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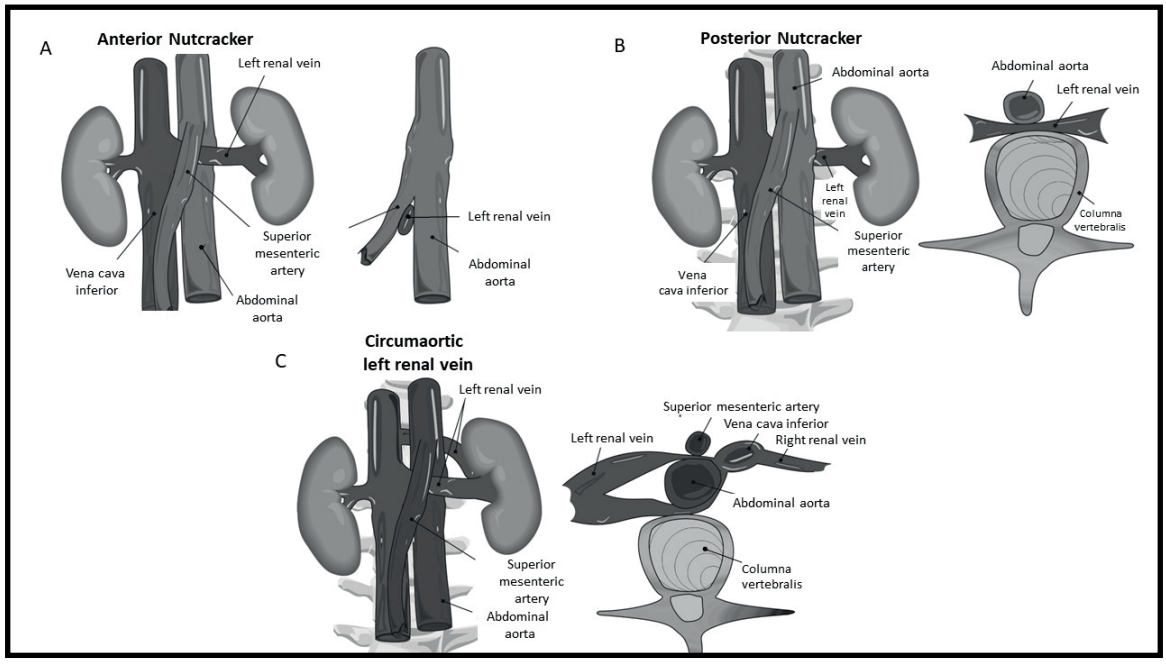

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Kızılay Mah. Gazi Mustafa Kemal Bulvarı No: 23/8 06420 Çankaya/Ankara, Türkiye
Phone: +90 (533) 166 80 80
E-mail: bilgi@akdema.com
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Assoc. Prof. Ayşe Anık, MD
E-mail: drayseank@yahoo.com
Department of Pediatrics, Division of Neonatology, Aydın Adnan Menderes University, Medical Faculty, Aydın, Türkiye
ORCID: https://orcid.org/0000-0002-0673-3403

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

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

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

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

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

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Review

Nutcracker syndrome in childhood

Emine Gülşah Özdemir[1], **Bora Gülhan**[2]

[1]Division of Pediatric Nephrology, Ankara Ataturk Sanatoryum Training and Research Hospital, Ankara, Türkiye
[2]Division of Pediatric Nephrology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye

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ABSTRACT

Nutcracker phenomenon (NP) is defined as the compression of the left renal vein, often occurring between the aorta and the superior mesenteric artery (SMA). Patients with symptoms associated with the Nutcracker anatomy are called "Nutcracker syndrome" (NCS). Renal vein compression results in venous congestion, outlet obstruction, and increased pressure in the left renal vein. The clinical manifestations of NCS in children vary widely depending on the severity of compression. It can range from being asymptomatic to presenting with intermittent or persistent micro or macrohematuria, orthostatic proteinuria, renovascular hypertension, abdominal pain, left-sided flank pain, dysmenorrhea, pain in the testicles or scrotum, and left varicocele. Hematuria, proteinuria, and flank pain are prevalent symptoms. The anatomical and physiological degree of compression of the left renal vein can be diagnosed through Doppler ultrasound (DUS), computer tomography (CT) scan, or magnetic resonance imaging (MRI). In cases with mild symptoms, conservative treatment is an appropriate option, and ACE inhibitors can be used for patients with proteinuria. In more severe cases where conservative approaches and medical treatment fail to yield satisfactory results, endovascular, laparoscopic, or open surgical interventions are employed.

Keywords: Nutcracker phenomenon, Nutcracker syndrome, left renal vein entrapment, hematuria, orthostatic proteinuria

INTRODUCTION

The Nutcracker phenomenon (NP) is defined as the compression of the left renal vein, often between the aorta and the superior mesenteric artery (SMA). The anatomical variation was first described by El Sadr et al.[1] in 1950 and later termed the "Nutcracker phenomenon" by De Schepper in 1972.[2] This phenomenon is characterised by the obstruction of flow from the left renal vein to the inferior vena cava (IVC) due to external compression. Patients with symptoms associated with nutcracker anatomy are referred to as having "Nutcracker syndrome" (NCS).[3]

NCS is typically diagnosed in adults in the third and fourth decades of life and is known to be more common in females.[4] There is limited data on the incidence and prevalence of NCS in childhood. Still, it is known to increase in frequency between the ages of 10 and 14.[5] Although NCS is not considered a hereditary disease, siblings have reported incidental cases.[6] During adolescence, the angle between the SMA and the aorta narrows due to growth, potentially exacerbating symptoms.

ETIOLOGY

Compression of the left renal vein between the aorta and SMA is termed "anterior NP"[7], while a less common compression type between the left renal vein and the vertebral column is termed "posterior NP".[8] A third type of NP has been identified, where a "circumaortic" left renal vein surrounds the aorta in addition to both anterior and posterior NP.[9] Types of NP are shown in Figure 1.

Correspondence: Emine Gülşah Özdemir **E-mail:** gkirnaz@gmail.com
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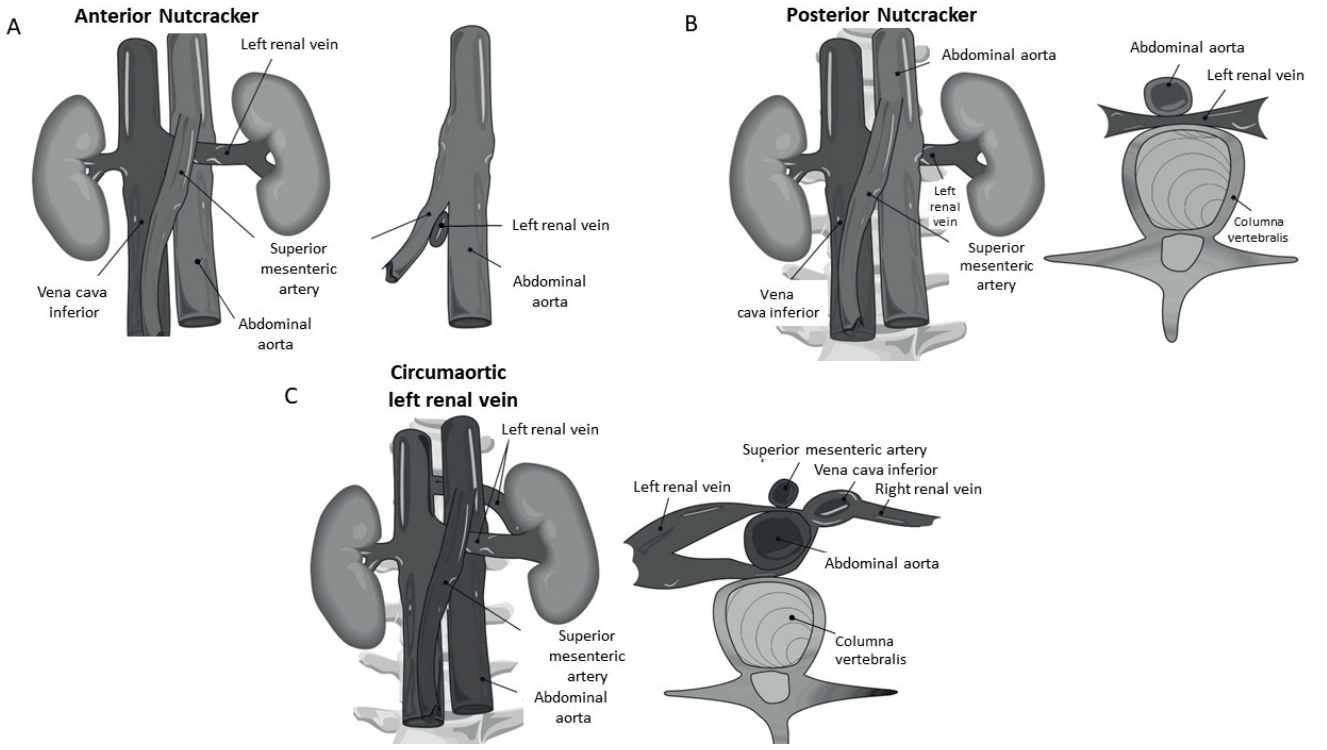

Figure 1. Types of NP. (A) Anterior NP; (B) Posterior NP; (C) Circumaortic left renal vein NP. NP: Nutcracker phenomenon.

