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Contact
The Journal of Pediatric Academy Office,
Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri, Türkiye
Phone: +90.352.2076666 (int) 25373
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The Journal of Pediatric Academy Office,
Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri - Türkiye
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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation in the topic of the research article published in the journal. The authors are selected and invited by the journal to provide such comments. The text should contain 1500 words or fewer. it includes 5 figures and/or tables or fewer and 15 references or fewer.

Research Articles:

This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with an Introduction, Methods, Results, Discussion, Conclusion, and References subheadings. Please see Table 1 for limitations for Research Articles.

Statistical analysis is usually necessary to support conclusions. Statistical analyses must be conducted by international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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Clinical observations may include case histories that demonstrate novel findings or associations, important clinical responses when a larger study is not needed to address a specific issue, or a unique laboratory observation linked to clinical care and/or practice. The text should contain 1500 words or fewer, with a brief abstract of 200 words or fewer. Abstracts outline background, observation(s), and conclusions. Include 5 figures and/or tables or fewer and 15 references or fewer.

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For educational purposes, the journal publishes original, interesting, and high-quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. The figure legend should contain no more than 100 words. It can be signed by no more than 5 authors and can have no more than 5 references and 3 figures or tables. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

Letters To The Editor:

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

Table 1
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	1000	No abstract	5	1	1

References:

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

Journal Article:

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

Journal Article published in non-English Languages:

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

Book Chapter:

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

Entire Book:

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

Software:

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

Online Journals:

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

Database:

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

World Wide Web:

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

URL (Uniform Resource Locator)

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

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Contents

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Invited Review

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Urinary Tract Infections in Children

Author(s)

Hakan M. Poyrazoğlu, Sibel Yel

Affiliation(s)

Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nephrology, Kayseri, Turkey

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Abstract

Urinary tract infections are one of the most common bacterial infections in children. It may cause severe complications in both acute and chronic periods. *Escherichia coli* is the most common microorganism that causes urinary tract infections in children. Recurrent urinary tract infection is a significant risk factor for kidney scarring. Early diagnosis and appropriate treatment of urinary tract infection, as well as determination of risk factors and prevention of recurrent urinary tract infections, should be the most critical goals in managing children with urinary tract infections.

Keywords: Urinary tract infections, children, urosepsis

Introduction

Until antibiotics were discovered in the mid-20th century, urinary tract infections (UTI) were a major life-threatening health problem. In an article published by Kenny JF et al.[1] in 1966, it was reported that 8 out of 11 infants hospitalized for *E. coli*-related pyelonephritis developed septicemia, and four of them died. Fortunately, urinary tract infections are not so severe in children today, but it remains a significant problem. Although death due to urinary tract infection is rare today, urinary tract infection may cause complications such as urosepsis, renal abscess and acute kidney damage in the acute period, chronic renal failure, proteinuria, and hypertension in the chronic period due to renal scarring. It is reported that 10-40% of children with pyelonephritis have renal scarring.[2-4] Therefore, urinary tract infections need to be diagnosed early, treated appropriately, and closely monitored.

Epidemiology

Urinary tract infections are the second most common bacterial infection in children. It was determined that 8.4 % of girls and 1.7 % of boys had urinary tract infections at least once in the first seven years of life. It has been found that a second UTI

Correspondence: Hakan M. Poyrazoğlu, Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nephrology Kayseri, Turkey
E-mail: drpoyrazoglu@yahoo.com

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develops in 30% of children with urinary tract infections. Urinary tract infections affect boys and girls equally in the first year of life but are more common in girls after one year.[5-8] Risk factors that facilitate the occurrence of urinary tract infection are given in **Table 1**.[9]

Etiopathogenesis

Escherichia coli is the most common microorganism that causes urinary tract infections in children. Other enteric Gram-negative bacteria causing UTI are *Klebsiella*, *Pseudomonas*, *Proteus*, *Enterobacter*, and *Citrobacter spp*. Some Gram-positive organisms can also cause UTI, such as *Staphylococcus saprophyticus*, *Enterococcus spp*, and *Staphylococcus aureus*. The vast majority of microorganisms that cause urinary tract infections originate from fecal flora that crosses from the perineum to the urethra and infect the bladder.[9] Bacterial virulence characteristics and impairments in host defense are the most critical factors in the occurrence of urinary tract infections. Virulence factors that make the microorganism uropathogenic are among the most important factors in the occurrence of urinary tract infection. These factors vary with different types of UTI. P-fimbriae, found in *E. coli*, helps bacteria attach to the uroepithelial cell and thus keep the bacteria in the urinary tract despite urine flow. Other virulence factors include hemolysin, O antigen, capsule K phenotypes, siderophores. Some strains of bacteria such as *Klebsiella* and *Pseudomonas* do not have such properties, so they need impaired host defenses to cause infection. Host defense factors that play a role in the pathogenesis of urinary tract infection include systemic or local anatomical or functional problems. Urinary flow is an important host defense factor in the urinary tract. It has been reported that anatomical disorders that prevent urinary flow, such as obstructive uropathies and severe vesicoureteral reflux (VUR), facilitate urinary tract infections. In these cases, the risk of urinary tract infection increases. Some functional abnormalities, such as bladder and/or bowel dysfunction, can disrupt the local defense system and facilitate the formation of urinary tract infection. The risk of urinary tract infection may increase in systemic immunodeficiency or immune suppression, especially in cases of systemic immunodeficiencies, such as impairment of Toll-like receptors or abnormal production of antibacterial peptides (eg cathelicidines and α-defensins).[10,11]

Highlights

- Urinary tract infections are one of the most common bacterial infections in childhood and the most common cause is *Eshericia coli*.
- The diagnosis is based on the detection of significant bacteriuria in the urine sample with clinical suspicion.
- Taking a proper urine sample is important for diagnosis. Especially in young children, catheterization or suprapubic aspiration methods are recommended to obtain urine samples.
- Early diagnosis and appropriate treatment can prevent renal scar development.
- Predisposing factors (especially bladder and bowel dysfunction) should be investigated in children with recurrent urinary tract infections.

Table 1.
Risk factors that facilitate the occurrence of urinary tract infection

• Bowel and bladder dysfunction
• Urinary tract abnormalities
Structural
- Vesicoureteral reflux, posterior urethral valves, prune belly syndrome, ureteropelvic /ureterovesical junction obstruction, megaureter, polycystic kidney disease
Functional
- Neurogenic bladder
• Indwelling catheter
• Immunosuppressed status
• Neonates
• Uncircumcised boys

Clinical features

Urinary tract infections can generally be presented in three different clinical presentations: Acute pyelonephritis, acute cystitis, and asymptomatic bacteriuria.

