight-threatening uveitis.[68]

As for the treatment of other manifestations, dosing strategies of systemic corticosteroids, usually chosen as initial therapy, are adjusted according to the severity of organ involvement.[69] Treatment with 5-aminosalicylic acid (5-ASA) preparations or azathioprine has been suggested for patients with gastrointestinal involvement and TNFis for patients with severe and/or resistant disease.[68] Furthermore, corticosteroids, azathioprine, cyclophosphamide, and IFN-α are used in the treatment of nervous system involvement and vasculitis, and TNFis are recommended in refractory cases.[41,70] In a study involving severe and/or refractory BD, the efficacy of TNFis treatment was demonstrated in 96.3%, 88%, 70%, 77.8%, 92.3%, and 66.7% of patients with severe and/or refractory ocular, mucocutaneous, joint, gastrointestinal manifestations, central nervous system manifestations, and cardiovascular manifestations, respectively.[71]

Prognosis

The clinical course of BD tends to follow a chronic course characterized by exacerbations and remission. The disease is usually more severe in patients with early-onset BD and male gender.[5,72] It can cause significant morbidity and mortality due to mostly ocular, vascular, and neurological involvement. Ocular involvement has been reported to be the leading cause of morbidity in BD due to the risk of visual loss.[73] Pulmonary artery aneurysm is also a significant cause of mortality and morbidity in BD.[74] In a study of 817 BD patients, including children and adults, the mortality rate was reported to be five percent. Younger age (15–25 years), male gender, arterial involvement, and increased number of flares were identified as risk factors for death. Major vessel involvement, especially arterial aneurysm, and Budd-Chiari syndrome was the cause of death in 43.9% of the patients.[75]

Comparison of pediatric and adult-onset BD

The clinical manifestations of BD vary not only from patient to patient but also according to age groups. Several differences exist between adult and pediatric BD. Pediatric cases usually present with an incomplete clinical picture, and the time from symptom onset to full-blown disease may be prolonged. As for clinical manifestations, pediatric BD patients were reported to

have more common neurologic involvement, gastrointestinal involvement, and family history of BD, and less frequent ocular manifestations.[44,46] Another study also revealed that articular features and a familiar predisposition for BD were more common in the pediatric cohort, while venous vascular events were more frequently observed in the adult group.[76] In addition, differences in treatment approach were also reported. Both traditional and biological disease-modifying antirheumatic drugs (DMARD) use was reported to be more common in the adult group, whereas pediatric patients more frequently received no treatment or corticosteroid monotherapy.[76]

CONCLUSION

BD is a systemic vasculitis characterized by multisystemic, relapsing, and remitting inflammatory disorder with a chronic course. The observed heterogeneity in clinical presentation makes the accurate diagnosis difficult. Given the morbidity and mortality risk in BD, early diagnosis and effective treatment are essential. Further research targeting pediatric BD's management and treatment strategies is necessary to provide a better prognosis.

Author contribution

Concept: ÜKA, YB; Design: ÜKA, YB; Data Collection or Processing: ÜKA, YB; Analysis or Interpretation: ÜKA, YB; Literature Search: ÜKA, YB; Writing: ÜKA, YB. All authors reviewed the results and approved the final version of the article.

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Original Article

Is it necessary to screen for celiac disease in all children with intussusception?

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ABSTRACT

Objective: While there is a close relationship between celiac disease (CD) and intussusception, it is not yet clear whether the detection of intussusception in children requires physicians to always screen for CD. In our study, we aimed to determine the frequency of CD in children with intussusception and to find the answer to whether CD screening is necessary for every child with intussusception.

Methods: The study included 50 symptomatic pediatric patients diagnosed with intussusception who were followed up and treated in the Health Sciences University Gülhane Training and Research Hospital Pediatric Surgery Clinic between 2020–2023. CD screening was performed in patients followed up with a diagnosis of intussusception.

Results: The mean age of the patients was 3.61 ± 2.02 years, and 33 (66%) were male. Of 62 intussusceptions observed in 50 patients, 46.8% were ileo-ileal, 35.5% ileo-colic, 11.3% jejeno-jejunal, 4.8% colo-colic, and 1.6% recto-sigmoid. CD was diagnosed endoscopically in three (6%) patients with an intussusception diagnosis and an anti-tissue transglutaminase level > 200 IU/ml. Intussusceptions in 43.5% of the patients were reduced by hydrostatic reduction, 41.9% spontaneously, 9.7% laparotomically, and 4.8% laparoscopically. A single intussusception attack occurred in 82% of patients; 14% had two, 2% had three, and 2% had four. No significant correlation was found between the number of intussusception attacks and the presence of CD (p = 0.34). There was also no relationship between the type of intussusception and age (p = 0.74), gender (p = 0.24), or treatment (p = 0.12) or between the presence of CD and gender (p = 0.26), age (p = 0.68), or type (p = 0.28) of intussusception.

Conclusions: CD is more common in symptomatic children with intussusception than in healthy children. Screening pediatric patients with idiopathic intussusception for CD may reduce the recurrence of intussusception and complications and morbidities that may occur due to a delayed CD diagnosis.

Keywords: Celiac Disease, intussusception, screen, children

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disease that destroys the intestinal mucosa due to a series of abnormal immune responses triggered by gluten intake in susceptible individuals.[1] Frequency studies show that the disease affects approximately 1% of the world's population and our country (Turkey).[2,3]

According to CD presentation, it can fall into one of three categories: the typical form (characterized by abdominal distention, chronic diarrhea, and failure to thrive), the atypical

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form (characterized by isolated short stature, delayed puberty, refractory iron deficiency anemia, chronic constipation, abdominal pain, aphthous stomatitis, enamel defects, and osteoporosis), or silent disease.[4,5]

Intussusception is a form of intestinal obstruction in which one part of the intestine telescopes inside of another. It is the most common cause of gastrointestinal obstruction in children three months to 5 years of age.[6] Rarely, lead points such as Meckel's diverticulum or lymphoma may be found, but approximately 90%–95% of pediatric cases are idiopathic. It may be associated with those of known etiology, Henoch Schönlein purpura, polyps, duplication cysts, viral infections, cystic fibrosis, taking old versions of the oral rotavirus vaccine, Crohn's disease, and CD.[6-9]

Although it is not common, there are reports in the literature that celiac patients may present with intussusception as an atypical presentation finding.[6,10] The general prevalence of symptomatic intussusception in adults with CD is 1.6% and 1.2% in children.[6] Whether the detection of intussusception in children requires CD investigation still needs to be determined.

Thus, this study aimed to investigate the frequency of CD in children with intussusception and whether screening for CD in every child with intussusception is necessary.

MATERIALS AND METHODS

This study included 50 symptomatic pediatric patients diagnosed with intussusception by abdominal ultrasonography who were followed up and treated in the Pediatric Surgery Clinic of Health Sciences University Gülhane Training and Research Hospital between 2020–2023. Written consent was obtained from the patient's families to participate in the study, and approval was received from the local ethics committee with the date and decision number 2020-101/10.03.2020.

For CD screening in patients followed and treated for intussusception, serum IgA levels were measured using Beckman Coulter kits (Brea, CA), and anti-tissue transglutaminase IgA antibody levels were measured using ELISA kits (Orgentec, Germany). A pediatric gastroenterologist performed an upper gastrointestinal endoscopy to confirm the diagnosis of CD in three children with serum anti-tissue transglutaminase levels >200 IU/ml. Upper gastrointestinal endoscopy was performed with an Olympus X260 scope (Olympus Optical Corporation, Japan). One biopsy specimen from the duodenal bulb and four from the second part of the duodenum were obtained from each patient who underwent an endoscopy to diagnose CD histopathologically according to the Marsh classification system.[11] The hospital data recording system obtained the clinical findings, laboratory results, imaging, endoscopy, and histopathology results.

Statistical analysis

Data were evaluated using the Statistical Package for the Social Sciences for Windows version 20.0. Descriptive statistics were presented as numbers and percentages, mean ± standard deviation, minimum-maximum values, and median values for numerical variables. The conformity to the normal distribution was examined with the Shapiro-Wilk test, and the median difference between the groups was analyzed with the Mann-Whitney U, and Kruskal-Wallis H tests when the numerical variables did not show a normal distribution. Analyzing categorical variables among themselves was performed with the Chi-Square test or Fisher's Exact test. The tests were considered significant if the p-value was < 0.05, examining the data at the 95% confidence level. The tests were considered significant if the p-value was < 0.05, examining the data at the 95% confidence level.

RESULTS

The mean age of the patients was 3.61 ± 2.02 years, and 33 (66%) were male. A total of 62 intussusceptions were observed in 50 patients: 46.8% ileo-ileal, 35.5% ileo-colic, 11.3% jejeno-jejunal, 4.8% colo-colic, and 1.6% recto-sigmoid. CD was diagnosed endoscopically in three (6%) patients who underwent intussusception and had an anti-tissue transglutaminase level >200 IU/ml. The clinical features of the three patients diagnosed with CD are shown in Table 1. The frequency of intussusception was 2.1% (3/139) in 139 celiac patients followed up in our center. Intussusceptions were reduced in 43.5% of cases by hydrostatic reduction, 41.9% spontaneously, 9.7% laparotomically, and 4.8% laparoscopically. A single intussusception attack occurred in 82% of patients, two in 14%, three in 2%, and four in 2%. No significant correlation was found between the number of intussusception attacks and the presence of CD ($p = 0.34$). There was no relationship between the type of intussusception and age ($p = 0.74$), gender ($p = 0.24$), or treatment ($p = 0.12$). There was also no relationship between the presence of CD and gender ($p = 0.26$), age ($p = 0.68$), or type ($p = 0.28$) of intussusception.

DISCUSSION

Although intestinal intussusception is generally seen in children between the ages of 3 months and 3 years, the highest incidence is seen between 4 and 9 months[12], and it is detected

Table 1. Clinical characteristics of those diagnosed with CD among intussusception patients						
Patient	Age of Intussusception/ CD diagnosis	Intussusception type	Number of intussusception attacks	Treatment	Histological classification	Follow-up
Patient 1	5 y 6 mo/ 5 y 7 mo	Jejeno-jejunal	1	hydrostatic reduction	Marsh 3A	Gluten-free diet, clinically good, 7 y 1 mo
Patient 2	5 y/5 y 1 mo	Ileo-colic	1	hydrostatic reduction	Marsh 2	Gluten-free diet, clinically good, 6 y 6 mo
Patient 3	17 mo/19 mo	Ileo-colic Ileo-ileal Ileo-colic Ileo-colic	4	hydrostatic reduction	Marsh 3B	Gluten-free diet, clinically good, 4 y 10 mo

approximately twice as often in boys than in girls.[13,14] Similar to the literature, the mean age of the patients in our study was 3.61 ± 2.02 years, and 66% were male.

Pediatric intussusceptions are divided into six types: ileo-colic, ileo-ileocolic, colo-colic, ileo-colocolic, ileo-ileal, and jejuno-jejunal. The ileo-colic type, in which the distal ileum invades the cecum through the ileocecal valve, is the most common type of intussusception, constituting 90% of cases.[12,13] Intussusception often recurs regardless of the reduction method. Some studies have shown that approximately 10% (8-15%) of patients experience recurrent intussusception.[15] In our study, recurrent intussusception was observed at a rate of 18%, and of all intussusceptions, 46.8% were ileo-ileal, 35.5% ileo-colic, 11.3% jejeno-jejunal, 4.8% colo-colic, and 1.6% recto-sigmoid.

The preferred initial treatment method in most cases of intussusception is an image-guided reduction with pneumatic or hydrostatic enema.[16] Conditions requiring surgical intervention include peritonitis, shock, sepsis, perforation, recurrent enema failure, and persistent symptomatic small bowel obstruction.[17] In our study, 43.5% were reduced by hydrostatic reduction, 41.9% spontaneously, 9.7% laparotomically, and 4.8% laparoscopically. Small bowel intussusception (ileo-ileal and jejuno-jejunal) accounted for 88.4% of patients with spontaneous reduction.

Intussusception may occur in patients with CD, but it is mostly asymptomatic. Controversy continues regarding whether all children with idiopathic intussusception should be screened for CD to prevent future episodes of obstruction.[18] Because CD is a chronic inflammatory condition, the suggested cause of intussusception in CD cases is inflammation and thickening of the intestinal wall, leading to hyperperistalsis and subsequent enlargement of the small intestine. One intestinal loop segment is thought to be invaginated into the other due to dilated drooping rings that disrupt normal peristaltic waves.[18,19]

Borkar et al. investigated the prevalence and natural history of intussusception in newly diagnosed CD prospectively and found subclinical intussusception in 25% of children with newly diagnosed CD.[10] Another study revealed that 1.2% of children with CD experienced an intussusception before treatment with a gluten-free diet.[6] Reilly et al. found a higher incidence of intussusception among children with CD compared to the general pediatric population in their study, and they argued that the underlying cause of intussusception in children might be related to CD, even if the patient appears well.[6] The reported prevalence of intussusception in adult patients with CD is approximately 1.6% to 20%.[20] In a study of American adults, intussusception was identified as the first sign of celiac disease in 57% of cases. Paul et al. suggested that while radiologists investigate intussusception with ultrasonography, they can also evaluate key features of CD, such as increased bowel wall thickness, free peritoneal fluid, and enlarged mesenteric lymph nodes.[21] The frequency of intussusception was 2.1% (3/139) in 139 celiac patients followed up in our center.

In a large population-based case-control study on the relationship between intussusception and CD, it was found that there was no relationship between intussusception and future CD. However, there was a 2-fold increase in intussusception risk after a CD diagnosis.[22] Aldaher et al.[23] found that the frequency of CD in children with intussusception was as high as 10.5% (6/57). In our study, CD was diagnosed endoscopically in 3 (6%) of 50 symptomatic pediatric patients with intussusception. One of the patients diagnosed with CD had recurrent intussusception with four attacks in the two months before diagnosis. There was no significant relationship between the number of intussusception attacks and the presence of CD or the presence of CD and gender, age, or type of intussusception in our study. While we did not include a control population of healthy children to see the prevalence of CD in healthy children of the same age in our community, in a study of 20,190 healthy children in Turkey, the

prevalence of CD was 0.47%, and the global prevalence of CD was approximately 1%.[2,3] The frequency of CD in our symptomatic patient population with intussusception (6%) was significantly higher than that of the healthy population.

In conclusion, CD was seen more frequently in symptomatic children who have undergone intussusception than in normal healthy children. Our study's important limitations are that it was single-center and conducted with a limited number of patients. Screening pediatric patients with idiopathic intussusception for CD may reduce the recurrence of intussusception and complications and morbidities that may occur due to a delayed CD diagnosis.

Ethical approval

The study was approved by the local ethics committee (2020-101/10.03.2020).

Author contribution

Study conception and design: MA, GBB, NB; data collection: MA, CFÖ, EGB, SEÜB, HEA; analysis and interpretation of results: MA, GBB, MBÇ; draft manuscript preparation: MA. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

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Original Article

The effect of mother's and infant nutrition on functional constipation in children between 1-4 months

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ABSTRACT

Objective: Constipation is the infrequent and painful passage of hardened stools, occurring less than three times a week, often accompanied by excessive straining and discomfort. Functional constipation is the most important gastrointestinal complaint of childhood. Limited literature explores the correlation between functional constipation and infant nutrition. Our study aims to investigate the association between maternal and infant nutrition and functional constipation among infants between 1-4 months.

Method: The research is a cross-sectional study. Two groups involved cases from the pediatric clinic, which presented complaints of constipation within the age range of 1 to 4 months, and the control group, which consisted of individuals without any reported constipation issues. Mothers participating in the study completed a questionnaire comprising two sections: one focusing on patient assessment and the mother's diet.

Results: The study encompassed seventy-five cases reporting constipation issues, with the control group comprising thirty cases. Functional constipation was most observed at 78 days of age. Children experiencing functional constipation exhibited lower weight and height values, demonstrating statistical significance. Additionally, 94.7% of infants facing defecation challenges had a history of meconium within the first 24 hours of birth. Factors such as alterations in familial defecation patterns and a history of constipation among first-degree relatives were notably higher in the case group. The incidence of functional constipation was notably elevated by cesarean section and those not receiving breast milk. Furthermore, maternal dietary habits indicated higher consumption of milk, fruit juice, yogurt, vegetables, and legumes among the healthy group, with statistically significant disparities observed.