Paraaortic lymphadenopathy, retroperitoneal mass, abdominal aortic aneurysm, duplication of the left renal vein, ectopic ventral right renal artery, left renal ptosis, severe lordosis, pregnancy, intestinal malrotation, and rapid weight loss are some of the less common etiologies of the left renal vein.[3,10]

NCS is thought to be associated with a low body mass index (BMI). The angle between the aorta and SMA is generally between 38° and 65°, surrounded by lymph nodes, mesenteric fat tissue, and other soft tissues.[11] The absence of supportive mesenteric fat tissue can displace the intestines downward, narrowing the SMA angle. Another view suggests that the "stretching" of the left renal vein over the aorta occurs when transitioning from a supine to an upright position, resulting in venous compression.[10] Studies indicate that symptoms associated with NCS improve with an increase in BMI.[12]

All anatomical variations causing renal vein compression result in outlet obstruction. This obstruction leads to increased pressure in the left renal vein with a measurable renocaval gradient. The average pressure difference between the distal renal vein and the IVC is <1 mmHg. A renocaval gradient of ≥3 mmHg suggests NP. Increased pressure in the left renal vein leads to the formation of varices and collaterals. These varices and collaterals create venous sinuses adjacent to the renal calyx, causing clinical manifestations such as proteinuria and hematuria.[13]

CLINICAL FINDINGS

The clinical manifestations of NCS in children vary widely depending on the hemodynamic consequences of anatomical changes. Asymptomatic cases can coexist with micro or macroscopic hematuria (intermittent or persistent), orthostatic proteinuria, renovascular hypertension, abdominal pain, left-sided flank pain, dysmenorrhea, testicular or scrotal pain, left varicocele, nephrolithiasis, hypercalciuria, and fatigue. Recently, a systematic review of 423 children with NCS and a mean age of 12 years found that hematuria emerged as the primary symptom at presentation (55.5%), followed by proteinuria (49.9%). Notably, only 19.1% of the patients exhibited flank pain.[5] Another systematic review of 159 patients ≤17 years of age with NCS reported that two-thirds were asymptomatic. In children with NCS, painless microscopic hematuria is more common compared to adults.[14,15] Anecdotal cases have reported acute blood transfusion due to secondary severe anaemia resulting from hematuria.[3,15]

Another significant finding in NCS is orthostatic proteinuria, with a higher incidence during puberty. It is estimated to affect 2-5% of children and young adults, with the majority having a benign course.[16] The exact pathogenesis and mechanism of orthostatic proteinuria is still unknown. It is thought that venous hypertension induces a subclinical immune cascade in the vessel wall within the nephron[17], leading to excessive release of norepinephrine and angiotensin II during upright posture.[16] An enhanced physiological response to sudden changes in renal hemodynamics is thought to contribute to orthostatic proteinuria.[10]

Atypical left-sided pain is observed in one-third of pediatric NCS patients, often explained as visceral pain secondary to the dilation of the left renal vein. It is a well-known "triad" symptom, along with hematuria and proteinuria.[18,19] Approximately 10% of pediatric cases may present with atypical diffuse abdominal pain secondary to pelvic venous compression.[3,18-20] Both flank and abdominal pain may occur in these patients due to the activation of the inflammatory cascade triggered by venous hypertension.[4]

Hypertension is not a classic symptom of NCS, and only a few cases of NCS associated with hypertension have been identified in children. NCS should be considered as a potential cause in patients with unexplained hypertension, especially those who do not respond to antihypertensive medication. The underlying mechanism is not well understood, but increased plasma renin activity and aldosterone levels in the peripheral blood may explain it without renal artery stenosis or a renin-secreting tumour.[21]

In addition to renal symptoms, varicocele in males (usually on the left) and painful menstrual periods in pubertal girls may occur as a result of the development of gonadal venous varices in NCS. Chronic fatigue syndrome and symptoms of autonomic dysfunction such as hypotension, syncope, and tachycardia may rarely occur in patients with high renal vein and IVC pressure gradients in NCS.[3,19]

DIAGNOSIS

Due to the lack of standard diagnostic criteria, the diagnosis of NCS can be challenging, even in patients with a suspicious clinical history. The presence of clinical features forms the basis for diagnosis. A detailed history and physical examination are essential, and in cases where NCS is suspected, comprehensive diagnostic procedures are necessary to confirm the diagnosis. Urinalysis and renal imaging should be performed. Various imaging modalities such as Doppler ultrasonography (DUS), computed tomography (CT), magnetic resonance imaging (MRI), and retrograde venography are used for the diagnosis of NCS.[5,22,23]

DUS, being non-invasive and radiation-free, is the first-line imaging modality in suspected cases of NCS. It has high sensitivity (69-90%) and specificity (89-100%) for diagnosing NCS.[24] The normal SMA originates from the back of the pancreatic neck and typically forms a sharp angle where it exits the aorta. In children, the average SMA angle is 45.8 ± 18.2º in males and 45.3 ± 21.6º in females, while the SMA-aorta distance is 11.5 ± 5.3 mm in males and 11.5 ± 4.5 mm in females.[25] The ultrasound diagnostic criteria of NCS were defined by Zhang et al.[26]: 1) the flow rate of the LRV stenosis accelerates significantly in the supine position, and acceleration exceeding 100 cm/s is more pronounced after the patient has stood for 15 minutes; 2) the ratio of the inner diameter between the renal hilum and the stenotic segment of the left renal vein is >3 in the supine position and >5 after the patient has been standing for 15 minutes. However, using these criteria in children is limited because the measurements change with the patient's position and because of technical challenges due to a tiny sampling area.[3,24] Additionally, the peak flow velocity ratio on DUS is above 4-5 between the compressed narrowed part of the renal vein and the noncompressed dilated renal hilar vein, offering a sensitivity of 80% and specificity close to 95% for NCS.[7] In cases where DUS is not diagnostic, axial imaging may be required. Both CT and MRI can show compression of the left renal vein in the fork formed by the SMA and abdominal aorta, as well as dilation of the gonadal veins and pelvic congestion. However, neither CT nor MRI is a dynamic modality, so they cannot accurately measure flow rate and orientation. The most specific finding on CT for NCS is a left renal vein hilum/aorto-mesenteric diameter ratio ≥4.9 (100% specificity). However, the highest diagnostic accuracy observed on axial CT images is achieved by combining the "beak sign" and the left renal vein diameter ratio (AUC 0.903 for both). Although non-invasive, CT carries the risk of radiation exposure and the use of contrast agents. MRI is radiation-free and has the advantage of better visualisation of soft tissue anatomy in the compression area.[24]

In selected and rare cases, measuring the pressure gradient between the left renal vein and the IVC through catheterisation may be considered an invasive evaluation. In the normal population, the pressure difference between the left renal vein and the IVC is less than 1 mm Hg, and a pressure difference greater than 3 mm Hg may suggest NCS. Retrograde venography, although an invasive test, is the most informative method and is considered the gold standard for the diagnosis of NCS. It not only confirms anatomical changes but also shows a pressure gradient along the compression zone. It is not commonly performed in patients without severe symptoms.[3,23,24]

TREATMENT

Management of NCS in childhood is primarily based on clinical findings and the severity of the left renal vein hypertension. A conservative approach (e.g., "watch and wait" strategy) is strongly supported as the first-line treatment in patients with mild symptoms.[12,27] In addition, it has been observed that NCS in children may resolve spontaneously due to the development of adipose tissue or the reduction of the pressure gradient in the left renal vein by the development of collaterals.[18] The best option is to start with at least two years of observation and a conservative approach without medication in patients under the age of 18. Complete resolution occurs in 75% of patients with hematuria during this period. Angiotensin-converting enzyme inhibitors (ACEIs) may be effective, particularly in patients with severe and prolonged orthostatic proteinuria.[10,24,27]

Surgery and more invasive treatment methods, such as endovascular techniques, may be required in rare and selected cases presenting with severe abdominal or (left) flank pain, recurrent macroscopic hematuria, renal dysfunction, left varicocele, anaemia, and persistent symptoms after 24 months of conservative treatment.[5,24] Renal autograft or non-autograft left renal vein transposition is the most preferred surgical technique. The left renal vein is dissected from the IVC and reimplanted distally to the SMA.[4] Other possible surgical techniques for the surgical treatment of NCS include SMA transposition, nephropexy, nephrectomy, renocaval bypass, left gonadal vein transposition, or laparoscopic procedures (laparoscopic splenorenal venous bypass and laparoscopic left renal vein-IVC transposition). Another option is the endovascular approach, in which a self-expanding stent is placed in the left renal vein. Although less invasive, endovascular treatment is not preferred because of the potential risks associated with stent displacement and the challenging management of anticoagulant therapy in children.[24,28-30]

In light of current literature data, a conservative approach should be considered the first-line treatment for children. In selected cases that do not benefit from a conservative approach and medical management, clinicians should consider other interventional treatment options after conducting a careful risk-benefit assessment.

CONCLUSION

NCS should be considered in patients with unexplained hematuria, proteinuria, and pelvic and/or flank pain. The left renal vein's anatomical and physiological degree of compression can be assessed with DUS, CT, or MRI. DUS has additional diagnostic value in determining the highest velocity ratios in the same positions. In mild cases, conservative treatment is an appropriate option, and ACEIs may be used in patients with proteinuria. In more severe cases that do not benefit from conservative and medical treatment, endovascular, laparoscopic, and open surgical treatments are used. As it is a rare disease, no clinical studies compare treatments. Larger-scale and longer-term studies are needed for further evaluation of these treatments.