Acute pyelonephritis reflects infection of the kidney parenchyma and pelvis. Patients usually present with high fever (may rise to 39-40°C) and systemic symptoms such as nausea, vomiting, anorexia, flank, or abdominal pain. Acute cystitis refers to bladder infection and is the most common form of UTI. In this clinical situation, complaints and findings are generally localized in the lower urinary system rather than systemic. Dysuria, frequent urination, a feeling of urgency, pain in the lower abdomen are the most common complaints. Generally, there is no fever, or it may be mild (rarely up to 38°C). Asymptomatic bacteriuria is the asymptomatic presence of bacteria in the urine without significant pyuria. Children often show symptoms of bladder dysfunction.[9,10]

Urinary tract infections are clinically defined in two different types as simple or complicated. Complicated urinary tract infection describes urinary tract infection occurring in the presence of risk factors such as structural or functional urinary tract abnormalities, indwelling devices, stones, and immunosuppression. On the other hand, any risk factor does not accompany urinary tract infection in the simple urinary tract infection type.[9] Defining simple or complicated UTI is essential in terms of treatment and follow-up planning.

It is important to determine whether it is the first urinary tract infection or recurrent urinary tract infection in the child diagnosed with urinary tract infection.[9] If a child has had two or more urinary tract infections, a recurrent urinary tract infection is mentioned. Recurrent urinary tract infection is important because it has been reported in different studies that recurrent UTI is a risk factor for kidney scarring. The risk of kidney scarring increases as the number of repeats increases.[9,10]

It has been suggested that some factors facilitate the occurrence of urinary tract infection or the recurrence of urinary tract infection. These risk factors include age (3-5 years, typical toilet training age), Caucasian race,

high-grade VUR, female gender, bowel, and bladder dysfunction. For example, it has been reported that the presence of vesicoureteral reflux is a predisposing factor for the occurrence of urinary tract infection, and the rate of recurrence of urinary tract infection increases as the degree of vesicoureteral reflux increases. As mentioned above, children with urinary tract infections should be evaluated for the presence of risk factors since urinary tract infection, especially recurrent urinary tract infection, may cause renal scar formation.[8-10]

Is renal scarring important?

It is well known that renal scarring leads to three crucial chronic problems. These are reduced kidney function, hypertension, and pregnancy complications.[10] Toffolo et al.[12] analyzed long-term follow-up data from 19 studies involving 3148 pediatric patients with urinary tract infections. Although heterogeneous results, the prevalence of decrease in renal functions was determined as 0-56%, the prevalence of hypertension as 1.2-35%, and pregnancy complications such as hypertension, proteinuria, or preeclampsia were detected in 12% of pregnancies.[12] Gebäck et al.[13] evaluated adult women's kidney function with childhood urinary tract infections in their study. They found that women with no renal scar in infancy had stable GFR.

In contrast, those with bilateral scarring in infancy had a significant decrease in their GFR and commented that individuals with bilateral scarring have a chance of developing clinically significant chronic kidney disease. In another study, Gebäck et al.[14] evaluated ambulatory blood pressure measurements of adult women with childhood urinary tract infections after 35 years of follow-up. They found a higher rate of systolic blood pressure in the group with scarring in childhood.

Diagnosis

There are two main goals when diagnosing a urinary tract infection: early diagnosis and avoiding unnecessary antibiotic use. The clinical diagnosis of UTI is based on the presence of symptoms and the demonstration of bacteriuria in the urine. Bacteriuria is a mandatory finding for the diagnosis of UTI.[9,10,16] UTI symptoms can range from asymptomatic to a severely ill child with a high fever and secondary bacteremia.[2] It is not always easy to diagnose a urinary tract infection. Symptoms can be nonspecific, especially in young children. Therefore, it is an important problem for clinicians to consider a UTI and which patient will be screened for urine. The first step in the diagnosis of urinary tract infection is suspicion. Also, the presence of risk factors can be considered to predict the probability of UTI in febrile infants and young children (2-24 months). The presence of more than 2 of the following risk factors in baby girls increases the likelihood of UTI by more than 2%: Caucasian, age less than 12 months, fever more than 48 hours, no other source of fever, fever of 39°C or higher. The presence of more than 3 of the following risk factors in circumcised baby boys increases the likelihood of UTI by more than 2%: Non-black race, fever for more than 24 hours, no other source of fever, fever of 39°C or higher.[9]

The American Academy of Pediatrics (AAP) and other guidelines recommend that the diagnosis of UTI be made according to the presence of pyuria and significant bacteriuria. Pyuria is defined as the presence of 10 or more white blood cells per mm^3 or five or more white cells per high power area (HPF). The presence of leukocyte esterase in the stick test also indicates pyuria. The definition of significant bacteriuria varies according to the method of collection of the urine sample. Isolation of a single uropathogen greater than 50,000 colony forming unit (CFU) per ml in urine culture sample collected by catheterization or suprapubic aspiration, or more than 100,000 CFU per ml in urine culture sample collected by the midstream method or bag, is considered to be significant bacteriuria according to the AAP guidelines.[15]

In the study conducted by Shaikh et al.[16] clinical and laboratory findings were evaluated to confirm the diagnosis of urinary tract infection. While malodorous urine, uncircumcised boy, presence of previous UTI, and fever of unknown origin were determined as the most important clinical findings indicating urinary tract infection, nitrite test positivity, leukocyte esterase test positivity, and presence of pyuria were determined as the most important laboratory findings.[16]

A calculator (UTICalc) that can assist clinicians has been developed to estimate UTI probability in children younger than two years old. This online calculator (https://uticalc.pitt.edu) was designed using clinical findings that most likely indicate urinary tract infection.[17] Ebell et al.[18] proposed a guideline (The DUTY Clinical Decision Rules) to facilitate UTI diagnosis in emergency services and primary health care, using the most common clinical and laboratory findings indicating UTI.

Laboratory findings are more prominent in diagnosing urinary tract infection, and urine analysis and urine culture must be performed. The urine collection method is important for urine tests. How to obtain the appropriate urine sample may be related to the child's age and clinical condition. The urine sample can be obtained through a bag, clean catch, midstream voiding urine, catheter, or suprapubic aspiration. It is generally not recommended to diagnose a UTI based on a urine sample taken from a bag placed in the perineum. Because there is a high probability of contamination in bag urine samples, they should exclude UTI but not diagnose UTI. If a UTI is suspected based on the bag sample, a repeat urine sample should be collected by urinary catheterization or suprapubic aspiration (SPA).[15,19,20] Instead of collecting urine with a bag, a clean urine sample can be collected from the perineum (clean-catch) using suprapubic and sacral stimulation procedures. Culture results obtained with this collection method should also be interpreted carefully. When bacterial growth is detected in the urine culture, the urine culture should be repeated, preferably with a catheter or SPA urine sample.[15,21]

In the diagnosis of urinary tract infection, a urine examination is done in two steps. After the urine sample is taken, it is divided into two parts. While one part is reserved for urine culture, the other part is used for urine analysis. In urine analysis, especially nitrite test, leukocyte esterase test, presence of leukocyte in microscopic examination (pyuria), and bacteria presence in Gram staining are investigated.