Conclusion: Functional constipation in infants can associated with cesarean section, a high number of siblings, low parental education levels, familial history of altered defecation patterns, and constipation among first-degree relatives; additionally, formula feeding, maternal consumption of low-fiber foods, and inadequate fluid intake by the mother.

Keywords: functional constipation, infant, mother, nutrition

INTRODUCTION

Functional constipation ranks among childhood's most prevalent gastrointestinal issues, representing a significant portion of cases seen in pediatric gastroenterology outpatient clinics.[1] When characterizing constipation, the consistency and water content of stools are emphasized over the frequency of defecation. It is typically described as infrequent bowel movements, occurring less than three times a week, accompanied by hard and painful stool passage.[1-3] The prevalence of childhood constipation ranges from 0.7% to 29.6%, comprising 3-5% of visits to general pediatric clinics and up to 25% of consultations in pediatric gastroenterology.[3,4]

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Constipation poses a significant concern for families, particularly during the initial months of a child's life, when parents closely monitor their offspring's defecation patterns.[5] Although constipation may signal serious organic disorders, especially in newborns, approximately 90% of cases in older children lack an organic explanation, falling under the category of "functional constipation".[6]

Research exploring the link between constipation and nutrition indicates lower constipation rates in breastfed infants compared to those not breastfed, particularly when supplementary feeding is introduced early.[7,8] Additionally, studies reveal that constipated children consume less fiber and macronutrients than their non-constipated counterparts, underscoring the importance of adequate fiber and fluid intake for soft stools.[9]

Furthermore, maternal nutrition significantly influences functional constipation in breastfed infants. However, limited studies suggest a correlation between maternal and infant constipation.[10,11]

Our study aimed to investigate the impact of maternal and infant nutrition on functional constipation among children aged 1-4 months.

MATERIAL AND METHODS

Our research comprises a single-center cross-sectional survey conducted from January 2015 to August 2016. The survey included cases of patients admitted to pediatric outpatient clinics and diagnosed with functional constipation. The study commenced following approval from the local ethics committee (dated and decision number provided). Mothers who consented to participate were required to provide both verbal and written informed consent, after which questionnaires were administered via face-to-face interviews.

Given that the patients fell within the age range of 1 to 4 months, diagnostic criteria for functional constipation were based on the number of defecations and stool hardness criteria outlined in the Rome III criteria. Criteria such as fecal incontinence, excessive fecal continence, and large stools that could obstruct the toilet, more appropriate for older children, were not utilized. Exclusion criteria encompassed infants with sacral dimples, sacral agenesis, perianal fistula, abnormal positioning of the anus, perianal scarring, hypothyroidism, cow's milk protein allergy, as well as alarm symptoms like fever, vomiting, and bloody stools.

Seventy-five cases aged 1-4 months diagnosed with functional constipation, and 30 healthy infants as the control group were enrolled in the study. Both groups underwent a questionnaire comprising two sections: patient evaluation and diet evaluation. The patient assessment segment encompassed inquiries concerning age, gender, weight, height, mode of delivery, birth weight, gestational week, time of first meconium passage, dietary habits, weight gain, defecation frequency, stool characteristics, medication usage, parental education level, family history of constipation, family income, number of siblings, parental age, and employment status. The second part focused on maternal nutrition.

Statistical analyses were conducted using the "SPSS for Windows 20.0" software package. Measurement variables were presented as standard deviation (SD) or median (interquartile range), while categorical variables were expressed as numbers and percentages (%). Comparative analyses of qualitative variables between paired groups utilized the Chi-square and Fisher's Exact test. Student's t-test was employed for normally distributed parameters, whereas the Mann-Whitney U Test was applied for non-normally distributed parameters. When comparing multiple groups, chi-square, one-way ANOVA, and Kruskal-Wallis Analysis were used for different scenarios. A significance level of $p<0.05$ was set for data analysis.

RESULTS

Our study comprised a total of 105 cases, with 75 experiencing functional constipation (Group 1) and 30 healthy individuals (Group 2). No significant difference was observed between the two groups in terms of mean age and gender distribution (Group 1: 78±28 days, Group 2: 82±30 days).

Upon anthropometric evaluation, patients with functional constipation exhibited significantly lower height and weight measurements ($p=0.012$, $p=0.041$) than the control group (Table 1). None of the children in the healthy group fell below the 3rd percentile.

Analysis of the mode of delivery revealed a significantly higher prevalence of normal deliveries in the control group, with no notable difference observed in birth weight. Most cases experiencing functional constipation were delivered at term, with no significant difference observed compared to the control group (Table 1).

Regarding meconium passage history, 71 cases (94.7%) with functional constipation had a history of meconium expulsion within the first 24 hours after birth. Only two cases exhibited delayed meconium passage beyond 48 hours without any identifiable organic cause. All control group patients had a

history of meconium passage within the initial 24 hours, with no significant difference observed between the two groups (Table 1).

The proportions of breast milk and/or formula feeding were similar in both groups, with no statistically significant difference noted (Table 1).

Among cases experiencing functional constipation, 33.3% reported hard stool patterns.

In the control group, there were no parents without formal education, and mothers had a higher mean age. The proportion of non-working mothers was comparable between both groups, and there was no disparity in family income levels. However, the mean number of children was notably higher in the group with functional constipation exhibiting a significant difference upon comparison. Instances of hard defecation patterns among siblings, parents, and relatives were markedly more prevalent in cases with functional constipation (Table 2).

Regarding medication usage for defecation problems among patients with difficulty, it was found that 20 patients (26.7%) received no treatment. In contrast, one patient (1.3%) was prescribed probiotics, 20 patients (26.7%) were administered laxatives and suppositories, 16 patients (21.3%) consumed herbal drinks (with fennel tea being the most common), and 18 patients (24%) received combined treatments (often involving laxatives, suppositories, and herbal drinks).

The maternal nutrition section of the survey noted that mothers in both groups consumed at least one liter of water daily, with significantly higher fruit juice and milk consumption observed in the control group (Table 3). None of the mothers reported alcohol consumption. In addition, the smoking ratio was similar between the groups. Analysis of solid food consumption revealed

Table 1. Anthropometric examination, nutritional status, and defecation history of babies aged 1-4 months

Parameter	Group 1 (Difficult defecation)	Group 2 (Control)	*P*
Age (days) (mean±SD)	78±28	82±30	0.460
Gender, n (%)			
Male	38 (50.7%)	18 (60%)	0.560
Female	37 (49.3%)	12 (40%)	
Weight (kg)	5.3±1	5.8±1	**0.012***
Height (cm)	56.6±4.7	5.1±4.1	**0.041***
Mode of Delivery, n (%)			
NSVD (%)	22 (29.3%)	20 (66.6%)	**0.001***
C/S (%)	53 (70.7%)	10 (33.4%)	
Birth weight (kg)	2.97±0.6	3.1±0.69	0.540
Birth week (n, %)			
Premature (%)	44 (5.7%)	4 (13.3%)	
Mature (%)	27 (37,3%)	26 (86.7%)	0.812
Postmature (%)	4 (4%)	0	
Time to first passage of meconium (n, %)			
First 24 hours (%)	71 (94.7%)	30 (100%)	0.520
>24 hours (%)	4 (5.3%)	0	
Type of nutrition (n, %)			
Breast milk	45 (60%)	21 (70%)	
Breast milk and Formula	26 (34.7%)	8 (26.7%)	0.140
Formula	4 (5.3%)	1 (3.3%)	

C/S: Cesarean Section, NSVD: Normal Spontaneous Vaginal Delivery

Table 2. Socio-demographic characteristics of parents			
Parameter	**Group 1 (Difficult defecation)**	**Group 2 (Control)**	***P***
Educational status			
Mother's level of education (n, %)			
Uneducated	8 (10.7%)	0	**0.002***
Primary school	23 (30.7%)	6(16.6%)	
Middle school	21 (28%)	7(20%)	
High School	12 (17.3%)	14(40%)	
Master's degree	11 (13.3%)	8(23.4%)	
Father's level of education (n, %)			
Uneducated	1(1.3%)	0	**<0.001***
Primary school	35(46.7%)	1(3.3%)	
Middle school	9(12%)	7(20%)	
High school	21(28%)	15(43.4%)	
Master's degree	9(12%)	12(33.3%)	
Maternal employment status (n, %)			
Employed	7(9.3%)	6(16.7%)	0.460
Unemployed	68(90.7%)	29(83.3%)	
Maternal age (years)	27.8±5.3	24.9±3.5	0.380
Number of children in the family (average)	1.8±0.83	1.3±0.55	**0.008***
Income Level (n, %)			
Below minimum wage	(13.3%)	(16.6%)	0.480
Above minimum wage	(86.7%)	(83.4%)	
Presence of Functional Constipation in the Family (n,%)			
In the brothers	(18.7%)	0	**0.001***
In parents	(48%)	(3.3%)	**<0.001***
In relatives	(32%)	(3.3%)	**0.002***

a statistically higher intake of yogurt, vegetables, and legumes in the control group. However, no significant differences were observed in the consumption of cheese, fruit, potatoes, fiber-rich foods such as wholemeal bread, bread and pastry, and convenience foods (Table 4).

DISCUSSION

In our study, cesarean delivery, a high number of siblings in the family, low parental educational attainment, familial history of altered defecation patterns, presence of constipation among first-degree relatives, formula feeding, maternal consumption of low-fiber diets, and inadequate fluid intake by the mother were identified as factors contributing to functional constipation in infants.

Among infants with functional constipation in our study, 50.7% were boys, and 49.3% were girls. Reviewing the literature, studies on constipated children have reported equal gender ratios.[12-15] Similarly, our study revealed no significant difference between genders, which is consistent with existing literature findings.

The cases experiencing functional constipation in our study exhibited lower height and weight measurements. Although the literature suggests an association between constipation

Table 3. Fluid consumption of mothers			
Liquid consumption (day)	**Group**	**Average**	***p***
Tea (cup)	Group 1	6.86 ± .93	0.380
	Group 2	7.0 ± .00	
Milk (cup)	Group 1	1.87 ± 2.72	**0.001***
	Group 2	5.27 ± 1.91	
Fruit juice (glass)	Group 1	2.08 ± 2.76	**0.016 ***
	Group 2	2.06 ± 2.31	
Cola-carbonated drink (glass)	Group 1	1.08 ± 1.66	0.540
	Group 2	1.60 ± 1.30	
Coffee (cup)	Group 1	2.08 ± 2.75	0.980
	Group 2	1.20 ± 0.45	
Water (liter)	Group 1	7.00	0.160
	Group 2	7.00	

Table 4. Solid food consumption of mothers			
Consumption of solid food	**Group**	**Average**	***p***
Yogurt (portion)	Group 1	5.01 ± 2.50	**0.001***
	Group 2	6.60 ± 0.93	
Cheese (matchbox)	Group 1	6.49 ± 1.69	0.120
	Group 2	7.00 ± .00	
Fruit (portion)	Group 1	4.38 ± 2.64	0,540
	Group 2	4.70 ± 1.70	
Salad (portion)	Group 1	3.96 ± 2.70	0.091
	Group 2	4.83 ± 1.51	
Potato (portion)	Group 1	2.09 ± 1.40	0,082
	Group 2	2.60 ± 1.10	
Vegetables (portion)	Group 1	2.36 ± 1.82	**0.010***
	Group 2	3.60 ± 1.32	
Whole wheat bread (slice)	Group 1	0.50 ± 1.78	0.570
	Group 2	0.73 ± 2.13	
Bread, cake, pastry	Group 1	6.40 ± 1.53	0.460
	Group 2	6.63 ± 1.24	
Legumes (portion)	Group 1	1.24 ± 1.10	**0.015***
	Group 2	1.83 ± 1.14	
Convenience food (portion)	Group 1	0.59 ± 1.35	0.990
	Group 2	0.17 ± .46	

and obesity[16], limitations arose from the young age of our subjects and the predominance of breast milk, hindering a comprehensive comparison.

Our study found a higher rate of cesarean births in the group with functional constipation. While the literature on the influence of birth type on constipation is scarce, we hypothesize that intestinal microbiota may play a role, as vaginally born infants are typically colonized with maternal vaginal and fecal bacteria.

In our study, 28 cases (37.3%) were premature. Previous research indicates a higher prevalence of constipation among low birth-weight babies.[17,18] The delay in meconium excretion in premature infants is attributed to immature motor mechanisms of the digestive system and inadequate stimulation of digestive system hormones due to insufficient enteral nutrition.[19] However, due to the limited number of premature cases in our study, significant insights could not be gleaned.

Among cases diagnosed with functional constipation in our study, only 2 had a history of defecation after 24 hours, with no identifiable organic cause. Contrary to much literature, which suggests a higher incidence of constipation among children passing meconium after the first 24 hours[16,20], our cases with functional constipation exhibited a history of meconium passage within the initial 24 hours.

Most infants experiencing functional constipation in our study were predominantly breastfed. Existing literature underscores the positive impact of breast milk on defecation patterns.[21,22] Research indicates a higher average daily number of stools in babies exclusively fed with breast milk at one, two, and four months old.[20] This may be attributed to factors such as motilin in breast milk, which enhances gastric emptying, the digestibility of lipids, particularly long-chain fatty acids present in breast milk, and the presence of prebiotics. Moreover, studies suggest a higher average number of stools per day in exclusively breastfed infants[15,20], indicative of diverse nutrient contributions to gastrointestinal system development post-birth. Our study observed a notable effect of breast milk on increasing stool frequency, particularly during exclusive breast milk in the initial months. However, three cases of not receiving breast milk hindered clear assessment.

In cases of functional constipation, not only the frequency but also the consistency of stool hold significance. Among our cases experiencing functional constipation, stool patterns were predominantly reported as normal. The Bristol stool scale, typically utilized for assessing stool shapes, was omitted from our study due to the infancy age group. Reviewing the literature, Kocaay et al. found that 58.3% of constipated infants exhibited Bristol type 1 hardball stools, 37.5% had hard stools, and 4.2% had stool shapes close to normal.[23] Similarly, another study involving 116 constipated cases found that 84% of stools were solid, 34% were cylindrical and thick, and 28% were hard, akin to Bristol type 1.[24] However, in our study, contrary to literature findings, instances of hard and goat dung-like stools were infrequent.

Upon analyzing the influence of parental education levels on constipation, it was noted that parents in the control group tended to have higher education levels. It was speculated that conscious childcare practices and the adoption of healthy dietary habits might have contributed to this observation.

In our study, a history of changes in defecation patterns among siblings, parents, and relatives was notably higher in the group experiencing functional constipation, with a statistically significant difference observed compared to the control group. While the role of genetic factors in functional constipation remains controversial, many studies have indicated a familial history of constipation among individuals with functional constipation.[25-27] Similarly, our study detected instances of functional constipation within families of constipated children, aligning with existing literature. This observation was attributed to shared dietary habits within families.

Among the treatment methods employed for defecation problems in our study, laxative-herbal suppositories and herbal drinks were the most frequently utilized. Reviewing the literature, a study conducted in our country reported olive oil, insertion of soap into the anus, and the use of suppositories and enemas as common traditional remedies for constipation.[28] Similarly, our study employed a laxative-herbal suppository approach, albeit it failed to yield positive outcomes for the prevailing complaint.

In our study, we investigated maternal fluid consumption and found that mothers of infants aged 1-4 months with functional constipation consumed less fluid. Although the literature on the effect of maternal nutrition on infantile functional constipation is limited, low fluid intake remains a significant risk factor for constipation. Increasing fluid intake is crucial for treating constipation as it promotes softer stools.[29] In our study, mothers in the healthy group consumed more fluids, indicating that increased fluid content in breast milk might effectively reduce constipation.

Our study observed higher milk and yogurt consumption among mothers in the control group. However, the number of studies investigating the role of cow's milk in developing functional constipation is limited. Some research suggests that calcium combined with fats from cow's milk in the intestinal lumen may

form soap, which does not stimulate intestinal motility and may contribute to constipation.[30] Nevertheless, contrary to these findings, our study suggests that maternal consumption of cow's milk and dairy products might not affect constipation, as infants in our study were not fed cow's milk.

Our study result should be interpreted regarding some limitations. First, the study's cross-sectional nature did not allow detection of the cause-effect relationship. Second, in the period that we performed the study, the Rome III diagnostic criteria were valid. However, the Rome IV diagnostic criteria for functional constipation became valid during the time the paper was written.