Author contribution

Concept: EGÖ, BG; Design: EGÖ, BG; Data Collection or Processing: EGÖ, BG; Analysis or Interpretation: EGÖ, BG; Literature Search: EGÖ, BG; Writing: EGÖ, BG. 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

Risk factors determining the development of food allergy intolerance at the first age in infants with atopic dermatitis

Berfu Vurmaz Mammadov[1], **Pınar Uysal**[2]

[1]Department of Pediatrics, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Türkiye
[2]Department of Pediatric Allergy and Immunology, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Türkiye

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ABSTRACT

Objective: Very few studies have examined the risk factors for developing tolerance to food allergy in infants with atopic dermatitis (AD). To understand the risk factors for developing tolerance to food allergy in the first year in infants with atopic dermatitis and food allergy coexistence.

Methods: Ninety-three infants were included in this retrospective study. Food allergy was detected using food-specific IgE, skin prick, and oral food challenge tests. The severity of the disease was evaluated using Scoring Atopic Dermatitis (SCORAD). Demographic parameters were recorded from medical records.

Results: The rate of patients who tolerated food allergy in the first year was 61 (65.6%). The median age to tolerate food allergy was 12 (6-18 months). According to the SCORAD, 8 (8.6%) patients had mild, 50 (53.8%) had moderate AD, and 35 (37.6%) had severe AD. The median SCORAD value was 45.2 (35.2-54.6). There was no difference between the groups who tolerated food allergy and those who could not at the first age of life in terms of age, gender, gestational week, maternal age, and familial atopy history (p>0.05 for all). Egg allergy [p=0.035; OR:6.623 (CI:0.996-44.043)], parental atopy [p=0.024. OR:2.450 (CI:0.699-23.056], and AD severity [p=0.030. OR:1.240 (CI:1.001-22.105)] emerged as statistically significant variables at potential risk factors for food allergy intolerance in the first year.

Conclusion: Egg allergy, parental atopy, and severity of atopic dermatitis emerged as potential risk factors for intolerance to food allergy in the first year of life in infants with atopic dermatitis and food allergy coexistence.

Keywords: Atopic dermatitis, allergy, cow's milk, egg, food allergy, tolerance

INTRODUCTION

Atopic dermatitis is a chronic and inflammatory disease with itchy skin lesions, which is quite common in childhood.[1] The disease occurs due to environmental, genetic, and immunological factors that lead to impaired barrier function in the epidermis layer of the skin and immune system dysfunction.[2] Atopic dermatitis presents in the first six months of life in 45% and in the first year of life in 60% of the cases. It is classified as early-onset atopic dermatitis. Around 85% of those affected within the first five years of life.[3]

Food allergy is the leading trigger of atopic dermatitis.[3] Clinically diagnosed immunoglobulin E (IgE)-mediated food allergy has been observed in approximately one-third of infants with moderate-to-severe atopic dermatitis. It has been shown that 90% of the food allergy seen in atopic dermatitis patients is IgE-mediated.[4,5] Therefore, detecting the presence of food allergy

Correspondence: Pınar Uysal **E-mail:** druysal.pinar@gmail.com
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plays an essential role in the prevention and treatment of atopic dermatitis.

Food allergy, like atopic dermatitis, occurs at an early age and constitutes as one of the atopic march steps.[6,7] Many studies have been conducted to support the triggering role of food in atopic dermatitis.[3] Although the incidence of food allergy in children with atopic dermatitis can be observed at different rates due to the use of different methodologies in studies, approximately 1/3 of moderate-to-severe atopic dermatitis patients have a food allergy in double-blind placebo-controlled studies demonstrated by the oral food challenge test.[7]

This study aimed to investigate the possible relationship between food allergies and the development of tolerance within the first year, and the risk factors determining tolerance in infants diagnosed with atopic dermatitis.

MATERIAL AND METHODS

The study was planned in a retrospective cross-sectional design between January 2018 – April 2020. For the study, demographic, clinical, and laboratory data were recorded from the hospital's electronic record system of the Pedaitric Allergy and Immunology outpatient clinic database. The data recorded in the system were obtained from the routine examinations of the patients at the time of diagnosis and during the follow-up. Detailed demographic characteristics were the patients' age, gender, week of birth, age of onset of symptoms, age of diagnosis, duration of symptoms, history of atopy, and presence of atopy in the family.

After evaluating the history and laboratory information in detail, the patients' existing food/foods hypersensitivity and food allergy were recorded. In the history, the nutritional status of the patients was questioned as to whether they were breast-fed or consuming milk, formula or complementary foods.

The diagnosis of food allergy was made by clinical history and/or laboratory tests, and an oral food challenge test with a suspected food trigger. For the diagnosis of food allergy, a food elimination diet was applied in which the patient's clinic was followed closely for those who could not undergo an oral food challenge test (familial preferences or a history of severe acute reaction or life-threatening reaction such as anaphylaxis with food). Food allergy was also diagnosed in patients whose symptoms improved after at least four weeks of an elimination diet.

The tolerance status of patients with food allergies was evaluated. The patient's tolerance development status was recorded after a minimum duration of 12 months to assess the tolerance situation. The patients whose records were missing were called by phone, and their tolerance status was learned by interview with the parents.

Exclusion Criteria for Infants

Patients with immunodeficiency or chronic disorders such as liver and renal disease, cancer, diabetes, and growth retardation are excluded. Patients with eczema or skin disease symptoms other than atopic dermatitis, patients using systemic or topical corticosteroids for another disease, and patients with missing data were excluded from the study.

Determination of Atopic Dermatitis Severity (SCORAD)

Atopic dermatitis disease severity scores, which were calculated routinely in the detailed physical examinations performed at the time of admission, were recorded. The atopic dermatitis severity scale (Severity Scoring of Atopic Dermatitis Index, SCORAD) was used to classify the severity of atopic dermatitis.[8]

In the evaluation, objective (A and B data) and subjective (C data) data were evaluated together, and a calculation method was used.

a. The extent of the spread of the lesions was determined according to the rule of 9s. After the body was divided into anterior and posterior facets, the body surface was divided into multiples of 9. Hands and genital area were given one point each. Thus, the lesion areas in the body were expressed as a percentage value.

b. Subjective findings 1. Erythema 2. Edema/papulation 3. Oozing 4. Excoriation 5. Lichenification 6. Dryness was evaluated by the doctor and scored between 0 and 3 (0=none;1=light; 2=medium; 3=heavy). Lesions of average weight were chosen rather than the worst skin lesions when making the evaluation.

c. The markers evaluated subjectively by the patient were pruritus and sleep disturbance. Children older than seven years of age were assessed on a scale of 0-10 according to the severity of their complaints in the last three days/nights.

All these results were calculated according to the formula A/5+7B/2+C. As a result of the total score, values below 25 points were classified as mild, values between 25 and 50 points as moderate, and values above 50 points were classified as severe atopic dermatitis.[9-11]

Parental Atopy

Parental atopy was defined as any history of allergic diseases such as asthma, hay fever, allergic eczema, or allergic conjunctivitis in one or both parents of the child.[12]

Collection of Recorded Data

Registered survey questions: gender of patients, age at admission, age of symptom onset, duration of symptoms, age at diagnosis, maternal age, family history of atopy, type of birth, presence of prematurity, presence of comorbidity, history of lung infection, history of hospitalization, presence of smoking exposure, diet (mother milk/formula/mixed/complementary), which food was suspected (cow's milk/egg/wheat/other), disease severity, duration of elimination diet, and tolerance development status.

Laboratory Findings

a. Absolute eosinophil rate and count

Absolute eosinophil counts were studied using an automated hematology analyzer (BC-6800 Hematology Analyzer, Mindray, Shenzhen, China). Absolute eosinophil rate and count results from the complete blood count were obtained from the records, and the data were included in the analysis.

b. Serum total IgE level

The total IgE level in serum samples was measured using the chemiluminescent method using an Immulite 2000 (Siemens) device in the Biochemistry Laboratory, and the results were given in the kU/L unit. Values above the normal range for age groups were considered high.

c. Evaluation of food sensitivity and allergy

Patients who had a positive response to food sIgE or at least one trigger in the skin prick test were considered sensitive to food allergens. Food-specific IgE measured using the ImmunoCAP system (PhadiaAB, Uppsala, Sweden) was considered positive if higher than 0.35 kIU/L. Food sensitivity was assessed using food-specific IgE for cow's, egg, or food panel (F5), including milk, egg, wheat, soy, peanut, and fish, and/or the skin prick test (SPT) for milk, egg, wheat, peanut, hazelnut, and soy.[12]

An induration diameter greater than or equal to 3 mm more than the diameter of the negative control was considered positive for the skin prick test. Food-specific IgE and SPT positivity were defined as food sensitivity.[12]

Food allergy was determined by oral food provocation tests. Milk, egg, formula, and other foods were used in the oral food challenge test, and the test results performed according to the recommendation of international guideline.[13]

Ethics

The study was conducted according to the principles of the Declaration of Helsinki, followed by good clinical practice, and was approved by the University Ethics Committee (2023/158).

Statistical analysis

Statistical Package for Social Science (SPSS) 21 program was used to analyze the data (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). For the descriptive statistics of the study, the median and 25-75 percentile values were used in the continuous variables since the data did not follow the normal distribution. The number and percentage were used in the categorical variables. The conformity of continuous variables to normal distribution was evaluated with descriptive statistics, steepness and skewness coefficients, histogram, and Shapiro-Wilk test. The chi-square test was used to analyze categorical data for statistical analysis. Mann Whitney U test was used to compare independent groups since the data did not fit the normal distribution. Correlations between two continuous variables were evaluated with the Spearman correlation test. Univariate logistical regression was used to identify risk factors for tolerance for food allergy. A multivariable logistic regression analysis was performed. Any Type I error level was determined as 0.05%.