The urinary nitrite test is highly specific for UTI but may not always be positive in the presence of UTI by low sensitivity (50%).[23] It can take up to 4 hours for organisms to degrade nitrate to nitrite, so urine must wait in the bladder for a while. Especially in patients who urinate frequently, there may not be enough time for the nitrite test to be positive. Besides, not all uropathogenic bacteria have urease enzymes and do not produce nitrite.[10]

Leukocyte esterase positivity indicates the presence of leukocytes in the urine. Pyuria is identified by urinalysis (UA): greater than or equal to 10 white blood count (WBC)/mm^3 or greater than or equal to 5 WBC per high-powered field (HPF).[9] Leukocyte esterase positivity or pyuria are findings suggestive of urinary tract infection. Nitrite positivity with leukocyte esterase positivity in the stick test has 93% sensitivity and 72% specificity for UTI. Leukocyturia (pyuria) / leukocyte esterase positivity is found in most children with UTI. AAP considers pyuria or leukocyte esterase positivity as a prerequisite for diagnosing UTI.[9,10,15] However, in the urine of 10% of children with UTI, especially in cases of UTI caused by non-*E. coli* organisms, leukocytes are absent, or leukocyte esterase may be negative. Children with UTI caused by *Enterococcus spp*, *Klebsiella* spp, and *Pseudomonas aeruginosa* may have a lower incidence of pyuria than children with *E. coli* with UTI.[22,23] Although it is a basis or a prerequisite for the diagnosis of UTI, the presence of LE is not specific for UTI, and both the sensitivity and specificity of the test are low. Sterile pyuria may occur in the urine without UTI in cases of Kawasaki disease, glomerulonephritis, acute interstitial nephritis, appendicitis, and intense exercise.[9] Although not widely used in practice, Gram staining in a fresh, non-centrifuged urine sample is considered a reliable test for identifying UTI.[22] The association of bacteriuria and pyuria in microscopy has a positive predictive value of 84% for UTI.[9]

The gold standard for diagnosing urinary tract infection in children is to show bacteriuria in the urine sample.[9,10] There are some problems in detecting and identifying significant bacteriuria in children. Contamination of the urine sample with preputial or vaginal flora is the most important problem in urine samples taken with bags. In one study, simultaneous bladder puncture and urine samples with clear-voided urine or bag were compared, and the contamination rate was found to be 25%.[24,25] Collecting urine samples with a catheter significantly increases the diagnostic accuracy compared to bag urine cultures. Suprapubic bladder puncture gives the most accurate culture result, but it is an invasive method. Many centers or guidelines recommend using a catheter or suprapubic aspiration for urine sampling, especially in young children. There are also differences in the definition of bacteriuria.[15,26-28] Different guidelines for collecting urine samples and identifying significant bacteriuria in children with UTI are given in **Table 2**.

Definition of the significant bacteriuria threshold value may differ between guidelines. 10^5 CFU/ml is usually accepted as the threshold value for significant bacteriuria in urine samples collected by urination or bag. The American Academy of Pediatrics (AAP) recommends using a cut-off value of 5×10^4/CFU/mL for specimens collected with a catheter. However, in many countries, 10^4 CFU/mL is accepted as the threshold for significant bacteriuria.[15] It is recommended to consider the threshold value of 10000 CFU/mL in urine samples taken by catheter from infants at risk of UTI with fever and pyuria. However, in young children with proven UTIs, it has been shown that approximately 20% of their urine cultures have bacterial colonies lower than the commonly used threshold of 10^5 CFU/MI.[10,29] A recent study conducted in Japan suggested using 10^3 bacterial colonies in urine culture taken by catheter in infants younger than four months as a threshold for diagnosing upper urinary tract infection.[30] However, it should be noted that lowering the threshold value can reduce false-negative results but increase the number of false-positive results.

Blood tests are not diagnostic in the diagnosis of urinary tract infection. However, measuring complete blood count and acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be helpful in the diagnosis of acute pyelonephritis. An increase in leukocytosis, CRP, and ESR may indicate pyelonephritis. Procalcitonin has been suggested as a helpful marker in the diagnosis of pyelonephritis recently. A meta-analysis conducted by Shaikh et al.[32] in 2020 was analyzed the diagnostic value of CRP, ESR, and procalcitonin levels in UTI. In this study, it was interpreted that ESR was not helpful enough to differentiate pyelonephritis and cystitis. A CRP level below 20 mg/dl was useful in excluding that procalcitonin was more beneficial for the diagnosis of pyelonephritis.[31] In another study, a cut-off value of 1.0 ng/ml of procalcitonin is predictive of acute pyelonephritis in young children.

Table 2.
Comparison of different guidelines for collecting urine samples and identifying significant bacteriuria in children with UTI

	NICE[27]	AAP 2011[15]	EAU/ESPU[28]	Okarska-Napierała M et al.[26]
Urine collection in non-toilet-trained children	Clean catch mid-stream void Alternatively: collection bag	Bladder catheterization or SPA (relates to children aged < 2 years)	Clean catch, midstream void, bladder catheterization or SPA for diagnosis Collection bag only as a method of exclusion	Bladder catheterization or clean catch mid-stream void Collection bag only as a method of exclusion
Significant bacteriuria	No identification	Catheterization: 5x104 CFU/ml	Clean-catch urine, midstream, catheterization: 103 -104 CFU/ml SPA: any growth of bacteria	Catheterization: ≥ 103 CFU/ml Clean voided urine: >104 CFU/ml with symptoms or > 105 without symptoms SPA: any growth of bacteria

SPA: Suprapubic aspiration, CFU: Colony-forming unit, NICE: National Institute for Health and Care Excellence, AAP: The American Academy of Pediatrics, EAU/ESPU: European Association of Urology /European Society for Paediatric Urology

Imaging

The primary rationale for imaging in children with UTI is to identify genitourinary abnormalities that require additional evaluation or treatment rather than a diagnosis of urinary tract infection. For this purpose, the first recommended radiological research method is urinary ultrasonography. Ultrasonography (US) is an easy-to-do, simple, non-invasive method that is not exposed to radiation and can be found everywhere. However, there may be differences in interpretation among radiologists. The American Academy of Pediatrics recommends performing renal-bladder US after the first febrile UTI for all children aged 2-24 months.[15] National Institute for Health and Care Excellence (NICE) recommends kidney-bladder US for infants younger than six months and children older than six months with atypical or TIA.[27] Atypical UTI includes severe illness, poor urinary flow, abdominal or bladder mass, elevated creatinine, septicemia, infection with a non-*E. coli* organism, and inability to respond to antibiotics within 48 hours. Recurrent UTI is defined as two or more upper UTI or one upper UTI with at least one lower UTI or at least three lower UTI.[27] The American Academy of Pediatrics guideline recommends that ultrasonography be administered after UTI treatment rather than during acute infection.[15] Acute infection can alter the size and echogenicity of the renal parenchyma, which causes temporary hydronephrosis. So that leads to erroneous interpretations. However, the European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) guidelines advise renal and bladder ultrasound within 24 h advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract.[28] Miller et al.[9] also recommend an ultrasound of the kidney and bladder at 48 hours of treatment to exclude renal abscess or pyonephrosis if the disease is more severe than expected or if there is no clinical improvement despite appropriate treatment.