Additionally, our study revealed that dietary fiber and fibrous foods consumption was significantly higher among mothers in the healthy group. Reviewing the literature, it is well-established that increasing water-soluble and insoluble fiber sources in the diet is a fundamental nutritional approach for treating constipation. Numerous scientific studies have demonstrated that a high dietary fiber intake helps prevent constipation.[24,25,27]

CONCLUSION

Cesarean history, low parental education levels, a high number of siblings, familial history of constipation, formula feeding, maternal consumption of low-fiber foods, and inadequate fluid intake are identified as factors contributing to functional constipation in infants.

Ethical approval

This study has been approved by the İzmir Tepecik Training and Research Hospital Local Ethics Committee (approval date 02.05.2016, number 2016/09-23).

Author contribution

Study conception and design: GT, MB; data collection: GT, MB; analysis and interpretation of results: GT, MB; draft manuscript preparation: GT, MB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of attempted suicide events through oral intake among children in a metropolitan city: A single-center study

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ABSTRACT

Objective: Suicide remains one of the leading causes of death worldwide, according to the World Health Organization's latest estimates. This study aims to evaluate sociodemographic data, the causes of suicide attempts, the methods employed in suicide attempts, and the factors that increase the likelihood of the recurrence of suicide attempts.

Method: This retrospective study was conducted among children who were hospitalized for attempting suicide between 2017 and 2022. Sociodemographic data, presence of a chronic illness or psychiatric disorder, substance abuse, reasons for suicide attempts, and the methods of suicide attempts were documented in the patients' files.

Results: 114 children who attempted suicide (mean age 15.7 ±1.6 years, 93 female)) had been enrolled in the study. Most of those children were high school graduates (n=75, 65.8%). Almost all of the children attempted suicide by drug overdose, and 51.8% of them consumed multiple drugs. The most common drugs used for suicide attempts were antipsychotics (35.1%), antidepressants (32.5%), and analgesics/antipyretics (29.8%). Arguing with a family member was the most frequent reason for suicide attempts. Psychiatric disorder diagnosis was detected in 38.6% of the children, and depression was the most common prevalent psychiatric disorder. Important risk factors for the recurrence of suicide attempts were determined to be the presence of diagnosed psychiatric disorders (95%CI, 1.289-9.657; p=0.014) and a family history of attempted suicide (95% CI, 2.559-92.781; p=0.003).

Conclusion: Identifying the factors that contribute to suicide attempts in children and providing appropriate support and treatment are crucial for preventing suicide attempts, which are a serious health concern.

Keywords: causes, children, methods, risk factors, suicide attempt

INTRODUCTION

As per the World Health Organization's (WHO) most recent estimates, published in "Suicide Worldwide in 2019", suicide continues to be one of the major causes of death globally. Worldwide, the annual number of suicide deaths is estimated to be 703000. In 2019, suicide accounted for around one in every 100 deaths (1.3%), and it was the fourth most common cause of death for individuals aged 15 to 29.[1] The term suicide, consists of suicidal thoughts, suicide attempts (SA), and completed suicides. As per the Turkish Statistical Institute, 3161 people in Turkey committed suicide in 2018, with 75.6% of those casualties being men.[2] Male suicide rates are more than twice as high as female suicide rates worldwide.[1] SAs are more common among women, despite the fact that men have a higher completed suicide rate.[3-5] In a recent large series from Iran, it was reported that

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49.88% of SAs were observed among the population aged 16 to 26.[6] Researchers emphasized that suicidality may be related to depression and family environment.[7-10] The types of SAs, such as drug overdose, chemical poisoning, hanging, firearms, and self-harm, vary according to personal traits and geographical regions.[11]

This study aimed to evaluate sociodemographic data, the reasons for SAs, the methods used in SAs, and the risk factors for the recurrence of SAs.

MATERIALS AND METHODS

This retrospective study was conducted among children who attempted suicide and were hospitalized in the Department of Pediatrics and/or Pediatric Intensive Care Unit (PICU) between 2017-2022. In our hospital, approximately 5800 patients are admitted to the pediatric clinic and 480 to the PICU annually. According to a thorough anamnesis completed by pediatricians and psychiatrists, the patients admitted to having taken drugs with the intention of a SA. Patients who accidentally took medication were not included in the study. Patients were admitted to the pediatric department if they had taken long half-life drugs overdose, multiple drugs with uncertain count, or if their blood drug level was above the toxic dose and/or an antidote treatment was necessary. Patients who displayed central nervous system depression, systemic symptoms such as hypotension and arrhythmia, and those who needed plasmapheresis treatment for drug overdose were admitted to the PICU. In patients' files, sociodemographic data such as gender, age, educational attainment, presence of a sibling, parents' marital status, presence of a chronic illness or psychiatric disorder, substance abuse, clinical findings, reasons, and methods for the SAs were documented. All patients admitted to the pediatric department were provided with a consultation by a pediatric psychiatrist. The patients admitted to the PICU were provided consultation by a pediatric psychiatrist once their stay in the PICU was no longer necessary. Furthermore, a pediatric psychiatrist conducted a separate evaluation of their parents.

Statistical analysis

Statistical data analysis was evaluated with the SPSS-22 (Chicago, II, USA) program. The compatibility of continuous variables with normal distribution was analyzed using the Kolmogorov-Smirnov test. Normally distributed continuous variables were stated as mean ± standard deviation (SD), non-normally distributed continuous variables as median (minimum, maximum), and categorical variables as percentage (%). The Chi-Square test was used for the analysis of categorical variables. The Student T-test was used for comparison of categorical variables. Logistic regression analysis was used for age, sex, and parameters with p-value <0.050. In multivariate analysis, independent predictors in predicting outcomes using probable factors were examined by logistic regression analysis p< 0.050 was considered significant.

Approval was obtained from the local university Ethics Committee (approval date:05.10.2022, approval number: 2022/0461) before the experiment was started and was conducted in accordance with the principles set forth in the Helsinki Declaration.

RESULTS

A total of 114 children who attempted suicide (female/male = 93/21) had been enrolled in the study. The mean age of the children was 15.7 ±1.6 years old. Most of those were high school graduates (n=75, 65.8%), and 7 (6.1%) had no siblings. Almost all of the children attempted suicide through drug overdose, with only one using rat poison and another using bleach. Fifty-nine out of 114 children (51.8%) attempted suicide using multiple drugs. The three most common detectable drugs used for SAs were antipsychotics (n=40, 35.1%), antidepressants (n=37, 32.5%), and analgesics/antipyretics (n=34, 29.8%). SAs were shown to most frequently occur as a result of arguments with family members. The childrens' demographic and clinical data is presented in Table 1.

Four of the adolescents who were admitted were substance users. Alcohol, marijuana, ecstasy, and amphetamine were the reported substances. Prior to their SAs, 44 of the children were diagnosed with a psychiatric disorder and were on antidepressant and/or antipsychotic medications. Furthermore, 13 patients began receiving treatment following the SAs. Five patients who continued to have suicidal thoughts were hospitalized in the psychiatry clinic. A patient who had attempted suicide with high doses of colchicine was successfully treated with plasmapheresis. No patient died or developed chronic organ damage.

The rate of recurrence of SAs was 24.6% in this study. Recurrent SA subjects displayed a significantly higher occurrence of psychiatric disorders in both themselves (67.9% vs. 36%; p=0.003) and their families (42.9% vs. 16.3%; p=0.004), as well as a higher incidence of suicide within the family (32.1% vs. 2.3%; p<0.001) when compared to those with a single SA (Table 2). The presence of a diagnosed psychiatric disorder (95%CI, 1.289-9.657; p=0.014) and a history of SAs in the family (95% CI, 2.559-92.781; p=0.003) were found to be significant factors for recurrence (Table 3).

Table 1. Demographic characteristics of children who attempted suicide	
	n (%)
Age	15.7±1.6 (10.3-17.9)
Sex (female/male)	93/21 (81.6/18.4)
Season of suicide attempt	
Spring	36 (31.6)
Summer	33 (28.9)
Winter	27 (23.7)
Autumn	18 (15.8)
Education	
Primary school	12 (10.5)
High school	75 (65.8)
School droupout	27 (23.7)
Number of siblings	
Only child	7 (6.1)
2	42 (36.8)
3	32 (28.1)
>3	33 (29)
Marital status of parients	
Married	97 (85.1)
Divorced	11 (9.6)
Mother and/or father passed away	6 (5.3)
Suicide attempt in the family	11 (9.6)
Psychiatric disorder in the family	26 (22.8)
Diagnosed psychiatric disorder*	50 (43.9)
Depression	25 (21.9)
ADHD	6 (5.3)
Dissociative disorder	5 (4.4)
Schizophrenia	4 (3.5)
Bipolar disorder	4 (3.5)
Anorexia nervosa	3 (2.6)
Anxiety disorder	3 (2.6)
Anger managment disorder	3 (2.6)
PTSD	3 (2.6)
OCD	1 (0.9)
None	64 (56.1)

Table 1. Continued	
	n (%)
Presence of chronic disease	
Epilepsy	4 (4.5)
Familial meditteranean fever	1 (0.9)
Chronic renal failer	1 (0.9)
None	97 (94.8)
First suicide attempt	86 (75.4)
Recurrent suicide attempt	28 (24.6)
Suicide attempts	
Impulsive	109 (95.6)
Planned	5 (4.4)
GKS 15	85 (74.6)
<15-8	13 (11.4)
<8	16 (14)
PICU	70 (61.4)
Number of hospitalized to psychiatry clinic	5 (4.4)
The drugs have taken for SA	
Antipsychotic	40 (35.1)
Antidepressant	37 (32.5)
Analgesic/antipyretic	34 (29.8)
Antiepileptic	15 (13.2)
Antihypertensive	10 (8.8)
Antibiotic	7 (6.1)
Antidiabetic	7 (6.1)
Vitamin/mineral	6 (5.3)
Other**	30 (26.3)
The causes leading to SA	
Family argument	43 (37.7)
Partner argument	18 (15.8)
Drawing attention	13 (11.4)
Exam stress	12 (10.5)
Sexual abuse	6 (5.3)
Lose one's relative	5 (4.4)
Immigrant problems	3 (2.6)
Peer victimization	1 (0.9)
None	13 (11.4)

*Some patients had more than one disorder, Other** anticholinegic, colchicine, antihistamine, rat poison, bleach, ADHD: Attention- deficit hyperactivity disorder, PTSD:Post-traumatic stress disorder, OCD: Obsessive-compulsive disorder, PICU: Pediatric intensive care unit, SA: Suicide attempt

Table 2. Factors related to recurrent suicide attempt				
		Single SA (n=86) (n/%)	Recurrent SA (n=28) (n/%)	p
Age		15.87±1.24	15.70±1.70	0.614*
Sex	Female (n=93)	71 (82.6)	22(78.6)	0.636
	Male (n=21)	15 (17.4))	6 (21.4)	
Education	Primary education (n=12)	10 (11.6)	2 (7.1)	0,434
	High school (n=75)	58 (67.4)	17 (60.7)	
	Dropout (n=27)	18 (20.9)	9 (32.1)	
Marital status of parents	Married (n=97)	76 (88.4)	21 (75)	0.194
	Divorced (n=11)	6 (7)	5 (17.9)	
	Loss of parent (n=6)	4 (4.7)	2 (7.1)	
Patients with psychiatric disorder (n=50)		31 (36)	19 (67.9)	**0.003**
Diagnosed psychiatric disorder in the family (n=26)		14 (16.3)	12 (42.9)	**0.004**
Suicide history in the family (n=11)		2 (2.3)	9 (32.1)	**<0.001**

p: Chi Square Test or Fisher 's Exact Test *Student's t-test

Table 3. Binary logistic regression results for factors affecting the recurrent suicide attempt						
Risk factors	B	S.E	RR (95% CI)		Exp (B)	p
			Min	Max		
Sex	-0.255	0.541	0.268	2.237	0.775	0.637
Presence of diagnosed psychiatric disorder	1.261	0.514	1.289	9.657	3.528	**0.014**
Presence of diagnosed psychiatric disorder in the family	0.426	0.612	0.461	5.081	1.531	0.487
Presence of history of suicide attempt in the family	2.735	0.916	2.559	92.781	15.409	**0.003**

RR, Relative Risk; CI, Confidence Interval

DISCUSSION

According to this study, the majority of patients who attempted suicide were female, and nearly half of the patients were diagnosed with psychiatric disorders. The most frequent reason for SAs was family arguments. The majority of SAs were impulsive, and almost all cases involved drug overdoses. The most commonly used drugs for SAs were antipsychotic/antidepressant drugs. Furthermore, the presence of psychiatric disorders and a family history of SA were shown to be risk factors for recurrent SA.

In a recent multicenter study conducted in 27 German PICUs, it was reported that the mean age of children who attempted suicide was 14.8 (12-17.9), and 55.3% of those were female.[12] In Turkey, Özsoylu et al. [13] reported that the mean age of SAs among children was 14.5±1.2 (10.5-17), and 88.5% were female. Our study's findings were consistent with the literature. Previous studies have suggested that gender is an important risk factor in SAs in adolescents, and females have a higher risk of SAs compared to males.[8,14,15]

Researchers have mentioned that there is a seasonal pattern in SAs, and the rate of SAs tend to peak in spring.[13,16-18] However, Hryciuk et al.[19] reported that the number of suicide-related deaths increased in October. Studies conducted in our country have reported that the highest number of SAs were observed in May and June.[13,20] According to our study, spring was the period during which SAs were most frequently observed. In Turkiye, the academic calendar concludes in June, with all major exams scheduled during this time, such as the university and high school entrance exams. As a result, students go through the most intense period of exam stress during April and May. Those results suggest that stressors related to school success could be associated with SAs.

Researchers have pointed out the connection between mood disorders, personality disorders, and suicidality in adolescence.[8,21-25] Mood disorders are commonly associated with increased rates of suicidal behavior, particularly among adolescents. Previous studies have shown that depression is an important risk factor for suicide.[8,21,22] Furthermore, it was reported that SAs had more severe depressive symptoms than non-SAs and that the strongest independent risk factor for SAs was the degree of depression.[8,26] Additionally, researchers emphasized that adolescents with suicidal thoughts and SAs frequently suffer from personality disorders.[23,24] Furthermore, according to reports, the most important predictor of SAs and SA numbers is Borderline Personality Disorder.[24] Recent findings from a meta-analysis conducted with 27 articles revealed a positive correlation between suicidality and attention-deficit hyperactivity disorder (ADHD) across all age groups and genders.[27] It has been suggested that the impulsive behavior commonly seen in individuals with ADHD could be a factor in this connection. The fact that two-thirds of ADHD patients had at least one comorbid psychiatric disorder, such as a major depressive disorder, behavioral disorder, or substance abuse, is another factor contributing to the positive correlation between ADHD and suicidality.[27] In a study conducted in Turkey, Özsoylu et al.[13] found that among patients who attempted suicide, 28.8% had major depressive disorder, 11.5% had conduct disorder, 7.6% had adjustment disorder, and 3.8% had ADHD. In our study, 43.9% of patients had a psychiatric disorder that had been diagnosed prior to the SAs, with major depressive disorder (21.9%) being the most frequent co-existing psychiatric disorder and ADHD the second most frequent psychiatric disorder in children who attempted suicide. Furthermore, 95.6% of the SAs were impulsive.

Relationship problems with family members and friends were identified as the primary risk factors for SAs among children in earlier research.[5,13] Mete et al.[28] reported that the most common leading cause of SAs among children is relationship problems with family (60.6%). Doğan et al.[5] found that the leading causes of SAs were relationship problems with family (56.9%), relationship problems with a partner (30%), anxiety about academic failure (18%), and relationship problems with friends. Similar to the literature, family and partner arguments were the most common causes of SAs in our study. More frequent SAs in the spring may suggest that academic success is a significant cause of family arguments.

In the literature, it was mentioned that the death of a family member of suicide or SA increased suicidal ideation or attempts.[29,30] In a previous study, it was reported that 40% of suicidal adolescents had been exposed to suicide or SAs in their surroundings.[31] In another study, it was found that the rate of SAs was higher among the first-degree relatives of adolescents who completed suicide.[32] According to one study, people who witnessed suicide were more likely to have suicidal thoughts and attempted suicide.[33] Our study's results were similar to the literature.