RESULTS

Patient Characteristics

Ninety-three infants were included in this study. All the children with atopic dermatitis had food allergies, which were investigated using either food-specific IgE or the skin prick test and oral food provocation test. The number of patients who tolerated food allergy in the first year was 61 (65.6%). The median age of tolerating food allergy was 12 (6-18 months). The patients' demographic data are shown in Table 1.

Table 1. Demographic characteristics in children with atopic dermatitis and food allergy	
	Infants with Atopic Dermatitis and Food Allergy (n=93)
Demographic features	
Gender, n (%)	
Female	29 (31.2)
Male	64 (68.8)
Age, year; median (IQR)	4 (2-9)
Age of diagnosis, month; median (IQR)	4 (2-6)
Maternal age, years; median (IQR)	29 (26.5-32)
Gestational age, weeks; median (IQR)	39 (38-40)
Birth weight, grams; median (IQR)	3220 (2950-3500)
Prematurity, n (%)	
Yes	17 (18.3)
No	76 (81.7)
Type of birth, n (%)	
Normal spontaneous vaginal route, n (%)	33 (35.5)
Cesarean section, n (%)	60 (64.5)
Familial history of atopy; n (%)	
Yes	61 (65.6)
No	32 (34.4)
Age of symptom onset, months; median (IQR)	2 (1-4)
Symptom duration, months; median (IQR)	7 (3-14)
Distribution of lesions, n (%)	
Local, n (%)	72 (77.4)
Generalized, n (%)	21 (22.6)
SCORAD at the time of diagnosis; median (IQR)	45.2 (35.2-54.6)
Mild, n (%)	8 (8.6)
Moderate, n (%)	50 (53.8)
Severe, n (%)	35 (37.6)
First-year SCORAD; median (IQR)	30.1 (20.65-37.35)
Type of food allergy, n (%)	
IgE mediated, n (%)	30 (32.3)
Non-IgE mediated, n (%)	21 (22.6)
Mixed type, n (%)	42 (45.2)
Food allergy, n (%)	
Milk, n (%)	19 (20.5)
Egg, n (%)	35 (37.6)
Other, n (%)	4 (4.4)
Multiple, n (%)	35 (37.6)
Food allergy tolerance period, months; median (IQR)	14 (9-21)
Number of patients who tolerated food allergy in the first year, n (%)	
Yes	61 (65.6)
No	32 (34.4)
Elimination diet duration, months; median (IQR)	12 (6-18)
Laboratory features	
Absolute eosinophil	
Rate, n (%)	5.5 (3-8.48)
Count, median (IQR)	535 (310-877)
Serum total IgE level, median (IQR)	20.5 (8.25-45.75)
IQR: interquartile range, n: number, %: percentage, SCORAD: Scoring Atopic Dermatitis.	

According to the SCORAD, 8 (8.6%) patients had mild, 50 (53.8%) had moderate, and 35 (37.6%) had severe atopic dermatitis. The median SCORAD value was 45.2 (35.2-54.6).

There was no difference between the groups who tolerated food allergy and those who could not at the first age of life in terms of age, gender, gestational week, maternal age, and familial atopy history (p>0.05 for all) (Table 2).

Correlation analysis

The duration of tolerance development showed a strong positive correlation with the duration of an elimination diet in children with atopic dermatitis and food allergy coexistence (p<0.001, r=0.910). In children who developed tolerance in the first year, the duration of tolerance was positively correlated with the age of symptom onset (p=0.002, r=0.381) and the age at diagnosis (p=0.017, r=0.304). No correlation was found with any parameter in children who could not develop tolerance in the first year with any of the parameters (p>0.05).

Logistic regression analysis

Logistic regression analysis was applied to examine the effect of independent variables on food allergy intolerance in the first year of life. The predictive effect of the logistic regression analysis model was found to be 85.3% (p = 0.047, Negelkerke R2 = 0.366). Egg allergy [p=0.035; OR:6.623 (CI:0.996-44.043)], parental atopy [p=0.024. OR:2.450 (CI:0.699-23.056], and AD severity [p=0.030. OR:1.240 (CI:1.001-22.105)] emerged as statistically significant variables at potential risk factors for intolerance of food allergy in the first year. (Table 3).

Table 2. Comparison of demographic characteristics between first-year-old food tolerant and non-food-tolerant groups in children with atopic dermatitis and food allergy coexistence

	Food Allergy Those Who Tolerate (N=66)	Food Allergy Those Who Cannot Tolerate (N=27)	P value
Gender, n (%)			
Female	23 (34.8)	6 (22.2)	0.233[a]
Male	43 (65.2)	21 (77.8)	
Age, year; median (IQR)	4.5 (2-9)	4 (2-8.75)	0.392[b]
Age of diagnosis, month; median (IQR)	4 (2-6)	3 (1-6)	0.414
Maternal age, years; median (IQR)	29 (27-32.5)	29 (25-31)	0.613[b]
Gestational age, weeks; median (IQR)	39 (38-40)	38 (38-39)	0.916[b]
Birth weight, grams; median (IQR)	3250 (305-3500)	3065 (2760-3400)	0.120[b]
Type of birth, n (%)			
Normal spontaneous vaginal route	21 (31.8)	11 (40.7)	0.411[a]
Cesarean section	45 (68.2)	16 (59.3)	
Familial history of atopy; n (%)	41 (62.1)	20 (74.1)	0.271[a]
Age of symptom onset, months; median (IQR)	2 (1-4)	2 (1-4)	0.552
Symptom duration, months; median (IQR)	7 (3-14)	4.5 (2.25-14)	0.252
SCORAD at the time of diagnosis; median (IQR)	45.2 (34.85-54.05)	45.75 (34.12-55.3)	0.345
First-year SCORAD; median (IQR)	30.2 (21.25-36.1)	29.6 (18.7-44.52)	0.737

IQR: interquartile range, n: number, %: percentage, SCORAD: Scoring Atopic Dermatitis.
[a]: Categorical variables were compared using the χ2 test.
[b]: Comparison of non-normally distributed continuous variables was made using the Mann-Whitney U test.
p<0.05 is significant

Table 3. Logistic regression analysis of risk factors of intolerance of food allergy in the year of life

	B	S.E.	Wald	p	Odds ratio	95% CI	
						Lower	Upper
Parental atopy	2.798	0.775	5.164	**0.024**	2.450	0.699	23.056
SCORAD	1.039	0.031	4.178	**0.030**	1.240	1.001	22.105
Birth weight	-0.002	0.001	1.060	0.261	0.698	0.497	1.000
Gender	-1.099	0.949	1.342	0.247	0.333	0.052	6.139
Prematurity	3.156	1.613	1.829	0.145	0.475	0.395	1.927
Presence of smoking exposure	0.937	0.734	1.628	0.202	0.392	0.093	1.652
Maternal age	0.087	0.075	1.340	0.247	1.091	0.942	1.263
Presence of comorbidity	1.142	1.858	0.378	0.539	0.319	0.008	12.186
Cow's milk allergy	0.612	0.778	0.619	0.132	1.143	0.402	8.462
Egg allergy	1.891	0.967	3.826	**0.035**	6.623	0.996	44.043
History of atopy	0.156	1.178	1.594	0.247	0.043	0.004	0.429

SCORAD: Severity Scoring of Atopic Dermatitis Index, CI: Confidence Interval.
Logistic regression analysis was applied. Negelkerke R^2 of the model was 0.366. The overall percentage for the model is 85.3%. $p<0.05$ was accepted as a significance value.

DISCUSSION

In the present study, the severity of atopic dermatitis, the site of eczema involvement, the clinical course of the disease, the relationship of atopic dermatitis at the time of diagnosis with food allergy and tolerance period were evaluated in infants with atopic dermatitis. This study showed that the food allergy accompanying atopic dermatitis is mostly associated with cow's milk or egg allergy and the tolerance period is 12 months on average. The most important risk factors affecting intolerance within 12 months are the presence of egg allergy, the severity of atopic dermatitis, and the presence of parental atopy.

Atopic dermatitis presents in the first six months of life in 45%, in the first year of life in 60%, and in the first five years of life in 85% of the children.[3] In a study by Guttman-Yassky et al., the mean age of diagnosis of 21 patients with AD was found to be 1.7 years.[14] In a study conducted by Yüksel et al. with 531 children with atopic dermatitis, the mean age at diagnosis was 37.8±36.2 months.[15] The study conducted by Ulutaş et al. reported that in 298 children with atopic dermatitis, the age of symptom onset was found to be 18.1±21.5 months.[16] In this study, it was observed that the median age of symptom onset and age of diagnosis in atopic dermatitis were before the first six months of life, which aligns with the literature.

Many studies in the literature examine the relationship between atopic dermatitis and food allergy. Almost 50% of children with atopic dermatitis and 35% of adults are sensitive to environmental and food allergens, with rates ranging from 7% to 80% among different study populations. Food sensitization rates of patients range from 30% to 80%. However, clinically, the rates of food allergy may be lower, especially in the less severe phenotypes of AD. In fact, 20-30% of patients with AD have food allergies. Therefore, atopic dermatitis has been suggested as a major risk factor for food sensitization and IgE-mediated food allergy. However, symptoms suggestive of food allergy are mostly absent in patients with mild atopic dermatitis. Population-based studies have shown that patients with AD are up to six times more likely to have food sensitivities at three months of age compared to healthy controls. When hospital admissions are included, the prevalence of food sensitization is up to 66%, while proven food allergy with oral food challenges is 81%. The Danish Allergy Research Cohort (DARC) showed that up to 53% of children with atopic dermatitis aged six months to 6 years were sensitized to food allergens, with a confirmed food allergy in 15%. In Australia, in the Health Nut study, a large population-based study (n = 4453), infants with atopic dermatitis were six times more likely (95% CI 4.6-7.4) and were 11 times more likely to have a peanut allergy (95% CI 6.6-18.6).[17] In another study, moderate-to-severe children under five years of age with atopic dermatitis have shown that 37% of patients have IgE-mediated food allergies.[18]

The study of Strömberg et al. showed that in the diagnosis of food allergy in children with atopic dermatitis, these children

were shown to be sensitive to more than one food.[19] In a study by Martin et al., sensitivity to egg white was significantly higher than other foods in children with atopic dermatitis.[20] In the study conducted by Gray et al. 100 children with atopic dermatitis, food sensitivity was observed in 66% of the cases, food allergy was diagnosed in 44% by the food challenge test, and the highest rate of allergenic foods was peanut and cow's milk.[5] In our study, egg sensitivity was highest in children with AD, followed by cow's milk allergy.