Scintigraphy is useful not only in the diagnosis of urinary tract infection but also for detecting renal scarring. Tc-99m dimercaptosuccinic acid (DMSA) scan is considered the gold standard method in pyelonephritis. Uptake defect in renal isotope screening is indicative of pyelonephritis. However, most national guidelines do not recommend the routine use of DMSA scans to diagnose pyelonephritis due to the inconvenience, high cost, and radiation exposure.[15,27,28] However, both NICE and APA guidelines recommend DMSA 4-6 months or 6-12 months after acute infection to detect renal scarring.[15,27]

The voiding cystogram is not a primary radiological research method in children with urinary tract infections and should be performed in selected patients. APA recommends voiding cystourethrogram (VCUG) to be performed after the first febrile UTI when kidney-bladder US is abnormal and after the second febrile UTI when US findings are normal.[15] In the United Kingdom (UK), the NICE guideline recommends VCUG for infants with atypical, recurrent UTIs with dilatation on the US and a family history of VUR.[28] Some recommend performing a voiding cystourethrogram in infants with a first febrile UTI and a circumcised boy after the first febrile UTI.[9,28]

Treatment

UTI treatment should be planned considering the symptoms, location and type of UTI, previous medical history of the child, and resistance patterns of uropathogens in the area where the child lives. UTI treatment aims to eliminate infection and prevent urosepsis, relieve acute symptoms such as fever and dysuria, prevent recurrence of UTI, and long-term complications such as hypertension, renal scar, kidney growth, and dysfunction. All children older than two months can be treated on an outpatient basis. Indications for hospitalization and / or parenteral therapy are:[9,10,15,27,28]

- Age <2 months
- The presence of urosepsis
- Immunocompromised patient
- Vomiting or inability to tolerate oral medication
- Inadequate outpatient follow-up
- Non-response to outpatient medication

It is essential to initiate early (within the first 72 hours) and aggressive antibiotic therapy to prevent renal damage. Empirical antimicrobial therapy should be started immediately after urine sample collection. Delay in the treatment of febrile UTI is associated with an increased risk of kidney scarring. It is reported that a delay of more than 48 hours increases the probability of a new scar by 47%.[4]

Empirical antibiotic treatment should be directed against *E. coli*.[9] Local resistance data should guide the agent of choice in empirical treatment. The resistance properties of *E. coli* isolated from pediatric urine samples from 192 hospitals in the United States were evaluated, and 45% ampicillin resistance and 24% trimethoprim and sulfamethoxazole (TMP-SMX) resistance were detected in *E. coli* culture isolates.[33] Cephalosporins and aminoglycosides are the first recommended agents for empirical treatment of UTI in children. Because the resistance rate of *E. coli* is high, amoxicillin and ampicillin are not routinely recommended in empirical antibiotic therapy. If the enterococcal infection is suspected, ampicillin or amoxicillin can be used. But ampicillin or amoxicillin should not be used as monotherapy in these patients.[9] The French study group recommends aminoglycoside therapy in addition to cefotaxime or ceftriaxone in hospitalized children with febrile UTIs, and amikacin or ceftriaxone or cefixime as the first-line agent of choice in outpatient children with febrile UTI.[34] Again, this group recommends amoxicillin-clavulanic acid as the first choice in patients with cystitis until the culture result is obtained.[34]

It is suggested that children older than two months who do not vomit can be adequately treated with oral antibiotics.[9,15,28] Some clinical parameters that affect antibiotic usage form are patient's age, clinical suspicion of urosepsis, impairment in oral feeding, vomiting, diarrhea, and a course of complicated pyelonephritis. Oral antibiotic use is also an option following short-term parenteral antibiotic use. In the study conducted by Hoberman et al.[35] a patient group who received oral cefixime for 14 days was compared with the patient group who received iv cefotaxime + oral cefixime. No difference was found between the groups regarding sterilization of urine, recurrence of infection, and renal

scarring.Neuhaus et al.[36] found that once a day, ceftibuten therapy was equivalent to the treatment with ceftriaxone followed by ceftibuten. Fluoroquinolones (ciprofloxacin) are effective agents for *E. coli* infection, and resistance is rare in children. However, ciprofloxacin should not be used routinely as a first-line agent. The widespread use of fluoroquinolones can lead to increased resistance among other bacteria. The Infectious Diseases Committee of the American Academy of Pediatrics (AAP) recommends ciprofloxacin in *Pseudomonas aeruginosa* infections or UTI caused by resistant Gram-negative bacteria.[15] Oral agents such as nalidixic acid or nitrofurantoin are excreted in urine but cannot reach therapeutic serum concentrations. So they should not be used to treat UTIs in young children, as they may be insufficient to treat pyelonephritis or urosepsis.[15]

Children over three months old, well-hydrated children, and children without urological abnormalities who cannot tolerate oral therapy and are non-toxic can be treated with outpatient parenteral therapy. A single daily dose of gentamicin or ceftriaxone can be administered intramuscularly.[37]

Short-term antimicrobial treatment (3-5 days) is recommended for children with lower UTI and long-term therapy (usually 7-14 days) for children with fever.[9,10,15,27,28,37] Clinical findings improve within 24-48 hours in most patients given appropriate antimicrobial therapy. The most common causes of treatment failure are misdiagnosis, the presence of resistant bacteria, kidney abscesses, and urinary tract malformations.[9,15,28]

In children whose clinical condition does not improve or worsen as expected within 48 hours, antimicrobial therapy should be expanded. In this situation, kidney and bladder ultrasonography should be performed to evaluate the presence of kidney abscesses or surgically correctable abnormalities or obstruction.[15,28,37] If the patient does not respond to therapy or the uropathogen is not sensitive to the preferred antibiotic, urine cultures should be repeated after 48 hours of treatment. However, if the child has the expected clinical response and the uropathogen is sensitive to the antibiotic used for treatment, repeating urine cultures are not routinely required during antimicrobial therapy to document sterilization of the urine.[15,37]

The treatment of asymptomatic bacteriuria is a highly questioned and discussed issue. In a recent meta-analysis including 14 studies of 46806 children, the prevalence of asymptomatic bacteriuria was reported as 0.37% in boys and 0.47% in girls.[38] Asymptomatic bacteriuria may frequently occur in three different patient groups, depending on age and underlying urinary tract malformation: I) Children with genitourinary abnormalities or neurogenic bladder, II) Uncircumcised boys in the first year of life, III) Girls aged 3-10 years with recurrent UTIs.10 Patients in the third group often have symptoms of functional bladder and bowel dysfunction, and symptoms often persist, although bacteriuria is corrected with antibiotics. Controlled studies do not support the treatment of asymptomatic bacteriuria in these children. It has been suggested that asymptomatic bacteriuria may protect against the development of symptomatic UTI, and bacteria that cause asymptomatic bacteriuria may become avirulent over time.[10]