In the literature, it was mentioned that overdose drug intake was the most common method of SAs among children in Turkey.[4,5,13] In our study, almost all patients attempted suicide by overdosing drugs. Studies have reported that analgesic-anti-inflammatory and antidepressant drugs were the most common drugs used for SAs.[13,34,35] Antipsychotic, antidepressant, and analgesic/antipyretic drugs were most commonly used for SAs in our study. Unlike the previous studies, antipsychotic drugs were in the first place among the drugs used in SAs in our study. These drugs were mostly prescribed medications to the patients by their physicians. Consequently, it is critical that families and physicians who prescribe medication exercise greater caution in this regard.

The main limitation of this study is that this study includes suicide cases that required hospitalization, monitoring, and treatment; it does not include all suicide cases that were admitted to our emergency department. The fact that this study is retrospective is another drawback. However, our study's strength lies in the fact that our hospital is one of the important centers to which patients with SAs are referred because it has a dedicated Children's Psychiatry Department, one of just three in Istanbul, a city with a population of 16 million.

CONCLUSION

In conclusion, our study demonstrates that family issues were the most frequent reason for SAs. We think that it would be helpful for health professionals to enquire about family dynamics in addition to physical examinations to deter SAs. It is crucial to monitor these people more closely since psychiatric disease and a family history of suicide attempts are risk factors for recurrent SAs. Studies with larger cohorts may be beneficial in order to have a better understanding of the primary causes of SAs.

Ethical approval

This study has been approved by the Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Research Ethics Committee (approval date 05.10.2022, number 2022/0461). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: SY, MD, AA; Concept: SY; Design: SY, AA, MD; Data Collection or Processing: AA; Analysis or Interpretation: SY; Literature Search: SY; Writing: SY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The relationship between serum anti-mullerian hormone levels and puberty in girls with obesity

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ABSTRACT

Objective: The purpose of this study was to assess the serum anti-Mullerian hormone (AMH) levels and related factors in overweight and obese girls during their prepubertal, pu-bertal, and post-menarcheal periods.

Method: Anthropometric measurements, physical examination features, laboratory findings, and serum AMH levels were evaluated in girls with overweight and obesity admitted be-tween March and April 2021 in the Pediatric Endocrinology Clinic at Erciyes University Faculty of Medicine.

Results: Serum AMH levels were evaluated in a total of 40 girls: 12 (30%) prepubertal, 12 (30%) pubertal, and 16 (40%) post-menarcheal. Their ages were 7.7 (±1.7), 10.3 (±2.1), and 15.4 (±1.8) years, and their serum AMH measurements were 2.4 (±2.4), 2.1 (±1.1), and 4.6 (±3.7) ng/mL, respectively. The serum AMH levels between prepubertal and pubertal girls and post-menarcheal girls were significantly different (p=0.020). There was no significant difference when compared to normal AMH levels for their age (p=0.722).

In the age-adjusted correlation analysis of the patients, no significant relationship was found between AMH levels and anthropometric measurements (height, weight, weight-SD, BMI, BMI-SD, neck circumference-SD, mid-upper arm circumference-SD, waist circumference-SD, waist-to-height ratio, and waist-to-hip ratio). A positive correlation was found only in height-SD (r=0.334, p=0.038).

Conclusion: The study found that the serum AMH levels of girls with overweight and obesi-ty increased moderately during the prepubertal period, specifically several years preceding puberty, slightly decreased during the onset of puberty, and significantly increased during the post-menarcheal period, like healthy girls.

Keywords: Anti-Mullerian hormone, body mass index, body measurements, obesity, puber-ty

INTRODUCTION

Anti-Mullerian hormone (AMH, formerly also called Mullerian inhibiting substance; MIS) is a homodimeric disulfide-linked glycoprotein and a member of the transforming growth factor-beta (TGF-b) superfamily secreted by the granulosa cells in the ovaries.[1,2] Antral follicles, which contain a large number of granulosa cells, are considered to be the primary source of circulating AMH. Since AMH is secreted exclusively from ovarian follicles, its serum concentrations in females are thought to reflect the size of the ovarian follicle pool.[3,4]

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Lee et al. first described normal levels of AMH in humans from infancy to adulthood. AMH values in females were lowest and typically undetectable during infancy, with a mini-mal rise throughout childhood and puberty. The mean serum AMH values rise during late puberty and then decline as a function of age.[5] In later investigations with larger case numbers, it was discovered that while the AMH level was undetectable in the cord blood, it slightly increased in the infantile period in accordance with the mini-puberty phase, then fell and stayed at consistent levels until around 6–8 years of age. AMH levels were found to rise after the aforementioned ages (about 2-3 years before the onset of puberty development) and to decrease moderately with the onset of pubertal development. It has been demonstrated that AMH levels rise once more, reaching a peak in the mid-twenties and falling off until menopause.[6-10] In addition, while there was an inverse correlation between AMH and both follicle-stimulating hormone (FSH) and luteinizing hor-mone (LH) levels before puberty, it was noticed that this relationship disappeared with the onset of puberty.[7,10,11]

While researches in reproductive-age women with obesity found an inverse relation-ship between AMH levels and body mass index (BMI), studies in adolescent girls with obesi-ty found a favorable relationship.[12-16] Some of these studies have suggest-ed that the relationship between BMI and AMH levels in the context of obesity is more closely related to increased central adiposity, the presence of polycystic ovary syndrome (PCOS), or having a mother with PCOS.[13,14,16] In the first known study of adolescents by Hart et al., girls with PCOS were found to have significantly higher AMH levels, BMI, and BMI-SD values.[14] However, in certain studies involving girls and women with obesity, no link was found between AMH levels and BMI.[17-19]

Previous studies in obese women have also investigated the relationship between AMH and glucose metabolism parameters such as glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR).[2,20,21] In this respect, we wanted to elucidate this relationship, which has not been previously examined in children and adolescents with obesity.

The aim of this study is to evaluate AMH levels in girls with overweight and obesity during their prepubertal, pubertal, and post-menarcheal periods, compare them to normal values, and demonstrate the accompanying features.

METHODS

The anthropometric measurements and laboratory data of girls between the ages of 4 and 18 who were overweight or obese (BMI ≥ 85%) and had their AMH levels measured during their visit to the university hospital's pediatric endocrinology clinic in March and April 2021 were obtained retrospectively from the archives. Anthropometric measurements, including height and weight without shoes, were performed by a single experienced nurse. The meas-urement devices had an accuracy of 0.1 cm for height and 0.05 kg for weight. BMI was cal-culated using the formula weight/height^2 (kg/m^2). The anthropometric measurements of the patients were evaluated according to the auxological references of Turkish children, and BMI standard deviation (SD) values were calculated for all ages compared to normal.[22] The patient's physical examination and neck, waist circumference, hip circumference, and mid-upper arm circumference (MUAC) measurements were performed by pediatric endocrinology fellows using a non-flexible measuring tape with a precision of 0.1 cm as previously described.[23,24]

AMH, FSH, LH, estradiol, testosterone, and insulin levels were analyzed using the electrochemiluminescence method with the Roche Diagnostics Cobas® e801 module (Roche Diagnostic, Mannheim, Germany). Glucose levels were analyzed using the enzymatic (hexo-kinase) spectrophotometric method in the Roche Diagnostics Cobas® c701 module (Roche Diagnostic, Mannheim, Germany). Glycosylated hemoglobin (HbA1c) levels were analyzed using the turbidimetric inhibition method in the Roche Diagnostics Cobas® c501 module (Roche Diagnostic, Mannheim, Germany).

To evaluate our data, we divided them into two categories: those that showed a nor-mal distribution and those that did not. We used ANOVA and Kruskal-Wallis tests to evalu-ate our independent variables. To evaluate our dependent variables, we used paired sample t-tests for those that showed a normal distribution and Wilcoxon signed rank tests for those that did not. We used partial correlation analyses to evaluate the relationship between de-pendent quantitative variables. Statistical evaluation of the findings was performed using Statistical Packages for the Social Sciences version 25.0 software (SPSS, Chicago, IL, USA).

RESULTS

Serum AMH levels were studied from a total of 40 girls, 12 (30%) prepubertal, 12 (30%) pubertal, and 16 (40%) post-menarcheal. Their ages were 7.7 (±1.7), 10.3 (±2.1), and 15.4 (±1.8) years, and their serum AMH measurements were 2.4 (±2.4), 2.1 (±1.1), and 4.6 (±3.7) ng/mL, respectively (Table 1 and Figure 1). There was a significant difference in terms of AMH levels among the three groups (p=0.020), but no significant difference was observed when the patients' AMH levels were compared with their age averages (p=0.722) (Table 2).

Table 1. Comparison of the characteristics of patients according to pubertal periods				
	Prepubertal	Pubertal	Post-menarcheal	P
Age (year)	7.7 (±1.7)	10.3 (±2.1)	15.4 (±1.8)	<0.001[1]
Weight-SD	2.52 (±0.86)	2.03 (±1.15)	1.59 (±1.02)	0.072[1]
Height-SD	1.38 (±1.22)	0.01 (±1.28)	-0.58 (±0.94)	<0.001[1]
BMI-SD	2.2 (±0.5)	2.2 (±0.7)	1.9 (±0.6)	0.403[1]
Neck Circumference (cm)	30.9 (±3.8)	31.5 (±2.7)	34.0 (±1.8)	0.012[1]
Neck Circumference-SD	3.75 (±2.16)	2.21 (±1.47)	2.13 (±1.23)	0.028[1]
Mid-Upper Arm Circumference (cm)	24.9 (±4.6)	28.3 (±3.8)	30.3 (±2.7)	0.002[1]
Mid-Upper Arm Circumference-SD	3.87 (±1.33)	4.37 (±1.06)	3.47(±1.32)	0.187[1]
Waist Circumference (cm)	76.4 (±9.7)	82.8 (±10.6)	86.9 (±7.2)	0.017[1]
Waist Circumference-SD	4.00 (±1.50)	3.06 (±1.35)	1.6 (±1.23)	<0.001[1]
Waist-to-Height Ratio	0.57 (±0.04)	0.58 (±0.06)	0.55 (±0.04)	0.235[1]
Waist-to-Hip Ratio	0.89 (±0.05)	0.87 (±0.05)	0.83 (±0.06)	0.050[1]
AMH (ng/mL)	2.42 (±2.4)	2.14 (±1.1)	4.62 (±3.7)	0.020[2]
FSH (mIU/mL)	1.02 (±0.3)	8.6 (±17.7)	4.64 (±1.5)	<0.001[2]
LH (mIU/mL)	0.62 (±1.0)	4.12 (±8.9)	12.08 (±7.4)	<0.001[2]
Estradiol (pg/mL)	10.01 (±16.6)	19.3 (±21.3)	89.2 (±91.3)	<0.001[2]
Glucose (mg/dL)	87.5 (±10.4)	87.8 (±9.9)	88.3 (±9.4)	0.976[1]
Insulin (µU/mL)	17.52 (±10.6)	20.79 (±9.6)	26.85 (±26.3)	0.371[2]
HOMA-IR	3.89 (±2.4)	4.59 (±2.3)	6.17 (±6.7)	0.696[2]
HbA1c (%)	5.23 (±0.2)	5.35 (±0.1)	5.27 (±0.3)	0.302[2]

BMI: body mass index. AMH: Anti-Mullerian hormone. FSH: follicle-stimulating hormone. LH: luteinizing hormone. HOMA-IR: homeostasis model assessment of insulin resistance. HbA1c: glycosylated hemoglobin. [1] One-Way Anova Test p-value. [2] Kruskal-Wallis Test p value. p<0.05 was considered statistically significant.

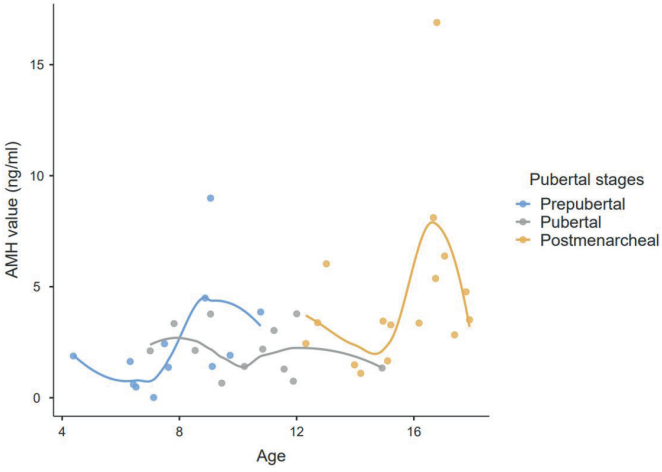

Figure 1. Trend of AMH levels according to age and pubertal stages

The results indicated no age-adjusted correlation between AMH levels and various body measurements, such as weight-SD, BMI-SD, neck circumference-SD, mid-upper arm circumference-SD, waist-to-height ratio, and waist-to-hip ratio (Table 3). A positive correla-tion was observed between serum AMH levels and height-SD (r = 0.167, p = 0.038). In addi-tion, no significant age-adjusted correlation was found between serum AMH and FSH, LH, estradiol, testosterone, glucose, insulin, HbA1c, and HOMA-IR measurements (Table 3).

DISCUSSION

In this study, the AMH levels of girls with overweight and obesity were found to be con-sistent with previous studies in the prepubertal, pubertal, and post-menarcheal periods. As in these studies, a moderate decrease in AMH levels compared to the prepubertal period with the onset of the pubertal period and then an increase in the post-menarcheal period were de-tected.[5,7-10] In addition, when the AMH levels of the patients

Table 2. Comparison of AMH measurements with age-specific norms			
	The mean AMH (ng/mL) value by age according to our study	The mean AMH (ng/mL) value by age, according to the study by Lee et al. (1996)	P[1]
Prepubertal	2.42 (±2.44)	2.60 (±0.50)	0.347
Pubertal	2.14 (±1.11)	2.85 (±0.64)	0.117
Post-menarcheal	4.62 (±3.78)	3.00 (±1.09)	0.234
Total	3.22 (±2.98)	2.83 (±0.82)	0.722

[1] Wilcoxon Signed Ranks Test p-value. p<0.05 was considered statistically significant.

Table 3. Age-adjusted correlation evaluation of AMH measurements with other parameters					
	Number	Mean	SD	r	P[1]
Weight-SD	40	2.00	1.06	0.158	0.335
Height-SD	40	0.18	1.38	0.334	0.038[a]
BMI-SD	40	2.09	0.66	0.009	0.955
Neck Circumference-SD	40	2.64	1.75	0.147	0.372
Mid-Upper Arm Circumference-SD	40	3.86	1.28	-0.090	0.586
Waist Circumference-SD	40	2.76	1.67	0.244	0.135
Waist-to-height ratio	40	0.56	0.05	0.023	0.889
Waist-to-hip ratio	40	0.86	0.06	0.224	0.169
FSH (mIU/mL)	35	4.64	9.65	-0.222	0.208
LH (mIU/mL)	35	6.20	8..27	-0.096	0.590
Estradiol (pg/mL)	34	45.12	70.02	-0.124	0.492
Testosterone (ng/dL)	19	25.95	19.35	0.020	0.938
Glucose (mg/dL)	40	87.9	9.6	-0.180	0.272
Insulin (µU/mL)	36	22.4	18.6	0.054	0.760
HOMA-IR	36	5.07	4.74	0.040	0.821
HbA1c (%)	36	5.28	0.28	-0.179	0.303

BMI: body mass index. AMH: Anti-Mullerian hormone. FSH: follicle-stimulating hormone. LH: luteinizing hormone. HOMA-IR: homeostasis model assessment of insulin resistance. HbA1c: glycosylated hemoglobin. SD: standard deviation. [1] p value for age-adjusted partial correlation test. [a] Statistically significant. p<0.05 was considered statistically significant.

were com-pared with the mean AMH levels of their age stated in previous studies, no difference was found.[5,11]

In the presented study, there was no age-adjusted correlation between serum AMH levels and various body measurements such as weight-SD, BMI-SD, waist circumference-SD, waist-to-height ratio, and waist-to-hip ratio in girls with overweight and obesity. There was a significant age-adjusted correlation only between AMH levels and height-SD. A recent research of 83 prepubertal and pubertal girls (23.6% of whom were overweight or obese) demonstrated that those with a greater waist-to-height ratio had higher AMH_{log} levels.[25] A prior study with women of repro-ductive age demonstrated that AMH levels were inversely associated with waist circumfer-ence and waist-to-height ratio, both of which are central obesity markers and BMI.[26] While there is an inverse relationship between BMI and AMH levels in research conducted with women of reproductive age, there are studies that show a positive correlation in research conducted during adolescence.[12-16,27] A previous study reported an inverse correlation between AMH levels and BMI-SD in girls with premature adrenarche.[28] Yet, some research with adolescents and adults found no link between BMI and AMH levels, which is in line with our study.[17-19,29,30] Another study found that in girls with central precocious puberty, AMH levels were negatively correlated with height-SD and BMI-SD.[31]

No significant age-adjusted correlation was found between serum AMH levels and FSH, LH, estradiol, testosterone, glucose, insulin, HOMA-IR, and HbA1c measurements of girls with overweight and obesity. In contrast to our outcomes, an earlier study in adolescent girls reported a negative relationship between serum AMH levels and estradiol levels.[32] A previous study on adolescents with PCOS reported a positive correlation between AMH levels and total testosterone levels.[16] Furthermore, studies in women with PCOS found a favorable association between total testosterone, LH, and AMH levels.[13,15] Unlike our study, investigations in adult women reported that individuals with high AMH levels have higher HOMA-IR.[2,20,21]

We believe that comparing the parameters of girls with overweight and obesity at dif-ferent stages of adolescence would not be reliable due to the limited number of cases in our study. Another important limitation is that serum AMH levels were not studied simultane-ously with an age-matched control group due to the retrospective nature of the study. None-theless, we assert that the similarity of AMH levels in girls with overweight and obesity in our research to the findings of investigations that reveal the normal AMH levels according to age is valuable. Undoubtedly, future studies with a larger sample size will make greater con-tributions to this field.