Staden et al. studied the specific oral tolerance-inducing therapy (SOTI) in pediatric patients with egg or milk allergy, including the group that received an elimination diet as the control group, and examined the tolerance periods. Accordingly, the duration of tolerance development in 20 children diagnosed with food allergy whose elimination diet duration was determined as 21 months, with a minimum of 12 months and a maximum of 47 months.[21] In this study, the time to develop tolerance to food allergy may extend up to 21 months in patients with atopic dermatitis, consistent with the literature. On the other hand, there is no significant difference in demographic characteristics and severity of atopic dermatitis between patients who can and cannot develop tolerance in the first year of life.

In the present study, the most important determinants for tolerance development in the first year of life were the presence of cow's milk protein allergy, parental history of atopy, and severity of atopic dermatitis. Individuals whose family (mother, father, sibling) has a history of allergic disease (atopic dermatitis, rhinoconjunctivitis, asthma) are more likely to develop an allergic disease. In addition, associations of atopic dermatitis, rhinoconjunctivitis, and asthma, which are among atopic diseases, are frequently seen in the family histories of cases with food allergies.[22,23] In the study of Apfelbacher et al., it was observed that parental atopic diseases were significantly associated with the development of atopic dermatitis in children.[24] In another study by Lowe et al., in which the risk factors for atopic dermatitis were examined, it was shown that there was a significant relationship between the presence of allergic disease in the parents and the development of atopic dermatitis in their children.[25] It is effective on the duration of tolerance in food allergy, as well as its relationship with the presence of dermatitis and food allergy. On the other hand, it has been shown that 70% of infants with atopic dermatitis recover from the disease in late childhood. Still, in those with early or severe onset atopic dermatitis, in the presence of a family history of atopic dermatitis and sensitization to allergens at an early age, the disease recovers at a later age.[26] While 43.2% of patients with early-onset atopic dermatitis had complete recovery after two years of age, 38% of patients with early-onset atopic dermatitis continued to have intermittent atopic dermatitis flare-ups until seven years of age. Disease severity and early sensitization (especially food sensitivity) were found to be among the poor prognostic factors in severe atopic dermatitis.[27] There is a higher rate of allergic sensitization in patients with early-onset and severe AD, and it has been reported that patients with AD are associated with sIgE positivity. Accordingly, it is thought that the severity of the disease affects the natural course of allergic sensitization and the atopic march in AD.[15] Similarly, having severe atopic dermatitis is a risk factor for a longer recovery from food allergy. The prevalence of food allergy is higher in children than in adults; in prospective studies of adverse food reactions in young children, about 80% outgrow their problem after the third year of life. One-third of food-allergic patients lose their sensitivity after two years of avoiding diet. The study of Pascual et al. showed that egg white protein is the most common allergen, followed by cow's milk and peanuts. These three food items represent half of the sensitizations in children under two years of age. Patients with milk allergies are more prone to losing their sensitization one or two years earlier than those allergic to eggs.[28] In our study, consistent with the literature, egg allergy was found to be a risk factor for food intolerance.

The strengths of the study are that it was conducted in a tertiary health centre where allergic diseases in children were evaluated in detail, the diagnosis of food allergy was made with a food challenge test, and food allergy sensitivity in infants was assessed with standardized food-specific IgE or skin prick tests. The fact that patients with atopic dermatitis are evaluated and recorded with their SCORAD in every visit in our clinic and the absence of missing data in patient records does not cause data loss in the analyses strengthened our results.

The limitations of the study are that the study design is retrospective, there is no healthy control group, and cases with food tolerance after the 12th month in the patient follow-ups cannot be evaluated. The fact that the study was conducted in a tertiary reference centre may cause more severe cases to be included in the evaluation. Therefore, it is not possible to generalize the results obtained to the general population.

CONCLUSION

In this study, egg and milk were found to be the most common allergens in concomitant food allergy in infants with atopic dermatitis. Tolerance to food allergy develops in more than half of infants by 12 months. Risk factors affecting the development of tolerance to food allergy in the first year of life were found to be the presence of hen's egg allergy, the severity of atopic dermatitis, and the presence of parenteral atopy. The results of this study provide us with important data in the close follow-

up of the development of tolerance in the clinical follow-up of the patients. The results of this study need to be confirmed with prospectively designed studies. We think that our results will be a light for future studies and will help determine individualized treatment approaches by more clearly revealing the risk factors affecting the development of tolerance.

Ethical approval

Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Ethics Committee approved the protocol of the study (Approval number: 2023/158). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: BVM, PU; Concept: BVM, PU; Design: BVM, PU; Data Collection or Processing: BVM, PU; Analysis or Interpretation: BVM, PU; Literature Search: BVM, PU; Writing: BVM, PU. 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

Pathogenic microorganisms and antimicrobial resistance patterns in the pediatric age group with urinary system infections

Güneş Işık[1], **Pınar Öner**[2]

[1]Pediatric Nephrology, Gaziantep City Hospital, Gaziantep, Türkiye
[2]Medical Microbiology, Elazığ Fethi Sekin City Hospital, Elazığ, Türkiye

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ABSTRACT

Objectives: Urinary system infections (UTIs) are among the most common infections affecting the pediatric age group. We aim to show the distribution of pathogenic microorganisms and antimicrobial resistance patterns of urinary tract infections (UTIs) and select the most appropriate antibiotherapy in the pediatric age group. Also, we wanted to determine signs and symptoms, predisposing factors, and imaging findings in UTIs.

Material and Methods: In this study, the Elazığ Fethi Sekin City Hospital health registry system was screened retrospectively to obtain data about the results of urinalysis, urine culture tests, and urinary imaging findings of patients, who presented to the pediatric nephrology clinic with signs and symptoms of UTI between January 2020 and September 2021. The study population consisted of children aged 1 month to 18 years.

Results: The study sample included 191 patients. Antimicrobial resistance of E. coli was seen at the highest level to ampicillin (55%), followed by amoxicillin (42%), trimethoprim-sulfamethoxazole (TMP-SMX) (36%), and cefuroxime (35%). The antimicrobial resistance of Klebsiella pneumoniae was seen most frequently in patients treated with ampicillin (100%), amoxicillin (50%), ceftazidime (31%), and nitrofurantoin (31%). The antimicrobial resistance of Proteus mirabilis was seen mostly in cases that received nitrofurantoin (88%), and TMP-SMX (55%). Enterobacter aerogenes demonstrated minimal antimicrobial sensitivity to ampicillin (66%), amoxicillin (33%), and nitrofurantoin (33%) in decreasing order of frequency.

Conclusions: The rate of resistance to ampicillin is very high in Klebsiella pneumoniae and in Enterobacter spp and rates of antimicrobial resistance to cephalosporin, TMP-SMX, and nitrofurantoin are increasing. The rational use of antibiotics is a globally important issue.

Keywords: Antimicrobial resistance, children, urinary tract infection, uropathogens

INTRODUCTION

Urinary system infections (UTIs) are among the most common infections affecting the pediatric age group.[1] Although different rates have been cited in the literature, the average reported incidence rate of UTI is 11% in females and 7% in males up to the age of 16.[2] Upper urinary tract infections (pyelonephritis), if not detected and treated at an early stage, cause renal scarring, and in the long term hypertension and chronic kidney disease, especially in children under the age of two. Because of development of chronic complications of UTI, diagnosis, treatment, and use of advanced imaging methods have critical importance.[3] Urinary system ultrasonography (US) and voiding cystourethrography (VCUG) are recommended imaging modalities in the presence of an abnormality seen in the US in children with febrile UTIs.[4] The National Institute for Health and Care Excellence (NICE) and The Italian Society for Pediatric Nephrology (SINePe) recommend Tc-99m dimercaptosuccinic

Correspondence: Güneş Işık **E-mail:** drgunes07@hotmail.com
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acid (DMSA) renal scintigraphy four months after the onset of atypical UTI.[1,5,6] Symptomatic patients are started on empirical antibiotherapy until urine culture and antibiotic susceptibility test results can be obtained. Despite regional differences, the incidence rates of antimicrobial resistance are increasing every day all over the world as in our country.[7,8] The risk factors for UTIs include constipation, dysfunctional voiding, enlarged bladder, weak urine flow, antenatal urinary anomalies, presence of spinal lesions, uncircumcised males, previous UTIs, and recurrent fever of unknown origin.[9]

Escherichia coli is the most common microorganism identified in pediatric UTIs, with a reported rate of approximately 80%.[9,10] Other pathogenic bacteria causing urinary tract infections are gram-negative *Klebsiella spp, Proteus spp., Enterobacter spp.*, and gram-positive *Citrobacter spp.*, *Staphylococcus saprophyticus*, *Enterococci*, and rarely, *Staphylococcus aerus.*[11,12] Empirical antibiotherapy administered should be effective against *Escherichia coli* and the antimicrobial resistance pattern in the region should be considered. In general, third-generation cephalosporins are preferred. More than 50% of the pathogenic microorganisms identified in UTIs are resistant to ampicillin and approximately 30% are resistant to TMP-SMX and the first-generation cephalosporins.[13,14] Ampicillin therapy maintains its importance in the treatment of UTIs caused by enterococci which constitute 6% of all cases of UTIs, especially in newborns. Enterococci are 100% resistant to cephalosporins. Resistance to amoxicillin-clavulanate and third-generation cephalosporins is increasing and the incidence of extended-spectrum beta-lactamase (ESBL) positive *E. coli* and multi-resistant microorganisms are on rise globally.[13-17]

Knowing the resistance of microorganisms to common antibiotics in the region is important for the initiation of appropriate empirical antibiotherapy and to increase the success of UTIs treatment. In our study, we wanted to draw attention to increasing antimicrobial resistance and the rational use of antibiotics.