I) Prophylactic antibiotics

Another goal in managing children with urinary tract infections is to try to prevent recurrent acute pyelonephritis attacks and renal scarring. Prophylactic antibiotics in children with recurrent urinary tract infections have been a topic that has been both applied and discussed for many years. Most of the evidence regarding the use of prophylactic antibiotics comes from studies on VUR and recurrent UTI. Garin et al.[39] reported that antibiotic prophylaxis does not have a significant effect on the recurrence of urinary tract infection in children between 3 months and 18 years of age with stage I-III VUR.On the other hand, In the PRIVENT study, Craig et al.[40] found a moderate decrease in urinary tract infection recurrence in patients aged 0-18 years who were treated with TMP-SMX prophylaxis. The Swedish study group investigated the use of prophylactic antibiotics in children aged 1-2 years with high-grade VUR and found different results between girls and boys. While it found a significant decrease in the frequency of urinary tract infections and renal scarring in girls, it did not detect a difference in boys.[41] In RIVUR study, lower infection rates were found in children who received prophylactic antibiotics. The RIVUR study determined that long-term antibiotic prophylaxis reduced the recurrence of UTIs from 27.4% to 14.8% over a 2-year follow-up period. The proportion of isolates resistant to TMP-SMX was higher (63%) in the prophylaxis group than in the placebo group (19%).[42] In contrast, Hari et al.[43] reported that children with VUR who received prophylactic cotrimoxazole had a 3-fold higher chance of recurrent infection than children given a placebo. There is still confusion regarding the use of prophylactic antibiotics. A 2019 Cochrane meta-analysis of nine studies that compared the antibiotic treatment to placebo or received no treatment showed that using prophylactic antibiotics was not beneficial for preventing recurrent UTIs or uptake defects seen in DMSA scans. This analysis highlighted the significantly increased antibiotic resistance to the drug used for prophylaxis.[44] However, Tullus et al.[10] suggest in a recent review that young children with high-grade VUR are likely to benefit from antibiotic prophylaxis. The most crucial problem in long-term prophylactic antibiotic use is the development of antimicrobial resistance to the drug.[45,46] Mattoo et al.[46] found that antibiotic prophylaxis was associated with a 3-fold increase in *E. coli* resistance and suggested that prophylaxis should be used in selected patient groups such as children with VUR, not in every patient. Both AAP and NICE guidelines do not recommend routine antibiotic prophylaxis in children after the first febrile urinary tract infection.[15,27]

II) Probiotics

Probiotics have not been shown to reduce the recurrence of urinary tract infections in randomized studies in children.[47] However, Lee et al.[48] found that the incidence of recurrent urinary tract infection was 8.2% in patients with lactobacillus prophylaxis, 10% in antibiotic prophylaxis, and 20.6% in children who did not receive prophylaxis in their study in which 191 infants with acute pyelonephritis and normal urinary anatomy were included.

III) Cranberry

Data on the use of cranberry juice in the prevention of urinary tract infections are also controversial. A meta-analysis of randomized controlled trials by Jepson et al.[49] reported that cranberry-based products do not reduce recurrent UTIs than placebo. In a study comparing eight clinical UTI studies, a decrease in UTIs and antibiotic use was found in healthy children using cranberry products. Still, the results were contradictory in children with urological abnormalities.[50] It has been suggested that cranberry products can be an effective option to prevent recurrence in children without anatomical abnormalities.[50] The use of cranberry is recommended to avoid recurrent urinary tract infections in the EAU/ESPU's newly updated guidelines.[28]

IV) Circumcision

It has been suggested that circumcision performed immediately after birth reduces the possibility of having an acute pyelonephritis attack in healthy boys by 90%.[51,52] However, the number of children needed to be circumcised to protect one case of acute pyelonephritis was found too high (the number needed to treat is 111).[27,28] Today, routine circumcision is not recommended in healthy children to prevent urinary tract infections, but it is advised in children with major urinary malformations who need general anesthesia for urological reasons.[9,28]

V) Treatment of bladder and bowel dysfunction

It is well known that bladder and bowel dysfunction is a significant risk factor for urinary tract infection in children. If vesicoureteral reflux accompanies bladder and bowel dysfunction, the risk of urinary tract infection increases further.[53] Therefore, it is recommended to investigate and treat bladder and bowel dysfunction in children with recurrent urinary tract infections. [9,10,28]

When should a child with UTI be sent to a nephrologist?

Indications for referral to a pediatric nephrologist or urologist are:[27]

- Recurrent UTI
- In the presence of dilated vesicoureteral reflux (Stage III-V) or obstructive uropathy
- Presence of kidney anomalies
- Impaired kidney function
- High blood pressure
- Presence of bowel and bladder dysfunction resistant to primary care approaches.

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Hereditary Red Blood Cell Enzymopathies

Author(s)

Tekin Aksu

Affiliation(s)

Hacettepe University Faculty of Medicine, Department of Pediatrics, Division of Hematology, Ankara, Turkey

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Abstract

Red cell metabolic disturbances result in hemolysis, which leads to a significant shortening of the erythrocyte life span. The most common enzyme deficiencies are glucose 6-phosphate dehydrogenase (G6PD) in the antioxidant pathway, pyruvate kinase in the anaerobic glycolysis pathway, and pyrimidine 5' nucleotidase (P5'N) in the nucleotide metabolism. While the X chromosome inherits G6PD and phosphoglycerate kinase deficiencies, other enzymopathies show autosomal recessive inheritance. Although the causes of hereditary hemolytic disorders are diverse, clinical, laboratory findings and complications overlap. A history of neonatal jaundice requiring phototherapy and exchange transfusion is quite usual. Mild to severe anemia may be accompanied with episodic or constant hemolysis associated with icterus, hyperbilirubinemia, growth retardation, gallstones, splenomegaly, and a variable degree of iron overload. Erythrocyte enzyme disorders should be suspected in patients with severe hemolytic episodes, or chronic hemolysis, after excluding hemoglobinopathies, membranopathies, and immune-mediated hemolysis.