CONCLUSION

The study revealed that the serum AMH levels in girls with overweight and obesity increased moderately during the prepubertal period, specifically several years preceding puberty, slightly decreased during the onset of puberty, and significantly increased during the post-menarcheal period, similar to healthy girls. In addition, there was no age-adjusted correlation between serum AMH levels and various body measurements such as weight-SD, BMI-SD, waist circumference-SD, waist-to-height ratio, and waist-to-hip ratio of prepubertal, pubertal, and post-menarcheal girls with overweight and obesity.

Ethical approval

The study was approved by the Ethics Committee of Erciyes University Faculty of Medicine (Protocol no. 2021-757/11.24.2021).

Author contribution

Study conception and design: ÜGŞ, and NH; data collection: ES, DÇ, LK, ESG, UB, and SM; analysis and interpretation of results: ES, ÜGŞ, NH; draft manuscript preparation: ES, ÜGŞ, and NH. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of bleeding diathesis in patients with Noonan syndrome and comparison with thromboelastography (TEG) test results: A single-center experience

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ABSTRACT

Objective: Patients with Noonan syndrome (NS), who may need various surgical interventions throughout their lives, need to be evaluated carefully in the preoperative period due to the risk of bleeding diathesis. There is a limited number of studies evaluating bleeding diathesis in patients with NS. In this study, we aimed to determine the frequency of bleeding diathesis in patients with NS and to evaluate the place of thromboelastography (TEG) in determining the risk of bleeding.

Method: In our study, bleeding score and coagulation test results obtained from the files of 12 patients with NS were evaluated.

Results: The most frequently detected factor deficiency is vWF deficiency (41%), followed by platelet dysfunction (33%). Two cases with a bleeding score of 2 or above were detected, and in one of them, both platelet dysfunction (response to epinephrine in platelet aggregometer, 7%) and vWF deficiency (vWF Ag: 20%), and in the other case, mild Factor VII deficiency (17%) were detected. TEG results of nine patients were normal. TEG abnormality was detected in three patients and 2 of them had bleeding phenotype.

Conclusion: As a result, although laboratory examinations in patients with NS often yield values consistent with bleeding diathesis, bleeding event does not occur in most patients. We suggest that with the use of the TEG method, the risk of bleeding can be predicted and unnecessary treatments can be prevented.

Keywords: bleeding disorders, laboratory test abnormalities, Noonan syndrome, thromboelastography

INTRODUCTION

Noonan syndrome (NS) is a clinically and genetically heterogeneous disease that is frequently inherited as an autosomal dominant and rarely as an autosomal recessive. Its estimated prevalence is between 1/1000 and 1/2500.[1] The clinic of the disease may vary from mild to severe form.[2] Typical NS findings include facial findings, short stature, skeletal abnormalities, congenital heart defects, chest deformity, lymphatic dysplasia, cryptorchidism, developmental delay, and bleeding disorders.[3,4] *PTPN11* gene mutation, which causes activation of the RAS/mitogen-activated protein kinase (RAS-MAPK) pathway, is responsible for approximately 50% of patients.[5,6] In addition, *SOS1*, *RAF1*, *KRAS*, *MEK1*, *RIT1,* and *BRAF* gene mutations have also been associated with this RASopathy.[7,8]

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When NS was first described, its relationship with hematological disorders could not be clearly established.[9] It has been reported in some studies that there is an increase in the risk of bleeding disorders in the following years.[3,4] However, the frequency of bleeding diathesis varies significantly between studies, ranging from 20% to 92%.[4] Factor XI deficiency and platelet dysfunction are most frequently reported in NS.[3] Although factor deficiency was initially reported more frequently, platelet dysfunction was the most frequently detected hematological disorder, with a frequency of 83% in studies conducted in recent years.[10,11] Many patients with NS may be exposed to repeated surgical interventions in early childhood for cardiac pathologies, cryptorchidism, or lymphatic vessel abnormalities. Bleeding events have been reported to occur in 4.5-20% of these patients in the postoperative period.[12,13] Therefore, preoperative evaluation of hemostasis is crucial. On the other hand, although it is thought that normal findings in standard coagulation tests in these patients are not sufficient to exclude the risk of bleeding, no consensus has been established on the standard approach.[3] To our knowledge, thromboelastography (TEG) has not been used in the literature when determining the bleeding risk of NS cases. TEG is a very useful test for evaluating general hemostasis and predicting bleeding in cases of bleeding diseases. This study aimed to determine the frequency of bleeding diathesis in patients with NS and to evaluate the place of TEG in determining the risk of bleeding.

MATERIAL AND METHODS

Patients

We reviewed the file records of 12 patients who were referred to our pediatric hematology outpatient clinic with the diagnosis of Noonan syndrome between December 2010 and December 2020.

The diagnosis of NS is made clinically according to the scoring system developed by van der Burgt.[14] This scoring system is divided into two subgroups, major and minor, according to the severity of the clinical findings. These findings include i) typical facial findings, ii) cardiac anomalies (pulmonary stenosis or hypertrophic cardiomyopathy), iii) short stature, iv) chest wall anomalies, v) family history, and vi) other (mental retardation, cryptorchidism, lymphatic dysplasia). According to this scoring system, the diagnosis is made if there are one major or two minor findings in addition to the major facies findings. In addition, if there are two major or three minor findings in addition to the minor facies findings, NS should be taken into account. Moreover, all patients in the study had PTPN11 mutation detected by the Next Generating Sequencing or Sanger sequencing method.

The pediatric bleeding score developed by Bowman et al.[15] (epistaxis, cutaneous, bleeding after minor injury, intraoral bleeding, gastrointestinal bleeding, bleeding after tooth extraction and pediatric-specific bleeding [post-circumcision, umbilical bleeding, cephalic hematoma, venous bleeding and macroscopic hematuria], post-surgical bleeding, central nervous system bleeding, menometrorrhagia, muscle hematoma, and scoring related to hemarthrosis) results were noted. A minimum of -3 and a maximum of 48 points can be obtained in the Pediatric Bleeding Score. A total score of 2 or above was considered significant in terms of bleeding tendency.

Laboratory methods

From the patient's file records, complete blood count, peripheral smear findings, prothrombin time (PT), activated prothrombin time (aPTT), fibrinogen level, platelet function analyzer (PFA-100), thrombin time, Factor V- VII- VIII- IX- X- XI - XII-XIII level, von Willebrand factor antigen level (vWf: Ag), von Willebrand factor ristocetin cofactor activity (vWf: Rcof), platelet aggregometer and TEG results were obtained. PT and aPTT values were evaluated according to age-appropriate normal ranges.[16] The PFA-100 result was considered normal if it was between 85–165 seconds for the Collagen/Epinephrine cartridge and 71–118 seconds for the Collagen/ adenosine diphosphate (ADP) cartridge.[17]

vWF: Ag and vWF: Rcof values below 30% were defined as vWF deficiency. If these values were 30-50%, which was considered the gray zone, it was accepted as vWF deficiency in the presence of bleeding clinic.[18] Factor V-VII-VIII-IX-X-XI-XII-XIII level was defined as factor deficiency if it was below 50%.

Haemoscope thromboelastograph analyzer (Haemoscope, USA) was used for TEG analyses. TEG is an in vitro test that provides information about clot formation, maximum clot thickness, and fibrinolysis. The R-value represents the time until the first evidence of a clot is detected. This time refers to the time from the beginning of the test to the point where the clot strength reaches 2 mm amplitude. Prolongation of the R time is associated with clotting factor deficiency, the presence of inhibitors, or the use of anticoagulants. K value means clot formation time and indicates the time it takes for the clot to reach an amplitude of 20 mm. It is related to both thrombin activity and fibrin formation. The angle formed between the tangent line drawn from the curve departing from the horizontal

axis and the horizontal axis (α angle) shows the speed at which the clot reaches maximum amplitude (MA). MA is affected by platelets and fibrinogen levels.[19] All TEG studies were performed with the CFMS LEPU 8800 device. R time was considered normal as 2-8 minutes, K time as 1-3 minutes, α angle as 55-78 degrees, and MA as 51-69 mm.[19]

Informed consent was obtained from all patients and their parents. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. This study was approved by the University of Bakırçay Ethics Committee (decision number: 803).

RESULTS

The average age of the 12 patients (6 girls, 6 boys) with NS included in the study is 6.4 years (range, 1.5-16 years). In 2 of the patients, the bleeding score was two or above. While platelet dysfunction (response to epinephrine in platelet aggregometer was 7%) and vWF deficiency (vWF Ag: 20%) were detected in one of them, mild Factor VII deficiency (17%) was detected in the other. PFA-100 values were high in six patients, and five of these cases had vWF factor deficiency or platelet dysfunction. Factor XI deficiency was not detected in any of the patients. Isolated type I vWF deficiency in 2 cases, both type I vWF deficiency and platelet dysfunction in 2 cases, both factor VII and type I vWF deficiency in 1 case, factor VII deficiency, factor X deficiency, and platelet dysfunction in 2 cases, isolated factor VII deficiency in 1 case, isolated platelet dysfunction in 1 case were detected. Bleeding diathesis was not detected in only 3 of 12 cases in terms of history and laboratory features. The most frequently detected factor deficiency was vWF deficiency (41%), followed by platelet dysfunction (33%). All factor deficiencies were mild factor deficiencies. Patient characteristics are shown in Table 1.

TEG results of nine patients were evaluated as normal. The first case (patient no:2) had a long K time and a decreased MA value. This patient with a high bleeding score had platelet dysfunction and vWF deficiency. The second case (patient no:4) with a high bleeding score had a prolonged R time and Factor VII deficiency. The third case (patient no: 7) had prolonged R time and vWF deficiency; however, the bleeding score of this patient was normal (Table 1).

Table 1. Bleeding score and laboratory results of the patients

Patient No	Bleeding Score	PFA-100	Platelet Count	PT	aPTT	Fibrinogen	Factor Levels	Platelet Aggregometer	Thromboelastogram
1	<2	col/epi:269-col/ADP:138	Normal	Normal	Normal	Normal	vWF Ag: %27	Normal	Normal
2	5	col/epi:219-col/ADP:106	Normal	Normal	Normal	Normal	vWF Ag: %20	Epinephrine response %7	Prolonged K-time, Decreased MA
3	<2	col/epi:171-col/ADP:98	Normal	Normal	Normal	Normal	Factor 7: %45	Normal	Normal
4	4	Normal	Normal	Normal	Normal	Normal	Factor 7: %17	Normal	Prolonged R-time
5	<2	Normal	Normal	Normal	Normal	Normal	Factor 7: %45 / vWF Ag: %3.6	ND	Normal
6	<2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
7	<2	col/epi:237-col/ADP:96	Normal	Normal	Normal	ND	vWF Ag: %7	Epinephrine response %6.5 / ADP response %56	Prolonged R-time
8	<2	col/epi:276-col/ADP:117	Normal	Normal	Normal	Normal	Factor 7: %46 / Factor 10: %37.8	Epinephrine response %10	Normal
9	<2	Normal	Normal	Normal	Normal	Normal	Normal	Epinephrine response %14.7	Normal
10	<2	col/epi:188-col/ADP:116	Normal	Normal	Normal	Normal	Factor 8: %40 / vWF Ag: %44	ND	Normal
11	<2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
12	<2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

ND: not done, PFA: platelet function analyzer, PT: prothrombin time, aPTT: activated partial thromboplastin time, vWF: von Willebrand factor, vWF Ag: von Willebrand factor antigen, ADP: Adenosine diphosphate

DISCUSSION

TEG was first described by Hellmut Hartert[20] in 1948, and its use in cardiac surgery and liver transplant surgery has become widespread over the years.[21] TEG is a very useful method to evaluate the entire coagulation process and predict the risk of bleeding. It is possible to quickly decide on treatment with the curve obtained in this method and to prevent unnecessary transfusions if TEG demonstrates the normal coagulation process in cases where abnormal results are detected in basic laboratory tests related to the coagulation process. To our knowledge, this is the largest study evaluating the usefulness of TEG in predicting bleeding in patients diagnosed with NS. In the study by Bruno et al.[22] a bleeding phenotype was identified in 5 of 12 NS cases evaluated for bleeding diathesis. Platelet dysfunction and at least one factor deficiency were detected in 4 out of 5 cases. In the same study, TEG results of 5 cases with bleeding phenotype and 4 cases without bleeding phenotype were reported as normal. Therefore, the authors suggested that it is not necessary to evaluate NS cases with TEG.[22] The 4 cases with bleeding diathesis in Bruno's study had platelet dysfunction, and the normal TEG in these patients may be since the standard activators in this test are not sensitive to platelet dysfunction (except Glanzman's thrombasthenia). In the study conducted by Barg et al., the bleeding status of 24 Noonan syndrome cases was evaluated with thrombin generation used to evaluate global hemostasis, and the parameters were found to be lower compared to the control group. However, no significant correlation was observed with the bleeding clinic.[23] In our study, TEG was found to be abnormal in 2 of the 2 cases with bleeding phenotype. However, in 1 case without bleeding phenotype, R time on TEG was prolonged. We showed that there were abnormalities in the TEG results of cases with high bleeding scores; however, the small number of patients we included made it difficult to generalize our results to NS patients. Studies involving a large patient population and TEG with platelet mapping (TEG-PM), which was developed to evaluate platelet functions in patients with NS, where platelet dysfunction is common, may be guiding.

In the study by Bertola et al.[24] abnormal laboratory findings related to coagulation were reported in 9 of 30 patients (30%). Factor deficiency was identified in five cases, thrombocytopenia in 1 case, and platelet dysfunction in 1 case. Factor XI deficiency was most commonly reported (3 in 9 cases), and mild deficiency was detected in those with factor XI deficiency.[24] In the study of Sharland et al.[25] it was reported that 65% of 72 NS cases had a history of bleeding, and 50% had factor deficiency (most commonly Factor XI deficiency). However, later studies reported that platelet dysfunction was more common in patients with NS.[4,23,26] Ruiz-Llobet et al.[26] reported platelet dysfunction in 15 of 22 children (68%) with NS. Moreover, it has also been reported that platelet transfusion was performed in 2 of 14 cases (one with blepharoplasty and the other with kidney biopsy) due to bleeding events during or after surgical intervention. In the study of Artoni et al.[4] it was found that 38.5% of the 39 patients with NS included had a bleeding score of 2 or more (approximately half of these cases had a bleeding score of 4 or more). In addition, factor deficiency or platelet function abnormality was reported to be detected in 93.7% of those with bleeding diathesis and 87.5% of those without bleeding diathesis.[4] In the same study, factor deficiency was identified in 46% of the patients (most commonly Factor VII deficiency), and platelet dysfunction was identified in 83%.[4] In the systematic review of Nugent et al.[3] a total of 428 NS patients from 31 studies were included, and it was reported that 43% of the patients had a bleeding history and 195 (46%) had a specific bleeding disorder. It has been reported that 78% of these patients have a single factor deficiency, and the most common deficiency is Factor XI (81 patients). In the current study, unlike the literature, vWF deficiency was the most common (41%), followed by platelet dysfunction (33%). This may be related to the small number of patients.