MATERIAL AND METHODS

Research and Publication Ethics: The study received the appropriate Institute Review Board (IRB) approval. This study was conducted under the approval of the Ethics Committee of Fırat University Hospital (date: 23.09.2021, number: 971328-52-100-92593). Informed consent was obtained from the participants or the parents of the participants under 18 years of age.

In this study, the Elazığ Fethi Sekin City Hospital health registry system was screened retrospectively for the results of urinalysis, urine culture tests, and urinary imaging modalities in patients, who presented to the pediatric nephrology clinic with signs and symptoms of UTI between January 2020 and September 2021. Children aged 1 month to 18 years and having a first episode of urinary tract infection were included in the study. Diagnosis of UTI was established based on the findings of leukocyte esterase positivity and nitrite positivity in urinalysis, the identification of 10^5 CFU/ml of a single pathogen in cultures of midstream urine specimens collected from continent children. Urine samples of incontinent children collected in a sterile bag or obtained from a catheter port were used for antibiotic susceptibility tests in patients with pyuria.[4-6] Only the patients with symptoms and clinical signs of UTI were included in the study. Patients with other sources of febrile episodes or infection were excluded from the study.

The clinical distinction of acute pyelonephritis (upper UTIs) and cystitis (lower UTIs) was made according to the following criteria. Bacteriuria, flank pain/tenderness, and body temperature ≥ 38°C were considered as criteria for UTIs. Toilet-trained children with bacteriuria in the absence of systemic symptoms or signs with dysuria, frequency, and suprapubic pain were considered to have lower UTIs.[1]

Microscopic analysis of samples

Urine samples were centrifuged at 2000 RPM for 5 minutes, and the urine sediment was examined under the light microscope at 40 x magnification for the identification of leukocytes and bacteria, and detection of ≥5 white blood cells per high-power field was evaluated as pyuria (4-6).

Isolation and identification of microorganisms

Urine samples were quantitatively inoculated into 5% sheep blood agar and eosin-methylene blue (EMB) agar media using disposable loops with a volume of 0.001 ml and a diameter of 4 mm. The culture plates were incubated at 35±2°C for 24–48 hours under aerobic conditions and evaluated at 18–24th of incubation. A positive culture was defined as the growth of $\geq 10^5$ CFU/ml of a single microorganism in midstream urine cultures and ≥50,000 CFU/ml of a single microorganism in the cultures of the urine samples obtained from catheter ports.[4-6] Samples with suspected contamination were excluded from the analysis.

Antibiotic susceptibility tests

Isolated microorganisms were identified by conventional methods such as Gram staining, catalase, oxidase, carbohydrate, and citrate tests, tryptophanase activity, urease production, and by using the VITEK® 2 (BioMérieux, Marcyl'Etoile, France) fully automated bacterial identification system. Antibiotic susceptibility test results were interpreted using the VITEK® 2 system based on the minimal inhibitory concentrations (MICs), in accordance with European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards.[18] The extended beta-lactamase positivity of microorganisms was taken into account.

Statistical analysis

The study data were analysed and basic statistical analysis was performed by using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp.). Frequency and percentage distribution analysis was used to determine the distribution of the descriptive characteristics (gender, age, distribution of pathogenic microorganisms, and antimicrobial resistance patterns), presenting symptoms, imaging findings, etc. of the patients evaluated in the study.

RESULTS

A total of 191 patients including 157 (82.2%) female and 34 (17.2%) male cases were enrolled in this study. The median age of the participants was 5 years (range 2 months -17 years). The presenting symptoms were abdominal pain in 4% and fever in 30.4%, constipation in 33%, and voiding dysfunction including inability to urinate, urgency, urinary incontinence, and enuresis in 49.2% of the patients. Additionally, there were no patients with systemic disease, immunodeficiency, history of urinary system surgery, or foreign body in the urinary system. The distribution of the microorganisms grown in the urine cultures of the patients is presented in Table 1. Lower UTIs were detected in 51.8% and upper UTIs in 48.2% of the patients. In addition, respective percentages of female patients had upper UTI (76.1%), and lower UTI (87.9%). Lower UTIs were detected more frequently (55.4%) in female patients, while upper UTIs were more common (64.7%) in male patients. In addition, 37% of the patients with upper UTIs and 60.6% of the patients with lower UTIs had voiding dysfunction which was more common in patients with lower UTIs. Patients with upper UTIs presented mostly with fever (60.9%) while patients with lower UTIs mostly with abdominal pain (91.9%). The US findings were normal in 59.7% of the patients. The abnormal US findings were increased bladder wall thickness in 23.6%, hydronephrosis in 13.1%, kidney stones in 2.6%, simple kidney cysts in 0.5%, and horseshoe kidneys in 0.5% of the patients. DMSA renal scintigraphy revealed renal scarring in 5.2% and vesicoureteral reflux (VUR) in seven (3.7%) patients. Grade II-III VUR was detected in four patients and grade IV-V VUR in three patients. Antibiotic prophylaxis was started in patients with VUR. The following microorganisms were identified in indicated percentages of culture specimens as follows: *E. coli* (79.6%), *Klebsiella pneumonia* (8.4%), *Proteus mirabilis* (4.6%) *Enterobacter aerogenes* (1.6%), and other microorganisms including *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Enterococcus faecium*, *Morganella morganii*, *Citrobacter amalonaticus*, and *Salmonella*, *Serratia odorifera* (5.8%).

Table 1. Distribution of the microorganisms grown in urine cultures

Microorganisms	n	%
E. coli	152	79.6
Klebsiella pneumonia	16	8.4
Proteus mirabilis	9	4.6
Enterobacter aerogenes	3	1.6
Klebsiella oxytoca	2	1.1
Pseudomonas aeruginosa	2	1.1
Enterococcus faecalis	2	1.1
Enterococcus faecium	1	0.5
Morganella morganii	1	0.5
Citrobacter amalonaticus	1	0.5
Salmonella	1	0.5
Serratia odorifera	1	0.5

ESBL-positivity was detected in 5.8% of culture specimens. The antimicrobial resistance patterns of the microorganisms grown in cultures according to the antibiotic susceptibility test results are presented in Table 2. Amikacin (90.1%) had the highest antimicrobial sensitivity, followed by nitrofurantoin (84.3%), fosfomycin (67.0%), TMP-SMX (62.3%), and cefuroxime (53.4%). The highest bacterial resistance developed against ampicillin (58.6%) then amoxicillin (41.4%). The highest antimicrobial resistance of *E. coli* developed against ampicillin (55%) followed by amoxicillin (42%), TMP-SMX (36%), and cefuroxime (35%). *Klebsiella pneumoniae* was mostly resistant to ampicillin (100%), followed by amoxicillin (50%), ceftazidime (31%), and nitrofurantoin (31%). *Proteus mirabilis* displayed maximum antimicrobial resistance to nitrofurantoin (88%), followed by TMP-SMX (55%). Ampicillin (66%), amoxicillin (33%), and nitrofurantoin (33%) demonstrated the lowest level of antimicrobial sensitivity against *Enterobacter aerogenes* in indicated percentage of isolates.

Table 2. Antimicrobial resistance rates (%) of various pathogenic microorganisms

	E. Coli	*K. pneumonia*	*P. Mirabilis*	*E. aerogenes*	*E. faecalis*	*K. Oxytoca*	*P. aeruginosa*	*M. morganii*	*E. faceium*	*C. amalonaticus*	*Salmonella*	*Serratia odorifera*
	(n:152)	(n:16)	(n:9)	(n:3)	(n:2)	(n:2)	(n:2)	(n:1)	(n:1)	(n:1)	(n:1)	(n:1)
Amoxicillin	42	50	11	33	0	50	0	100	0	100	0	0
Ampicillin	55	100	33	66	50	100	0	100	100	100	0	0
TMP-SMX	36	25	55	0	0	0	0	0	0	0	0	0
Amikacin	0	6	0	0	0	0	0	0	0	0	0	0
Gentamicin	6	25	0	0	0	0	0	0	0	0	0	0
Cefuroxime	35	37	11	0	0	50	0	100	0	100	0	0
Ceftazidime	30	31	11	0	0	0	0	0	0	0	0	0
Cefotaxim	3	0	0	0	0	0	0	0	0	0	0	0
Cefoxitin	13	6	0	0	0	0	0	0	0	0	0	0
Cefixime	34	31	11	0	0	0	0	0	0	0	0	0
Ertapenem	0	6	0	0	0	0	0	0	0	0	0	0
Nitrofurantion	0.65	31	88	33	0	0	0	100	0	0	0	0
Ceftriaxone	15	18	11	0	0	0	0	0	0	0	0	0
Fosfomycine	1	12	0	0	0	0	0	100	0	0	0	0