Keywords: Glucose 6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, glucose phosphate isomerase deficiency, triosephosphate isomerase deficiency, pyrimidine 5'-nucleotidase deficiency

Introduction

Erythrocytes use two main biochemical pathways to maintain their physiological state. The Embden-Meyerhof anaerobic pathway is used for energy, and the hexose monophosphate (HMP) shunt pathway for reducing potential toxicities. With the energy gained, cell shape, elasticity, intracellular cation, and water content are preserved. Purine and pyrimidine nucleotides are obtained through nucleotide metabolism. The most common enzyme deficiencies are glucose 6-phosphate dehydrogenase (G6PD) in the antioxidant pathway, pyruvate kinase (PK) in the anaerobic glycolysis pathway, and pyrimidine 5 'nucleotidase (P5'N) in the nucleotide metabolism. While the X chromosome inherits G6PD and phosphoglycerate kinase deficiency, other enzymopathies show autosomal recessive inheritance.[1]

Correspondence: Tekin Aksu, Hacettepe University Faculty of Medicine, Department of Pediatrics, Division of Hematology, Ankara, Turkey
E-mail: tekinaksu@gmail.com

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Red cell metabolic disturbances result in hemolysis, which leads to a significant shortening of the erythrocyte life span. Although the causes of hereditary hemolytic disorders are diverse, clinical, laboratory findings and complications overlap. A history of neonatal jaundice requiring phototherapy and exchange transfusion is quite usual. Mild to severe anemia may be associated with episodic or constant hemolysis associated with icterus, hyperbilirubinemia, growth retardation, gallstones, splenomegaly, and a variable degree of iron overload. Reticulocytosis due to compensatory erythropoiesis usually accompanies with the disease, except in some forms of PK deficiency cases with ineffective erythropoiesis. Erythrocyte enzyme disorders should be suspected in patients with severe episodic or chronic hemolytic anemia, after excluding hemoglobinopathies, membranopathies, and immune-mediated hemolysis. These patients may experience accelerated hemolysis with infections or aplastic crises due to parvovirus infection.

Highlights

- Glucose 6-phosphate dehydrogenase deficiency is often associated with episodic hemolysis triggered by infections, certain drugs, and fava beans.
- Pyruvate kinase deficiency should be suspected in patients with chronic hemolysis with subtle peripheral smear findings after excluding hemoglobinopathies, membranopathies, and immune-mediated hemolysis.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase deficiency is the most common enzyme deficiency in the HMP pathway that causes hemolytic anemia. G6PD is involved in the production of nicotinamide adenine dinucleotide phosphate (NADPH), which protects the cell from oxidant injury triggered by certain drugs or infections by ensuring a reduced state of glutathione (GSH).[2] Its deficiency mostly affects erythrocytes. Erythrocytes do not have alternative pathways for NADPH production. In NADPH deficiency, hemolysis occurs by precipitation of hemoglobin (Heinz body) in erythrocytes by oxidative stress and damaging the erythrocyte membrane.[2] G6PD deficiency leads to episodic or chronic non-spherocytic hemolytic anemia. It affects more than 400 million people around the world.[3] Its prevalence in the world is 4.9%.[3] While it is common in males due to its X-linked inheritance (hemizygous), in populations where mutations are common, the disease due to homozygous mutations is reported in females. Besides, in carrier womens, moderate-to-mild findings due to X chromosome inactivation (Lyon hypothesis) can be seen.[2] G6PD deficiency is common in Africa, Asia, the Mediterranean, and the Middle East regions. The disease is more common in areas where malaria was once endemic due to the protection of G6PD deficiency against Plasmodium falciparum malaria.[4] The frequency of the G6PD deficiency was reported to vary from 0.5-2.9% in Turkey.[5] It has been reported with a rate of 8.2% in the Çukurova region.[5] The World Health Organization classified G6PD deficiency according to enzyme activity and the degree of hemolysis (**Table 1**).[6] Of note, the normal enzyme is referred to as G6PD B (wild-type).

Normally, the G6PD activity declines with red blood cell aging. In mild G6PD variants (Class III), especially older erythrocytes are affected due to declining enzymatic activity. Whereas in the variants of the Class II, including the Mediterranean variant, erythrocytes of all ages are deficient in the enzyme. Class II variants are more susceptible to oxidant damage and may experience severe hemolysis.

Clinical findings

The patients with most G6PD variants are usually asymptomatic, and there are no associated laboratory findings related to hemolysis. The acute hemolytic episode may pursue oxidant injury within 24-48 hours, triggered by certain drugs, toxins, infections, and fava beans. It seems infections are the most common cause of hemolytic episodes, especially in children.[1] Jaundice, pallor, dark urine develop, and mild to severe hemoglobin decrease may be seen after exposure. Drugs and chemicals that cause hemolysis and should be avoided are listed elsewhere.[1,2,7] While some drugs do not cause clinically significant hemolysis in therapeutic doses, such as low-dose aspirin and trimethoprim-sulfamethoxazole, high doses are associated with hemolysis. An acute hemolytic process is seen due to fava beans consumption, which is called favism, particularly in Mediterranean and Asian G6PD variants. Fava contains divicine, isouramil, and convicine, which increase reactive oxygen products and induce hemolysis.

In the neonatal period, it may cause spontaneous hemolysis and hyperbilirubinemia, even kernicterus.[8] In most cases, jaundice is much more common than anemia. If the patient has Gilbert's syndrome [uridine-diphosphate-glucuronyl transferase 1 family, polypeptide A1 (UGT1A1) mutation], the severity of hemolysis increases. Neonates with severe jaundice should be tested for G6PD deficiency. Exposure of the neonate and mother to drugs that cause oxidant stress, acidosis, and hypoxia may trigger hemolysis.

Table 1
The World Health Organization classification of G6PD deficiency

Class I: Severe deficiency
Chronic non-spherocytic hemolytic anemia Sporadic and rare Residual enzyme activity: <10% of normal
Class II: Severe deficiency
Episodic severe hemolysis with oxidant injury Mediterranean or Asian variants Residual enzyme activity: <10% of normal
Class III: Mild to moderate deficiency
Intermittent acute hemolysis with oxidant injury Common A- variant African American Residual enzyme activity: 10-60% of normal
Class IV: Normal activity
Enzyme activity: 60-150% of normal No clinical findings
Class V: Increased enzyme activity
Enzyme activity: >150% of normal No clinical findings

In rare instances, G6PD Class I deficient patients have chronic nonspherocytic hemolytic anemia that indistinguishable from other glycolytic enzyme disorders. They have mild to moderate anemia with a high reticulocyte count between 10-15%.

Laboratory findings

With acute hemolytic episodes, patients with G6PD deficiency present with sudden drops in hemoglobin and hematocrit. Anemia is normochromic, normocytic, accompanied by reticulocytosis within five days of onset of a hemolytic episode. Polychromasia, anisocytosis, poikilocytosis, spherocytes, bite, or blister-shaped erythrocytes are seen in the peripheral blood smear. Hemolysis occurs both intravascular or extravascular. Oxidized or denatured hemoglobin deposits called Heinz bodies can be seen in erythrocytes with supravital stains, where these deposits will be cleared from circulation in 3 to 4 days. Hemoglobinuria, an increase in indirect bilirubin, free hemoglobin, and lactate dehydrogenase (LDH), decreased haptoglobin are other accompanying findings.