Our study has some limitations that should be acknowledged. This study is a single-center retrospective study, and this may have caused bias in case selection. Since mutations in the same gene were detected in all patients, genotype-phenotype correlation was not investigated. Additionally, the relatively small number of patients included made it difficult to draw clear conclusions about the results.

As a result, abnormalities in coagulation-related laboratory results were detected in 9 of 12 patients in this study. However, only two patients had a bleeding score of 2 or higher. Two of the patients with abnormal TEG results had a history of bleeding. NS patients, who require surgical intervention more frequently throughout their lives than the normal population, should be evaluated carefully in terms of bleeding risk. Although abnormalities compatible with bleeding diathesis are frequently detected in laboratory examinations in patients with NS, bleeding may not occur. TEG testing may be a useful test in predicting bleeding and preventing unnecessary treatments. Further studies are needed to standardize TEG, one of the preoperative tests, in these patients.

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Ethical approval

This study was approved by the Ethics Committee of Bakırçay University in İzmir, Turkey, in accordance with the Declaration of Helsinki. All of the children and/or their parents gave their written informed consent before the study (date/number: 21.12.2022/803).

Author contribution

Medical Practices: SOA, SG, YO, THK; Concept: SOA, THK; Design: SOA, NT, IOA, THK; Data Collection or Processing: SOA, ME; Analysis or Interpretation: SOA, SG, YO, THK; Literature Search: SOA; Writing: SOA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Pulmonary function is reduced in children with recurrent wheezing irrespective of Asthma Predictive Index results

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ABSTRACT

Objective: It is important to determine the risk factors for the development of asthma in patients with recurrent wheezing (RW). This study was intended to compare the lung functions of children with RW with and without Asthma Predictive Index (API) positivity.

Methods: This prospective cross-sectional study included 40 children with RW aged between 3 months and 3 years and 34 age- and sex-matched healthy controls (HC). Lung functions were measured using tidal breath analysis during the wheezing attack in the RW group. Peak tidal expiratory flow time (TPTEF), ratio of peak tidal expiratory flow time to expiratory time (TPTEF/TE), volume required for PTEF (VPTEF), ratio of volume required for PTEF to expiratory volume (VPTEF/VE), tidal volume/kg (VT/kg), inspiratory to expiratory ratio (TI/TE), inspiratory time (TI), and expiratory time (TE) represented the main tidal breath analysis parameters. API positivity was also calculated in the RW group.

Results: TPTEF, VPTEF, TPTEF/TE, VPEF/VE, TI, and TI/TE were all lower in the RW group than in the HC group ($p<0.05$). However, there was no difference in TPTEF/TE between the RW patients with positive and negative API. TPTEF and TE parameters were higher in the RW group with positive API ($p=0.026$ and $p=0.043$, respectively).

Conclusion: Greater bronchial obstruction was observed in the RW group compared to the HC group. No difference in bronchial obstruction was detected between the RW group with positive API and the negative API group. API positivity during wheezing attacks did not emerge as an important parameter in terms of decreased lung functions in this study.

Keywords: Tidal breath analysis, wheezing, asthma predictive index, lung function, child, asthma, infant

INTRODUCTION

Wheezing is a symptomatic sign of airway obstruction caused by various disease processes, characterized by a musical, high-pitched sound produced during expiration or inspiration, originating anywhere from the larynx to the distal bronchioles.[1] One in three children will experience at least one wheezing episode in the first three years of their lives.[2] One of the most striking epidemiological features of wheezing episodes in infants is their tendency to recur. Although many children in this age group may have a single episode of wheezing not followed by subsequent similar episodes, over 50% of such subjects will experience wheezing at least once within the next few months.[2] Additionally, parents of 30-40% of children who wheeze before the age of 3 report current wheezing at 6 years of age.[3] It is crucial to perform a differential diagnosis of patients with RW,

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to identify risk factors for asthma development, and to detect preschool children at risk of persistent asthma at an early age.[4]

Definitive screening tests to identify potential asthma in children with RW are not yet available.[5] The Asthma Predictive Index (API), first developed in the Tucson Cohort Study, is widely used to identify preschool children with RW who are at high risk of developing asthma later in life.[6] A positive API by 3 years is associated with a 77% risk of asthma between the ages of 6 and 13, while a negative API by the age of 3 entails a lower than 3% risk of developing asthma during school age.[7]

Pulmonary function tests are highly valuable in the diagnosis of asthma, evaluating the treatment response, predicting prognosis, and determining the risk of exacerbations. Bronchial obstruction and increased airway resistance cause irregular pulmonary mechanics with restricted inspiratory and expiratory gas flow.[8] The measurement of lung function in young infants is useful in terms of explaining possible damage to the large and small airways.[9-12] However, conventional spirometry tests cannot be performed on infants because they require difficult maneuvers and patient compliance. Devices capable of measuring tidal breathing are particularly advantageous in this context, especially in infants or children with cooperation difficulties.[10] Tidal breath analysis (TBA) is a standardized and simple technique with no side effects that measures parameters shown to correlate with lung mechanics.[13] Since TBA is easy to apply, independent of effort, and requires minimal patient compliance, it can easily be performed to measure lung functions in children during the first three years of life, including the neonatal period. However, insufficient data concerning TBA in children with RW is available.

The purpose of this study was to employ TBA to evaluate respiratory functions in children with RW younger than three years old, to compare these with healthy children, and to investigate the relationship between respiratory functions and the API.

METHODS

Study design

This prospective cross-sectional study was conducted between January and April 2020 in the pediatric allergy and immunology department and general pediatrics clinics or wards of a tertiary hospital in Türkiye.

Demographic characteristics (age, gender, weight, height, week of birth, mode of delivery, and birth weight), presence of allergic diseases such as atopic dermatitis, allergic rhinitis, food allergy, parenteral and sibling allergic disease, wheezing information (history of wheezing attack without respiratory tract infection, age at first wheezing attack, total number of attacks, history of hospitalization, and treatments used), environmental exposures (prenatal and postnatal exposure to cigarette smoking, pets, humidity, stoves, etc.), physical examination findings, and eosinophil counts were recorded for all cases. All patients' respiratory functions were evaluated using TBA. For children with RW, TBA measurement was performed during the wheezing attack and before treatment administration.

The API is used to predict which children with ≥4 episodes of wheezing will go on to experience asthma and consists of major and minor criteria. The major criteria are maternal or paternal physician-diagnosed asthma and physician-diagnosed atopic dermatitis. The minor criteria include physician-diagnosed allergic rhinitis, wheezing without common cold, and the presence of eosinophils at a level exceeding 4% in peripheral blood. Individuals who meet one major or two minor criteria are considered positive for the API.[14] Children with a history of atopy in first-degree relatives were recorded as high-risk infants.[15]

Inclusion criteria

Children aged between 3 months and 3 years, with ≥4 episodes of wheezing in the previous year, and who were followed up or hospitalized in general pediatrics or pediatric allergy and immunology outpatient clinics due to wheezing attacks were included in the study.

The healthy control (HC) group was randomly selected from age- and gender-matched patients who presented to general pediatric outpatient clinics for routine healthy child checks.

Exclusion criteria

Individuals with a history of prematurity (gestational age <37 weeks), chronic lung disease (cystic fibrosis, bronchiolitis obliterans, bronchopulmonary dysplasia, bronchiectasis, airway malformations, etc.), gastroesophageal reflux disease, upper airway obstruction (tracheomalacia, laryngeal web, croup, choanal atresia), primary or secondary immunodeficiency, chronic disease (congenital heart disease, metabolic disease, neuromuscular disease, etc.), use of drugs affecting lung functions (inhaled or systemic corticosteroid, antihistamine, montelukast, nebular salbutamol, adrenaline, ipratropium bromide etc.), and children unable to comply with the pulmonary function tests were either not included in the wheezing group or were excluded from the study.

In the HC group, children with atopy and a history of viral respiratory tract infection in the previous two weeks, in addition to the wheezing child exclusion criteria, were also excluded from the study.

Tidal breath analysis

A commercially standardized, portable apparatus connected the tidal breath monitor to the pulmonary function tester (Jaeger/Viasys Master Screen TNA; Yorba Linda, CA, USA) (ErichJaegerGmbH, Bavaria, Marktrendwitz, Germany). Flow measurement was performed using a heated pneumotachograph (HansRudolph Inc., USA) providing a flow of 0-10 L/minute. The pneumotachograph was connected to a transmitter capable of sensing different pressures and a 100 Hz signal generator. The current curves were performed with a capacity of up to 256 measurements per second with the digital detection of the current signal. A low dead space, transparent, latex-free, silicone-capped face mask (Rendell Baker, Soucek, Rusch UK Ltd. Bucks, UK) was placed over the patient's nose and mouth during respiratory measurements.[16,17] The mask was tightly connected to the pneumotachograph, and the dead space was kept as low as possible. The amount of dead space in the pneumotachograph was 1.66 mL, a total of 2.4 mL in the system, and 11-14 mL in the mask; these values are all being standardized. Prior to each recording, the practitioner calibrated the device using a 100 mL syringe.[18,19]

Tidal Breath Measurement

Tidal breath was measured when the children were calm or asleep and breathing spontaneously. The procedure was carried out by two nurses and observed by a pediatrician and pediatric allergy specialist. Tidal breath analysis was conducted before initiating any treatment to avoid potential improvements in lung function that could result from the treatment. Additionally, to ensure consistency and minimize variations in respiratory rhythm related to the disease, all measurements were taken during the same period, by the same practitioners, and under identical room conditions for each patient. The children were supported by extending the back of the neck in a neutral position and were placed in the supine, straight, or semi-recumbent position. This minimized the effect of airway and glottis obstruction on the measurements.[20]

After placing a mouth or face mask appropriate to the child's facial structure, 2-3 minutes were allowed to elapse for adaptation. The measurements commenced once the respiratory rhythm was regular.[9] In case of variability in respiratory rhythm, body movement, inability to install the mask sufficiently accurately, failure to reach the volume baseline of the previous expiratory extension at the beginning of inspiration, or in the presence of any artifact, that part was not evaluated.[18,19] Depending on the variability of the breathing pattern, measurements were taken as the flow-volume curve of 60 inspiratory and expiratory breath cycles, each of which varied less than 15% in total, was observed on the screen.[16,17] This was considered an epoch. Respiratory patterns in which at least 20 regular respiratory cycles of each epoch cycle were detected and the best values were selected. At least three epoxies were observed at least every five minutes. The values of all epoxies were recorded, and the average was calculated separately by two researchers. Flow/volume measurement in young children is performed with the CareFusion pneumatic method (dead space volume 7 mL).

Parameters including peak tidal expiratory flow (PTEF), peak tidal expiratory flow time (TPTEF), the ratio of peak tidal expiratory flow time to expiratory time (TPTEF/TE), the volume required for PTEF (VPTEF), the ratio of volume required for PTEF to expiratory volume (VPTEF/VE), respiratory rate (RR), minute ventilation (MV), tidal volume (VT), tidal volume/kg (VT/kg), inspiratory to the expiratory ratio (TI/TE), inspiratory time (TI), expiratory time (TE), expiratory flow when the tidal volume in the lungs is 75%, 50%, 25% (TEF75, TEF50, TEF25), and expiratory volume at peak tidal expiratory flow (EVaTPTEF) were measured with TBA in this study. The within-subject (or repeated measurements) coefficient of variation (CV) for VT was calculated as the ratio of the standard deviation to the mean of VT x 100. Measurements were included in the analysis only when CV for VT was ≤ 10% and no mask leakage occurred during quiet sleep.[21]

Ethical issues

The study was approved by the local clinical research ethics committee (no. 23, dated 23.01.2020), and written informed consent was obtained from the parents of the patients enrolled in the study.

Statistical analysis

The conformity of quantitative data to normal distribution was examined using the Kolmogorov-Smirnov test. The t-test was used to compare variables with normal distribution between independent groups, and descriptive statistics were shown as mean±standard deviation (SD). Quantitative variables that were inconsistent with normal distribution were expressed as median values (25-75 percentile). The Mann-Whitey U test was used for descriptive statistical comparisons between groups. Categorical variables were analyzed using the chi-square test, and descriptive statistics were presented as frequency values (%).

Pearson or Spearman correlation analyses were used to examine the relationship between variables. p values <0.05 value were considered significant.

RESULTS

There was no difference between the RW and HC groups in terms of demographic characteristics (Table 1). The features of wheezing symptoms in the RW group are shown in Table 2.

Levels of prenatal and postnatal cigarette exposure, humidity in the home, stove use, and contact with pets were higher in the RW group compared to the HC group (p<0.05). The frequencies of parenteral asthma or allergic disease, sibling asthma or allergic disease, and high-risk infants were also higher in the RW group (p<0.05) (Table 3).

The TBA values of TPTEF, VPTEF, TPTEF/TE, VPEF/VE, TI, and TI/TE were lower in the RW group than in the HC group (p<0.05) (Table 4). In the RW group, TPTEF and TE were higher in the API-positive children than in the API-negative group (p<0.05), but there was no difference between the groups regarding TPTEF/TE and VT/kg values (p>0.05) (Table 5).

A moderate negative correlation was found in the API-negative children between the number of wheezing attacks requiring systemic corticosteroids in the previous year and VT/kg (r= -0.438; p=0.042) and between the number of wheezing attacks requiring hospitalization in the previous year and TPTEF (r= -0.516; p= 0.014). A moderate positive correlation was observed between the number of wheezing attacks requiring hospitalization in the previous year and RR in the API-negative group (r=0.487; p=0.022).

Table 1. Comparison of demographic characteristics of children with recurrent wheezing and healthy control groups

		Group		p
		Recurrent Wheezing Group (n=40)	Healthy Control Group (n=34)	
Gender	Male	23 (57,50)	21 (61,76)	0,710
	Female	17 (42,50)	13 (38,24)	
Mode of delivery	Vaginal	16 (40,00)	19 (55,88)	0,173
	Cesarean	24 (60,00)	15 (44,12)	
Age (month)		13,50 (8,00-21,50)	13,00 (7,00-24,00)	0,765
Height (cm)		76,50 (70,00-81,50)	75,50 (67,00-90,00)	0,854
Weight (kg)		9,65 (8,30-11,05)	8,90 (6,30-12,00)	0,273
Gestational age (week)		38,00 (37,00-39,00)	38,00 (37,00-39,00)	0,136
Birth weight*(gr)		3,15±0,48	3,26±0,25	0,235

Data are presented as numbers (percentage) for categorical variables and median (IQR) for numerical variables.
*Presented with mean ± standard deviation values.
Abbreviations: cm, centimeter; IQR, interquartile range; kg, kilogram; gr, gram; n; number.

Table 2. Characteristics associated with wheezing symptoms in the child group with recurrent wheezing

Recurrent Wheezing Group	(n=40)
Age of first wheezing episode (months), median (IQR)	3,00 (2,00-6,00)
Number of wheezing episodes requiring steroids in the past year, median (IQR)	1,00 (1,00-3,00)
Number of wheezing episodes requiring hospitalization in the past year, median (IQR)	0,00 (0,00-1,00)

Abbreviations: IQR, interquartile range; n, number.