DISCUSSION

Urinary tract infections are common in childhood and cause long-term complications if not diagnosed early and treated appropriately.[18] Previous studies have demonstrated that UTIs were more frequently seen in females.[19] In line with the literature, in our study UTIs were detected in 82% of the female, and 18% of male patients. This study identified lower UTIs in 51.8% and upper UTIs in 48.2% of the patients. Female patients accounted for 76.1% of those with upper UTIs and 87.9% of those with lower UTIs. While 60.9% of the patients with upper UTIs presented mostly with fever, those with lower UTIs presented mostly (91.9%) with abdominal pain. Gürgöze et al. reported the presenting symptoms of UTIs as abdominal pain in 39.7%, fever in 35.7%, vomiting in 23.8%, and dysuria, pollakiuria and enuresis in relatively smaller proportion of patients.[20] Koçak et al. reported that their patients had presented with fever (71.1%), fatigue (19.7%), vomiting (14.8%), and abdominal pain (19%).[21]

In our study, the US findings were normal in 59.7% of the patients, while increased bladder wall thickness was detected in 23.6%, mild-to-moderate hydronephrosis in 13.1%, kidney stones in 2.6%, simple kidney cysts in 0.5%, and horseshoe kidneys in 0.5% of the patients. Increasing bladder wall thickness is a sign of voiding disorders especially voiding postponement and this habit predisposes to UTIs.[9] We detected renal scarring on DMSA renal scintigraphy in 5.2%, and vesicoureteral reflux in 3.7% (n:7) of the patients. While, Koçak et al. detected bilateral hydroureteronephrosis in 10%, kidney stones in 4.2%, and VUR in 26% of their patients.[21] Due to the high rate of spontaneous regression of vesicoureteral reflux in the first 5 years of age, voiding cystourethrography (VCUG) was performed only in patients with renal scarring detected in DMSA renal scintigraphy and urinary tract and kidney abnormalities in US. Consistent with this indication of VCUG we did not find high rate of VUR in our study like Gürgöze. Gürgöze et al. also identified caliectasis in four, VUR in three (1.7%), PUV, and ectopic kidney in one patient each.[20] *E. coli* was the most common microorganism identified in urine cultures in the world.[18-22] The detection rate of *E. coli* varies between 57% to 79.2% in the studies and in line with the literature *E. coli* growth was the most common (79.6%) finding in our study. *Klebsiella pneumoniae* growth was recorded as 8.4% in our study, this rate is changing between 7.2% and 22.8% in other studies. For *Proteus mirabilis*, the detection rate was 4.6% in our study, in the literature this rate varies between 4.5, and 12%.[22-25] Consistent with the literature data, *Enterobacter aerogenes* was detected in 1.6% of the isolates.[24] In our study, the antimicrobial resistance rates of *E. coli* to ampicillin (55%),

amoxicillin (42%), TM-STX (36%), and cefuroxime (35%) were as indicated, while in other studies, these rates were reported as 42-88%, 12.2-34.8%, 26.5-38%, and 19-34%, respectively.[20-25] The antimicrobial resistance of *Klebsiella pneumoniae* was the highest in patients treated with ampicillin (100%), followed by amoxicillin (50%), ceftazidime (31%), and nitrofurantoin (31%) in our study, the respective rates have been reported as 77.8-97%, 37%, 4.5-35.7%, 11.2-11.9% in other studies.[9,20-24] The antimicrobial resistance of *Proteus mirabilis* to nitrofurantoin was at the highest level (88%), followed by TMP-SMX (55%), while the respective rates were reported as 85-100%, 8.3-70% in the literature.[9,20] *Enterobacter aerogenes* demonstrated maximum antibacterial resistance to ampicillin (66%), followed by amoxicillin (33%), and nitrofurantoin (33%), in other studies these rates were indicated as 83.4-91.3%, 53.9%, 5.6-28%, respectively.[8,18] Consistent with the literature data, in our study, the highest antimicrobial resistance of *E. coli* and *K. pneumoniae* was detected to ampicillin and lowest to amikacin.[22-24] Based on the results of our study, amikacin (90.1%) had the highest antimicrobial sensitivity, whereas the highest antimicrobial resistance developed against ampicillin (58.6%), amoxicillin (41.4%), TMP-SMX (34%), cefuroxime (33.5%), and cefixime (30.4%). Despite regional differences, antimicrobial resistance rates are increasing every day all over the world, as in our country.[7,8] NICE guidelines suggest that the individual resistance and antimicrobial resistance rates in the population should be considered when selecting empirical antibiotherapy for UTIs.[1] While we empirically preferred intravenous amikacin treatment in patients with pyelonephritis, we preferred oral nitrofurantoin or TMP-SMX treatments in patients with cystitis. Because Amikacin (90.1%) had the highest antimicrobial sensitivity, followed by nitrofurantoin (84.3%), and TMP-SMX (62.3%) in our study. It is recommended that the resistance rate should not exceed 10–20% to initiate empirical treatment.[25]

CONCLUSION

We want to draw attention to the increasing antimicrobial resistance rates in society, especially the higher antimicrobial resistance to ampicillin, and the increasing resistance rates to cephalosporins. The rational use of antibiotics is globally important. When deciding on empirical treatment of UTI, the antimicrobial resistance patterns in the region should be considered and the most appropriate treatment should be determined.

Study limitations

This is a retrospective, single-center study. Multicenter studies to be performed in the future will further contribute to the clarification of this issue.

Ethical approval

This study has been approved by the Ethics Committee of Fırat University Hospital (approval date 23.09.2021, number 971328-52-100-92593). Written informed consent was obtained from the participants.

Author contribution

Concept: GI, PÖ; Design: GI, PÖ; Data Collection or Processing: GI; Analysis or Interpretation: GI, PÖ; Literature Search: GI; Writing: GI. 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

Sterile abscess formation with two different GnRH analogues: Three case reports

Gülin Karacan Küçükali[1], Şervan Özalkak[1], Havva Nur Peltek Kendirci[2], İlknur Bostancı[3], Şenay Savaş Erdeve[1], Semra Çetinkaya[1]

[1]Pediatric Endocrinology Clinic, Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital, University of Health Sciences, Ankara, Türkiye
[2]Pediatric Endocrinology Clinic, Hitit University Erol Üçok Training and Research Hospital, Çorum, Türkiye
[3]Pediatric Allergy and Clinical Immunology Clinic, Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital, University of Health Sciences, Ankara, Türkiye

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ABSTRACT

Gonadotropin-releasing hormone analogues (GnRHa) have been used safely for many years in the treatment of precocious puberty. Although rare, pain, swelling, and erythema at the injection site are known local side effects in patients receiving GnRHa treatment and are temporary. Sterile abscess development is also one of the rare local side effects. Here, we present three cases of treatment failure due to the development of sterile abscesses after GnRHa therapy.

Sterile abscesses developed in three girls who were followed up with a diagnosis of precocious/progressive puberty respectively in 4., 12. and 5. doses of GnRHa treatment. In the first case, a sterile abscess recurred despite the therapy being switched to another preparation. We had to follow up without treatment in three of our cases.

Although sterile abscess is a rare side effect, it is essential as it causes patients to be left untreated. In these cases, the drug's active substance accumulates in the localization at the sterile abscess and cannot be absorbed, so it cannot enter the systemic circulation. Therefore, puberty cannot be suppressed. Also, a remaining scar is annoying for patients and their families.

Keywords: Precocious puberty, GnRH analogues, local reactions, leuprolide acetate, triptorelin, sterile abscess

INTRODUCTION

Central precocious puberty is the onset of puberty with early activation of the hypothalamic-pituitary-gonad axis. GnRH analogues (GnRHa) have been used safely for many years in central precocious puberty treatment.[1] Local reactions with GnRH analogues, such as pain, swelling, redness, and temperature, are seen in 10-15%, and a sterile abscess is seen in 0.6-3%.[2-5] The sterile abscess is an abscess formation that is not caused by pyogenic bacteria.[5] Besides local reactions, treatment ineffectiveness is the main problem in these cases. Here, three patients who developed sterile abscesses during triptorelin (TA) and leuprolide acetate (LA) treatments will be presented in terms of difficulties in treatment and follow-up plans.

Correspondence: Gülin Karacan Küçükali **E-mail:** gulinkucukali@gmail.com
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CASE REPORT

The patients who were followed up with central precocious puberty between 2018 and 2020 in the Pediatric Endocrine Clinic of our hospital were evaluated for sterile abscesses. Three (1.07 %) of the 278 patients receiving TA or LA had sterile abscesses. None of the cases had a known allergy history. The characteristics of three cases, initiation of treatment, the development process of sterile abscess, and their subsequent management are given below. Anthropometric and laboratory data of the cases are presented in Table 1.

Informed consent was obtained from the parents of the patients for publication of this case series.