G6PD enzyme activity can be measured quantitatively by a spectrophotometric assay. However, normal or high enzyme levels due to reticulocytosis can be seen during the hemolytic episode, which leads to false-negative results. Therefore, in suspected patients, the enzyme activity should be reevaluated three months after the hemolytic episode when all ages of erythrocytes repopulated. Furthermore, in patients who have received erythrocyte transfusion in the last three months, the erythrocyte enzyme levels may be found to be normal, even if there is a deficiency. Moreover, molecular studies have shown more than 160 different gene mutations in G6PD deficiency.[9] These studies identified that almost all mutations are missense. Gene sequencing is not necessary for patients with common phenotypes, such as patients with episodic hemolysis. However, these studies help confirm the diagnosis of Class I G6PD deficiency.

Prevention and Treatment

The most important approach is to secure from hemolytic episodes. Family and patient should be educated about the hemolytic episode findings such as dark urine, jaundice, and weakness. Besides, they shouldn't consume foods containing fava beans and should avoid drugs with known effects of oxidant damage. When a hemolytic episode occurs, depending on the degree of anemia, transfusion may be required. Erythrocyte suspension should be given to patients whose hemoglobin level is below 7 g/dl or 9 g/dl and whose hemoglobinuria continues or is symptomatic with rapid hemoglobin decrease. Patients who do not need transfusion should be followed for at least 48 hours. Severe hemolysis can lead to acute renal failure, and supportive treatment may be required.

In patients with chronic anemia, the hemoglobin level should be kept between 8-10 g/dl and followed up for iron overload. Splenectomy can also be performed in patients with severe chronic anemia and who have symptoms of hypersplenism.

Disorders of the glycolytic enzymes

G6PD deficiency is far more common than glycolytic enzyme abnormalities. While the most common cause of glycolytic pathway disorders is PK deficiency, diseases related to deficiencies of all other enzymes have also been described. Glycolytic pathway enzymopathies usually show an autosomal recessive inheritance.

Pyruvate Kinase Deficiency

Hemolytic anemias resulting from the red cell metabolism's defects lack specific morphologic abnormalities on the peripheral blood smear since they are called hereditary nonspherocytic hemolytic anemias (HNSHA). Valentine et al. discovered that PK leads to HNSHA.[10] To date, over 600 families with PK deficiency have been reported, which is the most common glycolytic enzyme disorder that leads to HNSHA.[11,12] Its prevalence is reported as 51 per million.[13,14] The rarity of PK deficiency and the variable clinical findings cause difficulties in diagnosis, often underdiagnosed. The other factors contributing to underdiagnosis are regular transfusions interfering with diagnostic tests and PK enzyme measurements which are not standard between institutions. PK deficiency is caused by compound heterozygote or homozygote mutations in the gene PKLR.[11-13] Drastic mutations lead to a total loss of PK activity accompanied with a more severe disease such as intrauterine death or severe neonatal anemia. If PK enzyme activity is preserved at some point in different mutations, leading to milder phenotypic consequences. Mostly missense (70-80%), splicing, and premature stop codon mutations have been identified in the PKLR gene.[15,16]

The glycolytic pathway maintains ATP, 2,3-diphosphoglycerate (2,3-DPG), and NADH to modulate hemoglobin oxygen affinity and reduce methemoglobin.[17] PK catalyzes phosphoenolpyruvate's conversion to pyruvate in the glycolytic pathway and generates 50% of erythrocyte ATP production.[18] As a result of PK deficiency, ATP decreases, while intermediate metabolites, including 2,3-DPG, increase. ATP depletion results in cation loss, dehydration, and red cell damage that eventually clearance in the spleen.[19,20]

Hematological Features

The hematological features of PK deficiency, including increased reticulocyte count, reduced haptoglobin, and elevated bilirubin, overlaps with other hereditary hemolytic anemias.[1] Patients with PK deficiency may present with mild to severe anemia and reticulocytosis.[12] Red blood cell morphology is usually unremarkable, except for spiculated erythrocytes. Also, these spiculated erythrocytes increase after splenectomy. An increase of 2,3 DPG balances tissue oxygen delivery and mitigates symptoms of anemia. PK deficiency causes extravascular hemolysis where a significant increase in LDH is not expected.[17,21] The osmotic fragility test is normal, but the autohemolysis test is usually abnormal. Recently rare PK deficiency cases associated with inappropriately low reticulocytes and dyserythropoietic features at bone marrow examination are defined. These cases reflect ineffective erythropoiesis due to PK deficiency, resulting in misdiagnosis with CDAs.[17]

Clinical Features

Anemia-related symptoms, splenomegaly, and jaundice are common in patients with PK deficiency.[12,17,22,23] There are variable perinatal complications including, fetal anemia, nonimmune hydrops, and neonatal hyperbilirubinemia requiring phototherapy or exchange transfusion.[12] Even cases that could progress to liver failure in the neonatal period were reported.[24] Severe anemia due to chronic hemolysis may pursue until splenectomy in childhood.[12] There are also mild cases with a compensated anemia that may not be noticed until adult age. In adults, anemia is relatively stable, though acute worsening of anemia may occur during infections, aplastic crises, pregnancy, or increased hemolysis. Patients with biallelic null or non-missense mutations present with lower hemoglobin values and more transfusion need, high risk of complications, while they show inadequate response to splenectomy.[12,25]

Diagnosis

There is no simple screening test available for enzymopathies, and particularly it is more challenging in transfusion-dependent patients. Other hemolytic anemias, including immune-mediated hemolysis, hemoglobinopathies, or membranopathies, should be excluded.[11,17] Molecular studies or a low level of PK enzyme activity with a spectrophotometric assay can be diagnostic.[26] PK enzyme activity is confounded by increased reticulocytes, recent transfusions, and contaminating leukocytes with high specific enzyme activity. Moreover, the abnormal kinetics of the enzyme in vivo may not reflect in vitro results. Furthermore, the reduced activity of the PK enzyme does not correlate with the severity of the disease. If the PK enzyme level is close to normal or normal, but the other erythrocyte enzyme levels are high, particularly hexokinase (HK) and G6PD, PK deficiency should be suspected as well.[1,12,17] To exclude this issue, it is recommended to measure PK/HK ratio or PK/G6PD ratio.[1]

In transfusion-dependent patients, a survey reported various centers recommending 40-120 days to be spared after the last transfusion to perform an enzyme activity. That report suggests 50 days after transfusion may result in 6-12% contamination of donor erythrocytes and will not lead to a missed diagnosis.[11] Recent reports suggest two diagnostic algorithms for PK deficiency. The first approach recommends measuring PK enzyme activity then confirming the diagnosis by molecular studies. The second approach is to screen disease by next-generation sequencing (NGS) targeted panels and confirm the diagnosis by measuring enzyme activity.[11,17] Currently, most of the patients are screening by NGS panels targeted for hereditary hemolytic anemias, including PKLR.