Table 3. Comparison of familial and environmental factors in children with recurrent wheezing and healthy control groups				
		Group		p
		Recurrent Wheezing Group (n=40)	Healthy Control Group (n=34)	
Prenatal smoking exposure, n (%)	No	25 (62,50)	29 (85,29)	0,028
	Yes	15 (37,50)	5 (14,71)	
Postnatal smoking exposure, n (%)	No	17 (42,50)	29 (85,29)	<,001
	Yes	23 (57,50)	5 (14,71)	
Parenteral asthma or allergic disease, n (%)	No	29 (72,50)	34 (100,00)	0,001
	Yes	11 (27,50)	0 (,00)	
Asthma or allergic disease in a sibling, n (%)	No	30 (75,00)	34 (100,00)	0,001
	Yes	10 (25,00)	0 (,00)	
Exposure to humidity, stove heating, and household pets, n (%)	No	20 (50,00)	32 (94,12)	<,001
	Yes	20 (50,00)	2 (5,88)	
High-risk infant, n (%)	No	23 (57,50)	34 (100,00)	<,001
	Yes	17 (42,50)	0 (,00)	

Table 4. Comparison of tidal breath parameters of recurrent wheezing child and healthy control groups			
	Group		p
	Recurrent Wheezing Group (n=40)	Healthy Control Group (n=34)	
TPTEF (sec)	0,25 (0,15-,34)	0,32 (0,27-,45)	0,007
VPTEF (ml)	20,55 (15,15-35,90)	28,20 (22,20-41,20)	0,037
TPTEF/TE (%)*	28,06±12,02	36,66±11,64	0,003
VPTEF /VE (%)*	29,59±9,51	36,78±9,30	0,002
TEF75 (%)*	147,95±64,52	113,74±43,00	0,008
TEF50 (%)*	127,73±57,34	114,35±47,05	0,282
TEF25 (%)	94,50 (54,50-120,00)	78,50 (57,00-128,00)	0,927
VT/kg (ml/kg)	8,50 (7,15-10,50)	8,80 (7,60-9,60)	0,692
VT (ml)	75,35 (60,20-106,50)	76,05 (54,00-124,00)	0,862
RR (1/min)	34,50 (28,05-50,20)	33,80 (26,40-41,10)	0,334
TI (sec)	0,67 (0,42-0,84)	0,79 (0,60-1,02)	0,030
TE (sec)	1,04 (0,64-1,30)	1,02 (0,76-1,25)	0,757
TI/TE	0,68 (0,60-0,81)	0,77 (0,67-,82)	0,041

Data are presented as numbers (percentage) for categorical variables and median (IQR) for numerical variables.
*Presented with mean ± standard deviation values.
Abbreviations: TPTEF, Time to peak tidal expiratory flow; TPTEF/ TE, Ratio of time to reach peak tidal expiratory flow to total expiratory time; VPTEF, Volume expired before PTEF was attained; VPTEF/VE, Ratio of volume until peak tidal expiratory flow to total expiratory volume; RR, respiratory rate; VT, tidal volume; VT/kg, tidal volume/kg; TI/TE, the ratio of inspiration to expiration; TI, inspiratory time; TE, expiratory time; TEF75, TEF50, TEF25, Expiratory flow when 75%, 50% and 25% of tidal volume remains in the lungs; sec, second; ml, milliliter; min, minute.

Table 5. Comparison of tidal breath parameters according to asthma predictive index in children with recurrent wheezing

	Asthma Predictive Index		p
	Positive (n=18)	Negative (n=22)	
TPTEF (sec)	0,29 (0,22-0,39)	0,17 (0,14-0,30)	0,026
VPTEF (ml)	21,75 (17,70-37,10)	19,70 (15,10-28,30)	0,447
TPTEF/TE (%)	27,65(17,60-36,10)	26,50 (17,50-32,80)	0,463
VPEF/VE (%)	26,95 (21,30-36,40)	28,80 (21,00-33,60)	0,744
TEF75 (%)*	138,17±59,65	155,95±68,56	0,393
TEF50 (%)	118,50 (69,00-163,00)	129,00 (82,00-167,00)	0,724
TEF25 (%)	79,50 (52,00-126,00)	100,00 (63,00-119,00)	0,734
VT/kg (ml/kg)*	8,66±2,81	8,67±2,27	0,983
VT (ml)	84,00 (58,20-107,00)	70,80 (60,70-90,70)	0,430
RR (1/min)	33,50 (27,80-41,40)	44,10 (30,50-61,20)	0,197
TI (sec)	0,71 (0,40-0,83)	0,64 (0,42-,84)	0,903
TE (sec)	1,20 (0,98-1,33)	0,72 (0,62-1,20)	0,043
TI/TE	0,67 (0,57-,74)	0,70 (0,61-0,82)	0,605

Data are presented as numbers (percentage) for categorical variables and median (IQR) for numerical variables.
* Presented with mean ± standard deviation values.
Abbreviations: IQR, interquartile range; TPTEF, Time to peak tidal expiratory flow; TPTEF/ TE, Ratio of time to reach peak tidal expiratory flow to total expiratory time; VPTEF, Volume expired before PTEF was attained; VPTEF/VE, Ratio of volume until peak tidal expiratory flow to total expiratory volume; RR, respiratory rate; VT, tidal volume; VT/kg, tidal volume/kg; TI/TE, the ratio of inspiration to expiration; TI, inspiratory time; TE, expiratory time; TEF75, TEF50, TEF25, Expiratory flow when 75%, 50% and 25% of tidal volume remains in the lungs; sec, second; ml, milliliter; min, minute.

DISCUSSION

In this prospective cross-sectional study of children under three years old with RW, histories of parental or sibling atopy, prenatal and postnatal cigarette exposure, and contact with humidity, stoves, and animal contact were more common in the RW group than in the HC group. When respiratory functions were evaluated using TBA during wheezing attacks, TPTEF, VPTEF, TPTEF/TE, VPTEF/VE, TI, and TI/TE were lower in the RW group compared to the HC group. Bronchial obstruction was more prevalent in wheezing preschool-aged children compared to healthy children. However, there was no difference in bronchial obstruction or lung capacity between children with and without positive API.

There are very few studies in the literature evaluating respiratory functions in preschool children using the TBA method.[19,22,23] Studies involving infants have reported that a low TPTEF/TE ratio is indicative of obstructive airway diseases.[19,22,24,25] It has also been shown that tidal respiratory indices such as TPTEF/TE measured in healthy children early in life may be associated with wheezing or asthma in later years.[26]

A previous study by our team examined the relationship between TBA parameters and wheezing phenotypes and observed lower TPTEF/TE and TI/TE in the RW group than in healthy children.[27] In another study by the same team, TPTEF/TE and TI/TEwere significantly lower in children with acute bronchiolitis than in healthy children. In that study, TPTEF/TE and TI/TE ratios were low in the group with acute bronchiolitis even on the 30th day of treatment, and TBA findings indicating bronchial obstruction persisted despite clinical improvement.[23] Similarly, Dezateux et al. showed that TPTEF/TE was lower in wheezing infants than healthy children.[28] The TPTEF/TE ratio was lower in infants with lower respiratory tract infections than in the HC group, even in the asymptomatic period.[19] Qi et al. also reported that lung functions measured using TBA in wheezing infants were lower than those in healthy infants and remained low even three months after acute infection.[22]

The purpose of the API is to identify preschool children with RW who are at higher risk of developing asthma later in life.[6] However, the relationship between respiratory mechanics and API has not yet been fully clarified. A recent study showed that API-positive infants with RW had significantly lower forced

expiratory end-expiratory residual capacity (VmaxFRC), as measured using the rapid thoracoabdominal pressure method (RTC).[29] In another study conducted in infants with RW, forced vital capacity (FVC) and forced mid-expiratory flow velocity (FEF 25-75) were lower in API-positive cases compared to API-negative infants.[30] These findings suggest that there is a reduction in airway function among patients with positive API-wheezing when compared to those with negative API- wheezing. However, in our study, in contrast to prior research, we did not observe a significant difference in the TPTEF/TE ratio, which is a key indicator of airway obstruction in TBA device measurements among API-positive cases.

To the best of our knowledge, no previous studies in the literature have compared children with and without API positivity using the TBA method. In the present study, TPTEF and TE were higher in API-positive patients than in API-negative individuals. In the case of patients with negative API, there is a possibility that API will become positive if they experience wheezing attacks outside the infection period and develop allergic rhinitis, one of the minor API criteria. In light of this information, API positivity may develop at later ages during the follow-up of these patients, and the relationship with respiratory functions should be investigated again in future studies.

Smoking is one of the most important risk factors for wheezing. Exposure to cigarettes in the intrauterine period has been shown to adversely affect fetal lung functions.[31] Postnatal cigarette smoke exposure has also been shown to impact children's respiratory function.[28,32] A strong relationship is known to exist between the presence of a smoking parent in the home and the frequency and duration of wheezing attacks.[33,34] Consistent with the previous literature, although prenatal and postnatal exposure to cigarettes was high in the wheezing group in the present study, no difference was observed in terms of TBA parameters between the cigarette exposure and non-exposure groups.

The main strengths of this study are that the patients were examined and evaluated by the same pediatrician and that the TBA measurements were measured by the same experienced nurse, thus permitting greater standardization of the evaluation of the patient data. Patients' respiratory functions were evaluated using TBA during wheezing attacks before any treatment was administered, but we did not investigate the effect of treatment on respiration tests. The main limitations of this study are the small number of cases and the inability to subsequently study the TBA values again after the resolution of the acute episode.

TBA parameters such as TPTEF, TPTEF/TE, and TI/TE were lower in the RW group among patients presenting with wheezing attacks at younger ages. Given the insufficient number of studies evaluating the relationship between API and respiratory function parameters, we think this study can make a useful contribution to the existing literature. Although the API is used to predict asthma, no relationship has been shown between API positivity and obstructive changes in respiratory function parameters in children with wheezing. Early evaluation of lung functions using the TBA method may be more sensitive than the API for predicting permanent small airway damage in young children with RW. Further prospective studies with large case numbers are now needed to confirm these possibilities and to make positive contributions to the diagnosis and treatment of children with RW.

Ethical approval

This study has been approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (approval date 23.01.2020, number 23). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: SO; Concept: SO, DE, PU; Design: SO, DE, PU; Data Collection or Processing: SO, EC, ZGK; Analysis or Interpretation: SO, PU, IKO; Literature Search: SO, ZGK, DE; Writing: SO, ZGK, DE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Antenatally diagnosed congenital chloride diarrhea with a de novo mutation: The first reported case from Azerbaijan

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ABSTRACT

A case study reveals a prenatal diagnosis of congenital chloride diarrhea (CCD) in a consanguineous couple's fetus. Despite successful amnioreduction, persistent polyhydramnios led to genetic testing. A multidisciplinary approach involved obstetricians, geneticists, and neonatologists. Whole-exon sequencing identified a homozygous de novo SLC26A3 gene mutation. Treatment included oral electrolyte supplementation and lansoprazole, resulting in improvement. The case underscores the importance of early detection and intervention in managing CCD.

Healthcare providers should consider early prenatal screening, including advanced genetic testing such as whole-exon sequencing, for couples with consanguineous relationships due to the association of congenital chloride diarrhea with such unions. A multidisciplinary approach involving obstetricians, geneticists, and neonatologists is crucial for comprehensive management, emphasizing the need for close collaboration among healthcare professionals.

Keywords: chloride diarrhea, congenital, SLC26A3 gene

INTRODUCTION

Congenital Chloride Diarrhea (CCD) is a rare condition when an autosomal recessive abnormality is detected before birth. It is characterized by severe and long-lasting diarrhea. An inquiry into the complex aspects of prenatal diagnosis, emphasizing the challenges, results, and approaches used in controlling the condition.[1] When intestinal electrolyte transport does not work right, it can cause low sodium, potassium, and chloride levels, as well as metabolic alkalosis, which is similar to Bartter syndrome.[2] Occasionally, instances of CCD have been documented as being identified prenatally, providing valuable information on the maternal symptoms and the manifestation of this hereditary condition in the newborn.[3,4] This case report specifically examines the identification of a fetus with CCD during the prenatal stage and discusses topics such as the diagnosis process, the genetic implications of de novo mutation, and the comprehensive management of the disorder, including multiple disciplines.

PRESENTATION OF THE CASE

Prenatal ultrasound demonstrated markedly dilated fetal bowel loops with a honeycomb appearance (Figure 1) and polyhydramnios in the fetus of a consanguineous couple in the second trimester. After successful amnioreduction in the second trimester of gestation, polyhydramnios persisted, and additional tests like genetics indicated that CCD should be diagnosed as hereditary. A multidisciplinary approach was implemented to address the challenges associated with the perinatal

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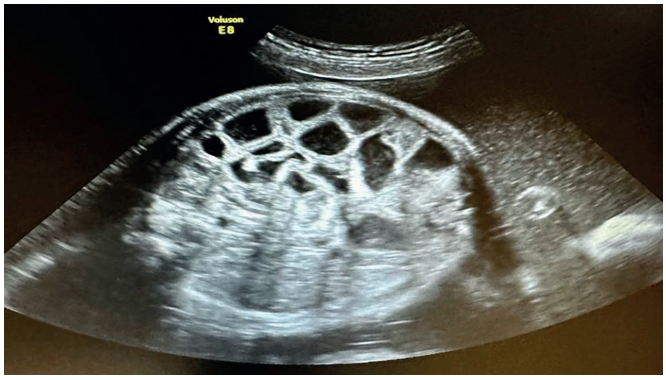

Figure 1. The honeycomb appearance of the bowel loops

management of CCD. This approach involved the collaboration of obstetricians, geneticists, and neonatologists. A whole-exon sequencing study using amniocentesis found a homozygous de novo *c.239 G>T/p.Gly80Val* mutation in exon 3 of the *SLC26A3* gene. There was no similar history in the family or relatives, and a male sibling aged five years has not had any illness or neurodevelopmental failure.

A cesarean section was performed for labor at 37 weeks of gestation, and a 3450-gram female was delivered. At 1 and 5 minutes, the Apgar scores were 8 and 9, respectively. The neonate's abdomen was considerably distended, and he had regular, unrelenting, watery diarrhea. Fecal chloride content was 141 mmol/L (normal <90 mmol/L), supporting CCD. On the third day of life, natrium, chloride, and potassium levels began to drop. Oral NaCl (1.5 mmol/kg/day divided into four doses), KCl (1.0 mmol/kg/day divided into two doses), and lansoprazole (1.0 mg/kg/day) were administered for better-tolerated treatment. On the seventh day of life, the infant was discharged from the hospital, and a strict follow-up program was planned for her. We referred our patient to an advanced center after she failed the hearing screening test (ABR). In the second month of her life, the number of daily stools and electrolyte needs continued to decrease.

DISCUSSION

The benign clinic of our patient may be explained by the genetic origin (de novo mutation) of the illness, particularly when it comes to antenatal diagnosis and early evaluation of the disease using a multidisciplinary approach (Table 1). Congenital chloride diarrhea is a chronic disease where one has watery diarrhea with elevated chloride.[5] Insufficient chloride absorption in the intestines is the cause of this uncommon and fatal disease, which is an autosomal recessive disorder. CCD is related to various mutations in the *SLC26A3* gene, which encodes an ion transporter in epithelial cells.[6-9] We were able to confirm a homozygous de novo *c.239 G>T/p.Gly80Val* mutation on the *SLC26A3* gene, which was never reported before.

Congenital chloride diarrhea was first reported in 1945 and involved infants who were severely ill from diarrhea, alkalosis, and electrolyte abnormalities.[10] It is more prevalent in nations with a high occurrence of consanguineous marriage.[11] Due to comparable antenatal ultrasonographic findings, CCD is frequently misdiagnosed as a surgically treatable condition, such as bowel obstruction, despite being a medically treatable condition.[12] Hence, obtaining an accurate diagnosis prior to commencing treatment is critical. Despite the publication of some methodologies for antenatal differential diagnosis, antenatal CCD diagnosis remains challenging.[13] The report helped in understanding the CCD prenatal diagnostic tools. In these, chorionic villus sampling and amniocentesis are used to find *SLC26A3* mutations during pregnancy.[12]

After that, the usual way of treating chronic diarrhea is by treating the symptoms, preventing dehydration, and preserving the balance of the electrolytes.[1,9] Symptomatic treatments like medications (captopril[14], cholestyramine[15] and butyrate[16]) and specialized regimens may also be used.[1] Proton pump inhibitors have been demonstrated to help reduce diarrhea in some circumstances.[17] It is, however, a chronic condition, and people with CCD can lead a relatively normal life with appropriate

Table 1. Similarities and differencies among the cases

Patients	GW, weeks	BW, grams	Antenatal Diagnosis	Antenatal amnioreduction	Electrolytes abnormalities	GI surgery	Hospital stay, days
Gils C. et al.	36	2915	-	-	+	+	>7
Hui P. et al.	36	2400	-	-	+	-	>7
Lee H.D. et al.	34	2780	-	-	+	-	21
Dogan E. et al.	36	3200	-	-	+	-	>7
Elbayiyev S. et al.	37	3450	+	+	+	-	7

management. Long-term clinical outcomes include enuresis, hospitalizations for gastroenteritis and intestinal inflammation, end-stage renal disease, hyperuricemia, male subfertility, spermatoceles, and inguinal hernias.[18] Sensorineural hearing loss should be evaluated in patients with *SLC26* gene mutations.[19] Antenatal detection is also significant because early detection and intervention are essential for better outcomes.