Table 1. The clinical and laboratory characteristics of the patients at admission

	1. Patient	2. Patient	3. Patient
Age (years)	$6^{5/12}$ -year-old	$7^{2/12}$-year-old	$8^{7/12}$-year-old
Complaint	Pubic hair	Breast development	Breast development
Weight (kg)/SDS	32 (2.38)	31.1 (1.62)	39 (1.8)
Height (cm)/SDS	130.5 (2.66)	124.3 (0.38)	137 (1.23)
BMI (kg/m^2)/SDS	18.85 (1.48)	20.13 (1.73)	20.7 (1.58)
Breast Tanner stage Pubic Tanner stage	III III Clitoromegaly	III I	III III
Bone Age	11 years	8 years 10 months	11 years
Mother'/Father' height (cm) MPH (cm)/SDS	Height of the parents is unknown (adopted child)	149/170.6 153.3(-1.67)	160/171 159(-0.7)
LABORATORY			
LH (mIU/L)	0.1	<0.07	9.41
FSH (mIU/L)	2	2.41	7.79
E2 (pg/ml)	<12.1	12.9	45.7
Peak LH	24.2	9.27	-
Peak FSH	17.57	14.6	-
Standard dose ACTH stimulation test	Peak cortisol 10µg/dl Peak 17OHP 42.2 ng/ml		
Pelvic USG	Pubertal	Pubertal	Pubertal
Tryptase (µg/l)	-	38.6	3.98
Diagnosis	CAH+ Central puberty precocious	Central puberty precocious	Rapidly progressive puberty
Treatment	Hydrocortisone+ leuprolide acetate	Leuprolide acetate	Leuprolide acetate
Which drug causes sterile abscess	Leuprolide acetate triptorelin	Leuprolide acetate	Leuprolide acetate
Last drug doses	7.5 mg/28 days	3.75 mg/28 days	7.5 mg/28 days
At what dose it developed	4.	12.	5.
Injection site change	Sterile abscess persisted	Sterile abscess persisted	Sterile abscess persisted

SDS: Standard deviation score, BMI: Body mass index, MPH: Mid parental height, USG: ultrasonography, CAH: Congenital adrenal hyperplasia, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, E2: Estradiol, ACTH: Adrenocorticotropic hormone, 17OHP: 17-Hydroxyprogesterone.

Case 1

An "adopted" girl, aged $6^{5/12}$ -years, was admitted to the outpatient clinic with a complaint of pubic hair. The case was diagnosed with non-classical congenital adrenal hyperplasia and central precocious puberty with the clinical and laboratory data presented in Table 1. She was commenced on subcutaneous (sc) leuprolide acetate depot 3.75 mg every 28 days and 12 mg/m^2/d hydrocortisone.

The patient complained only pain at the injection site after the first three doses. Since pubertal suppression could not be achieved at the time of the fourth injection, a GnRH test was performed to ascertain the adequacy of suppression of puberty, and the treatment dose had to be increased by 7.5 mg / 28 days.

Unfortunately, she suffered a local reaction with erythema consistent with an abscess. Since no microorganism was seen in the gram stain and no growth in the culture, a sterile abscess was considered.

Due to the reaction, the treatment was switched to TA. Sterile abscess formation also developed after the injection of TA. The patient was consulted with the allergy department. Sterile abscesses also developed during the test by changing the site in the allergy department. To exclude local reaction at the injection site, medication was applied to the area that had not been injected before, and a sterile abscess developed after the third day. It was planned to switch to a nasal GnRH analogue (nafarelin), but the drug could not be obtained due to the high cost. After the family consultation, the treatment was discontinued in the patient whose bone age was 12.

Case 2

A $7^{2/12}$-year-old girl was admitted to the outpatient clinic with complaints of breast development and was diagnosed with precocious puberty.

LA treatment was started at a dose of 3.75 mg per 28 days subcutaneously. In the first year of treatment, sterile abscess formation developed at the injection site. The allergy department consultation recommended measuring her serum tryptase level because her examination revealed a positive "Darier's sign". It was found to be quite high (38.6 µg/l, n=0-11.4). Repeated tryptase value revealed > 20 g/l, and due to the risk of anaphylaxis, the treatment was discontinued with the family's consent. The case was followed up for mastocytosis.

Table 2. The laboratory results of patients after GnRHa injection

	1. Patient	2. Patient	3. Patient
LH (mIU/mL)	18.9	5.5	6.33
FSH (mIU/mL)	26.6	7.89	10.09
E2 (pg/ml)	48.4	28.2	33.2

LH: Luteinizing hormone, FSH: Follicle stimulating hormone, E2: Estradiol.

Case 3

An $8^{7/12}$-year-old girl was admitted to the outpatient clinic with complaints of breast development. Her signs of puberty started at the age of 8. The patient was diagnosed with rapidly progressive central precocious puberty with the clinical and laboratory data presented in Table 1. LA treatment was started at a dose of 3.75 mg/sc every 28 days. It was learned that the patient had pain after the first injection, and then erythema was added to the pain with subsequent doses. Since LH values were not suppressed in the GnRH analogue test at the time of the fourth injection, the dose was increased (7.5 mg / every 28 days). After the dose increment, sterile abscess formation developed. Switching to TA was planned, but the family refused the treatment.

The laboratory results of patients after GnRHa injection are given in Table 2.

DISCUSSION

GnRHa therapy has been used safely for many years in the treatment of central precocious puberty.[1] It is known that GnRHa treatment may have local side effects.[1] The development of a sterile abscess, one of the local side effects, was first reported in one case by Neely et al.[2] As in our patients, due to the development of sterile abscess with both LA and TA, it is thought that this situation is not against the active ingredient but against the inert polymer (lactic and glycolic acid used as copolymer).[4-6]

The reports of cases developing sterile abscesses with daily leuprolide, which does not contain polymers, are conflicting. It has been reported that the patient who developed a sterile abscess with a three-month depot form containing inert polymer was successfully treated with non-polymer daily applied LA.[6] However, in two cases using depot leuprolide, the treatment was changed to daily administered LA due to local reaction (one

of which was a sterile abscess). While one case was treated successfully, it was reported that the treatment was discontinued in one patient because local erythema developed in the eighth month of the treatment.[2] It has been reported that after the first idiosyncratic reaction against the drug-copolymer combination, a reaction may develop against the drug alone or the copolymer alone.[7] When the first case of Kirkgoz et al. developed urticaria with TA, her treatment was changed to LA. The case developed anaphylaxis in the second year of LA treatment. However, no problem has been reported with the change of treatment in other cases in this series.[8]

Sterile abscess formation was observed in only 1.07 % of the patients who received treatment for early puberty in our clinic. This rate was reported as 0.6% by Lee et al.[5] Before abscess formation is observed in these cases, it is noteworthy that there is pain and swelling at the injection site. Similarly, it is observed that most of the cases reported in the literature have local side effects such as pain, swelling, and erythema before the development of sterile abscess.[4,5,9] It is essential to follow up closely for the development of sterile abscesses in cases with local side effects. A sterile abscess can heal with or without a scar. Scar appearance can cause discomfort in families and patients. For this reason, in cases with local side effects such as pain, swelling, and erythema after injection, it will be beneficial to continue the subsequent injections from the hip rather than the arm, which is a visible place, at least to hide the scar appearance due to the sterile abscess that may occur in the future.

Another problem besides local side effects is treatment failure due to impaired drug absorption. Although changing the preparation seems to be an option, it should be kept in mind that a sterile abscess may develop with the other preparation, as in our first case. In another study evaluating 49 precocious puberty cases, local reaction was observed in two cases, and one of them was stated to be a sterile abscess. It was also emphasized that there was a failure in the suppression of puberty in both cases.[9] Tonini et al. reported that two of the 20 cases (one girl and one boy) developed local reactions, one progressed to sterile abscess, and puberty precocious treatment failed.[3] There are also reported cases in the literature that followed an uneventful treatment process with preparation change.[4,5] As reported by Miller et al., in an 8-year-old patient who received a monthly 15 mg LA treatment, a 50 mg histrelin implant (nonbiodegradable, diffusion-controlled, polymer reservoir containing histrelin acetate) was placed sc on the arm after the development of a sterile abscess.[4] When a reaction was observed with this treatment, the treatment process was completed without any problem with intranasal nafarelin. It has been reported that the development of sterile abscess was observed with LA, TA, and goserelin in a male patient with puberty precocious due to hypothalamic hamartoma when he was two and a half years old. GnRHa treatment was terminated due to treatment failure and was switched to cyproterone acetate.[10] In addition, although it has been reported that local side effects are more common with LA[5], this result is thought to be due to the more common use of LA treatment in recent years.

No evidence that changing the injection site or choosing the subcutaneous/intramuscular (IM) method makes any difference in antigenic terms. Although the injection site was changed in our second case, sterile abscess formation was repeated. Lee et al. reported two cases taking LA (SC), and after the abscess formation, it was switched to TA (IM) with no further reactions. In the same report, the third case developed an abscess under the LA treatment; thereafter, the therapy was switched to the triptorelin acetate depot, which was IM injected in the buttock, but abscess formation was repeated.[5]

Tryptase is a serine protease released from mast cells and a reliable marker of mast cell activation.[11] There is a risk of mastocytosis development in any period of life in cases with serum tryptase > 20 g/l examined at two different times, and the cases should be followed up in this respect.[11] It was planned to follow up on our second case from this point of view and study the c-kit mutation.

CONCLUSION

In conclusion, GnRHa therapy is safe to use in central precocious puberty treatment. However, it should be remembered that local reactions such as sterile abscesses may occur rarely.

Limitations

The limitation of our study is the lack of microscopic examination of abscesses in our cases.

Ethical approval

Ethical approval was not received because it was a retrospective case study. Written informed consents were obtained from parents of the patients.

Author contribution

Surgical and Medical Practices: GKK, ŞÖ, HNPK, İB, ŞSE, SÇ; Concept: GKK,SÇ; Design: GKK, SÇ; Data Collection or Processing: GKK, ŞÖ, HNPK, İB, ŞSE, SÇ ; Analysis or Interpretation: GKK, İB, SÇ; Literature Search: GKK, İB, SÇ; Writing: GKK, İB, SÇ. 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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