CONCLUSION

In conclusion, prenatal genetic testing and ultrasound findings are essential for detecting and diagnosing congenital chloride diarrhea. In order to make proper decisions and come up with a controlled management plan, an early diagnosis is crucial.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

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The authors declare that there is no conflict of interest.

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Case Report

Repetitive intra-articular therapy in fungal arthritis: Adjunct to systemic therapy in a patient with pediatric acute lymphoblastic leukemia

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ABSTRACT

Invasive fungal infections are important causes of mortality and morbidity in immunodeficiencies, hematological malignancies, and transplant recipients. There is scarce information in the literature about the diagnosis, treatment methods, and management. Herein, a unique involvement site of invasive fungal infection caused by *Aspergillus flavus* in the nadir of the induction chemotherapy of a 13-year-old boy with the diagnosis of acute lymphoblastic leukemia is presented. Despite prolonged intravenous antifungal therapy, the patient exhibited an inadequate response. As a result, intra-articular antifungal treatment was implemented alongside curettage and joint space irrigation. These additional interventions led to significantly improved clinical outcomes. Since fungal osteomyelitis can be an important cause of mortality and morbidity in immunosuppressed patients, prompt diagnosis and multidisciplinary treatment are crucial.

Keywords: Fungal osteomyelitis, immunocompromised patients, aspergillosis, amphotericin B-resistant, management of invasive aspergillosis

INTRODUCTION

Aspergillus species are very common in nature, becoming increasingly important as an opportunistic agent in hematological malignancies, immunosuppressed patients, and transplant recipients, being the most common one. *Aspergillus fumigatus* is the major causative agent for invasive aspergillosis and also in osteomyelitis, identified in 80% of the cases, followed by *Aspergillus flavus (A. flavus)*. The most commonly affected sites are the lungs, sinuses, and brain.[1]

Herein, a case of *A. flavus* osteomyelitis in an adolescent with acute lymphoblastic leukemia (ALL) is presented.

CASE PRESENTATION

A 13-year-old male diagnosed with ALL was being treated according to ALLIC BFM 2009 protocol. He became neutropenic on day 30th of induction. On the 12th day of nadir, swelling on the left knee joint was observed while he was under treatment with amikacin, meropenem, and prophylactic fluconazole. The

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whole blood count revealed pancytopenia, and the CRP level was 320 mg/dL, whereas the erythrocyte sedimentation rate (ESR) was 118 mm/h. A magnetic resonance imaging (MRI) was performed and disclosed multiple lesions, compatible with abscess and osteomyelitis in the distal metaphyseal area of the left femur, available in Figure 1a and 1b.

Intraarticular washing was performed, and the soft tissue and bone curettage materials were studied both microbiologically and pathologically. The fungi were isolated from the fungal culture of specimens and identified as *A. flavus* (Figure 2a). In pathological evaluation, few fungi associated with osteomyelitis by Gomorimethenamine silver stain were observed; pictures of the microscopic image are available in Figure 2b. Galactomannan index (GMI) was positive for the soft tissue and bone curettage specimens, >1.00 according to new European Organisation for Research and Treatment (EORT) 2019 criteria, but negative for blood with optical density index. The median GMI was 6.7 for specimens, and 0.3 for blood.

Liposomal amphotericin B was initiated with a 3 mg/kg/day dose. In the second week of the treatment, he had a fever with ongoing complaints like pain and swelling in the knee joint. He was still neutropenic with elevated acute phase reactants. Due to the lack of clinical response, an MRI was performed, and the progression of the osteomyelitis-related findings was disclosed. The amphotericin B dose was increased to 5 mg/kg/day. The drainage material of the abscess, joint fluid, and tissue samples were obtained surgically again. The pathology report revealed fungal osteomyelitis. A. flavus was also reproduced from the tissue samples.

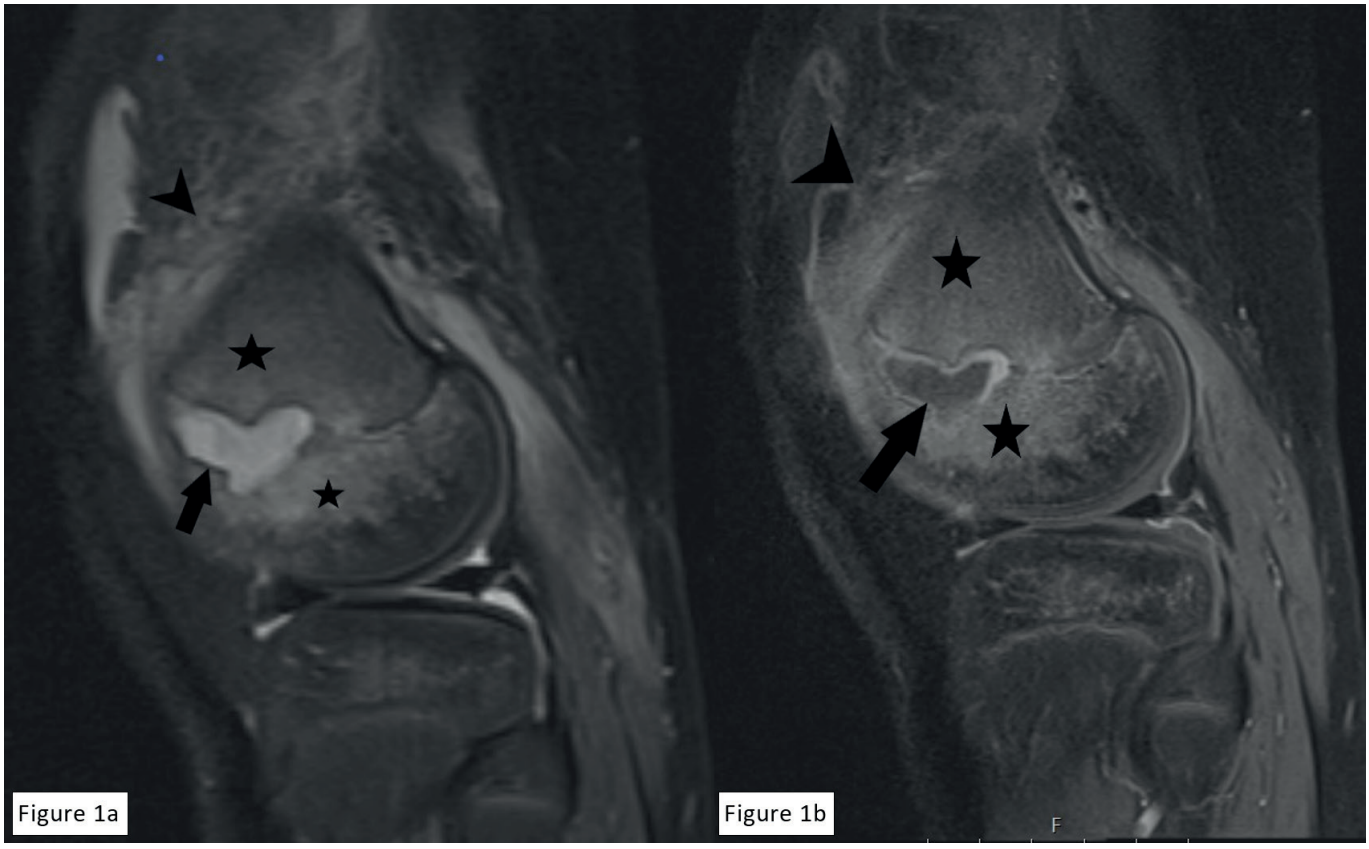

Figure 1a. Sagittal T2 weighted fat-suppressed image of the left femur shows a lesion with fluid signal in the physeal line (arrow). The bone marrow of the distal metaphysis and epiphysis has a diffuse high signal representing bone marrow edema (stars). Adjacent soft-tissue edema is also seen (arrowhead).

Figure 1b. Sagittal T1 weighted fat-suppressed image of the left femur after intravenous contrast administration shows that the lesion has a central low signal and peripheral enhancement (arrow). The central low signal represents pus, and the peripherally enhancing areas represent hypervascular granulation tissue. These findings confirm an intraosseous abscess. Contrast enhancement of bone marrow pointing out osteomyelitis is seen in distal metaphysis and epiphysis (stars). Also, contrast enhancement of soft tissue is seen (arrowhead).

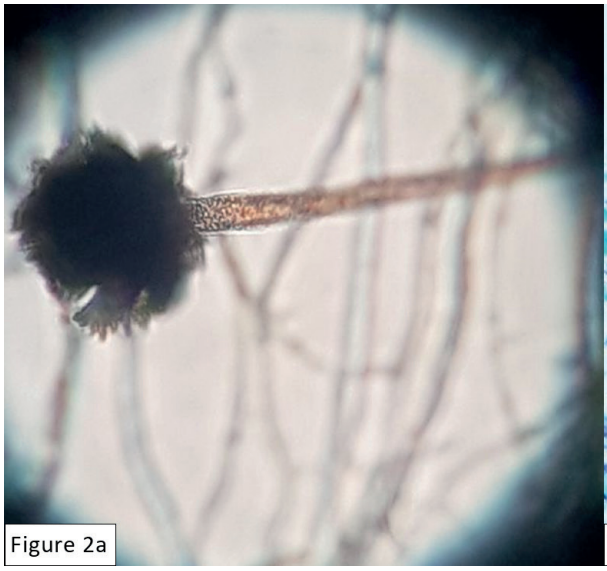
Figure 2a

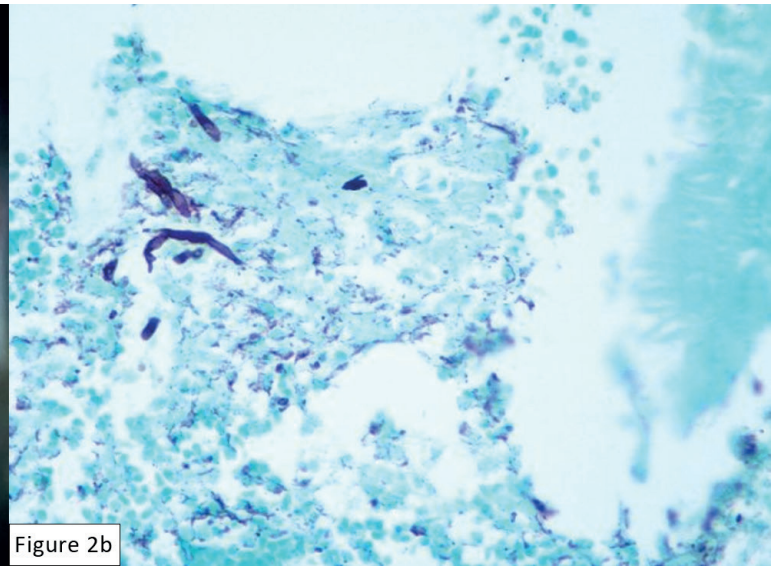
Figure 2b

Figure 2a. Image of Aspergillus flavus in slide culture.
Figure 2b. Fungal hyphae staining positively with Gomori Methenamine silver stain.

On account of the unresponsiveness, the minimum inhibitor concentration (MIC) values for amphotericin B, caspofungin, voriconazole, anidulafungin, itraconazole, and posaconazole were studied and resulted as; >2 µg/ml, 0.125 µg/ml, 0.064 µg/ml, 0.002 µg/ml, 0.25 µg/ml, and 0.125 µg/ml, respectively. Based on MIC results, since the fungus is resistant to amphotericin B, treatment was changed to solely voriconazole with a loading dose of 9 mg/kg/dose every 12 hours for two doses on day one and a maintenance dose of 8 mg/kg/dose every 12 hours.

On the second week of the voriconazole therapy, an MRI disclosed radiological progression. However, the whole blood count was improved, with ongoing elevation in acute phase reactants. He had gone through curettage for the third time and washing the joint space with voriconazole was performed. Intra-articular voriconazole treatment was administered as a single dose, utilizing 20 mL of the intravenous formulation at a concentration of 10 mg/mL. Specimens from the joint space were obtained revealing *Aspergillus*-like fungi. Also, the galactomannan (GM) antigen resulted positive in blood, with no reproduction in cultures. Caspofungin was added with a loading dose of 70 mg/m^2/dose on day 1, then 50 mg/m^2/dose once daily in maintenance. In the follow-up, the patient had the combination therapy of voriconazole and caspofungin for 16 weeks while he was being treated for ALL. He did not require surgical intervention again. After the treatment, he experienced sequelae related to walking and, therefore, received physical therapy. He completed his anticancer chemotherapy and is still in remission.

DISCUSSION

Fungal osteomyelitis and arthritis are rare but debilitating sites of involvement for invasive aspergillosis. Considering the osteomyelitis caused by aspergillus species, the most often affected bones are vertebral bodies, cranium, and ribs. Long bone and articular spaces are less frequently involved; among them, the most common site is the tibia.[2] Our patient had knee, joint space, and synovial fluid involvement, which is rare in the literature.

Diagnostic procedures generally consist of culture and/or histological evaluation of the specimens achieved by biopsy, as in our patient. Also, the positivity of serum GM-antigen can be determined.[2,3] However, similar to our patient's diagnostic process, making the exact clinical diagnosis can be challenging. Because, as previously described in the literature, while the GM-antigen in serum is negative, local samples may culminate positively. When used alone, GM-antigen has insufficient sensitivity and specificity in diagnosing invasive aspergillosis and must be correlated with clinical practice.[4] The patient should be overall assessed with respect to clinical history, underlying disease, immunity status besides the cultures, histopathological assessments, and direct analysis of the specimens with a high index of suspicion.[2-5]

Imaging methods have an important impact on diagnosis. The most frequently observed patterns comprise osteolysis, bone destruction, and erosion.[6] In our case, MRI findings were similar

and contributed to surgical sampling and guiding treatment by revealing progression during periods of unresponsiveness.

In addition to its rarity, there is scarce knowledge about knee joint involvement in terms of evidence-based treatment modalities. As observed in our case, amphotericin B resistance can be detected, and evaluation of MIC concentrations can guide treatment. Surgical debridement is one of the treatment methods. Although there is scarce data on the timing and necessity of surgical intervention in invasive fungal osteomyelitis, recent literature supports the utilization of surgical debridement to reduce the infective burden and allow better drug penetration.[2,7]

The management of osteoarticular infections in immunosuppressed patients presents significant challenges due to the complex clinical course and the limited availability of evidence-based clinical guidelines. Long-term treatment with effective antifungal agents is crucial. In immunosuppressed patients, mean treatment time is reported within at least 6-12 weeks.[5] As well, our patient had the antifungal treatment for 16 weeks. In addition to systemic therapy, local interventions such as intra-articular irrigation, curettage, and antifungal administration have improved clinical outcomes.[8] This is particularly relevant in patients with hematological malignancies or those who have undergone bone marrow transplantation, where joint involvement is associated with a poor prognosis. Due to the limited penetration of systemic antifungal agents into soft tissues and osteoarticular spaces, combining systemic therapy with local treatments—such as curettage, joint space irrigation, and intra-articular antifungal administration—has been demonstrated to yield superior outcomes.[9] In the current case, it is obvious that clinical response was obtained after combining intraarticular treatment with extended systemic long-term therapy and also with the recovery from myelosuppression.

Informed consent

The family of the patient signed the free and informed consent form. In addition, appropriate permissions have been obtained for reproduced images.

Author contribution

Surgical and Medical Practices: ŞA, AÖ, İK, EÜ; Concept: ŞE, EÜ; Design: EÜ, ŞA; Data Collection or Processing: NAE, MAA,ZFK, ŞA, KD, ANK; Analysis or Interpretation: ŞA; NAE; Literature Search: ŞA, AÖ, EÜ; Writing: ŞA, AÖ, EÜ. All authors reviewed the results and approved the final version of the article.

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