Therapy

PK deficiency patients are currently managed with supportive treatments such as erythrocyte transfusion, splenectomy, folic acid supplementation, and iron chelation.[17] The need for transfusion is higher in young children. The decision for transfusion should be made according to the hemoglobin level and by paying attention to the patient's tolerance of anemia and the patient's growth and development.[17] Splenectomy results in reticulocytosis, increased hemoglobin, decreased or even eliminating transfusion requirements, and decreased bilirubin level in patients with PK deficiency.[12] Unfortunately, splenectomy increases the risk of sepsis, thromboembolic events, and pulmonary hypertension.[12,17] Currently, mitapivat (AG-348) is an allosteric activator of erythrocyte PK enzyme used in clinical trials in PK deficiency patients.[27,28] Hematopoietic stem cell transplantation is an investigational treatment for PK deficiency patients and should not be recommended routinely.[29]

Iron overload may develop as high as 48% of the patients with PK deficiency due to transfusion-related or ineffective erythropoiesis, particularly in adults.[12] Besides, patients should be followed up regularly for the development of gallstones. Aplastic crises, leg ulcers, biliary tract disease, and extramedullary hematopoiesis may occasionally develop.[12]

Glucose Phosphate Isomerase Deficiency

Glucose phosphate isomerase (GPI) deficiency is the second most common glycolytic enzymatic defect, shows autosomal recessive inheritance.[1] GPI deficiency associated with HNSHA of variable severity.[30] Its approximate fraction constitutes 3-5% of all enzymopathies.[1] For diagnosis, measurement of this specific enzyme assay and molecular studies can be done. Clinical symptoms and complications of GPI deficiency overlap with PK deficiency. However, neuromuscular impairment such as hypotonia, ataxia, dysarthria, mental retardation has also been described in patients with GPI deficiency.[30] Splenectomy reduces the need for erythrocyte transfusion.[31]

In addition to PK and GPI deficiency, hexokinase, phosphofructokinase, aldolase, triosephosphate isomerase, phosphoglycerate kinase, adenosine deaminase excess, and adenylate kinase deficiencies are reported even rarer. These enzymopathies may present with mild to severe HNSHA and neurologic deficits, and myopathy.[1]

Triosephosphate isomerase deficiency

Triosephosphate isomerase (TPI) deficiency is a rare disease of the glycolytic pathway, shows autosomal recessive inheritance. TPI ensures the equilibration of the triosephosphates in the glycolytic pathway, wherein connection with lipid metabolism, glycerol-3-phosphate shuttle, and pentose phosphate pathway.[32] TPI deficiency does not affect the erythrocyte's energy metabolism; however, it leads to toxic accumulation of methylglyoxal. Progressive neurologic impairment, cardiomyopathy, and increased susceptibility to infections accompany hemolytic anemia, which is frequently fatal in early childhood.[32] No effective therapy is available for TPI deficiency. Other treatments are blood transfusions to treat anemia during hemolytic episodes and assisted ventilation to treat paralysis of the diaphragm. Hematopoietic stem cell transplantation was attempted in a few patients, but the outcome was poor.

Hereditary pyrimidine 5'-nucleotidase deficiency

Pyrimidine 5'-nucleotidase deficiency (P5'N), which is the most common enzyme deficiency in erythrocyte nucleotide metabolism, shows autosomal recessive inheritance; patients have less than 10% normal P5'N

activity. The prevalence of P5′N deficiency is not known. It occurs as a result of biallelic mutations in the NT5C3A gene on chromosome 7.[33] There is no clinical finding in heterozygous mutations. It causes hereditary non-spherocytic hemolytic anemia. P5'N provides catalysis of pyrimidine nucleotides. In P5'N deficiency, pyrimidine nucleotides accumulate in erythrocytes and cause basophilic punctuation in erythrocytes.[1] The mechanisms that cause erythrocyte destruction in this disease are not fully known. The median age at which the patients are diagnosed is 15 years (3 months-64 years).[33]

Symptoms overlap as other chronic hemolytic anemias such as jaundice, gallstones, and splenomegaly.[1] Patients receiving regular transfusions due to severe anemia are rare. In most of the patients, mild to moderate anemia have been reported. The median hemoglobin value was 9.5 g/dl (2.8–15.2 g/dl).[33] In addition to the laboratory findings of reticulocytosis and hemolytic anemia, the basophilic punctuation on the erythrocytes helps diagnose, but it is not specific. The demonstration that the accumulation of pyrimidine nucleotides and decreased P5'N activity in erythrocytes is diagnostic. There is no specific treatment for the disease, and supportive treatments are applied. Splenectomy usually does not stop hemolysis. Patients should be monitored for iron overload which can also be seen in non-transfusion-dependent patients.

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Lipid Emulsion Treatment in Tricyclic Antidepressant Poisoning in Children: An Observational Cohort Study

Author (s)

Esra Türe[1], Fatih Akın[1], Abdullah Yazar[1], Ahmet Osman Kılıç[2]

Affiliation (s)

[1]Department of Pediatric Emergency, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey
[2]Department of Pediatrics, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey

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Abstract

Tricyclic antidepressant (TCA) poisonings are among the most common childhood poisonings because of being cheap and readily available. In this manuscript, we aimed to share our experience with Intravenous lipid emulsions (ILE) treatment in addition to basic treatment steps and discussion of effectiveness of treatment in cases of poisoning caused by high-dose TCA intake. From the patients under 18 years of age who admitted to Pediatric Emergency Department due to drug intoxication between January 2014 and December 2019; those who had history of exposure to TCAs were included in our study. In conclusion of examination of six-year patient records, it was determined that there were a total of 619 intoxication cases and 108 (17.4%) of these were TCA poisoning. 21 (19.4%) patients who had hypotension, tachycardia and ECG changes which were refractory to all basic treatment steps were administered ILE. After ILE treatment, a marked improvement was observed in patients' clinical and ECG findings, as well as vital signs. Early administration of ILE treatment in emergency departments for cases with hypotension, conduction disorder, dysrhythmia or widened QRS which are refractory to sodium bicarbonate is thought to prevent potential cardiovascular complications.

Keywords: Intravenous lipid emulsions, tricyclic antidepressant, poisoning, child

Correspondence: Esra Türe, Necmettin Erbakan University, Meram Medical Faculty, Department of Pediatric Emergency, 42080, Meram-Konya, Turkey
E-mail: dresrature@hotmail.com

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Introduction

Tricyclic antidepressant (TCA) poisonings are among the most common childhood poisonings because of being cheap and readily available. Toxicity profiles of TCAs are almost similar and clinical development of toxicological findings may occur very rapidly and unexpectedly. Following exposure to toxic doses, patients may admit to emergency department with no symptoms, as well as with life-threatening cardiovascular or central nervous system symptoms.[1]

Highlights

- TCA poisonings cause high mortality and morbidity.
- Cardiotoxicity is the most important cause of mortality in TCA poisoning.
- Lack of a known antidote cause challenges in management.
- ILE is the leading one of promising treatment methods for TCA poisoning.

Therapeutic index of TCAs is very low and thus a single sugar-coated tablet may cause a severe poisoning in infancy. Due to their anticholinergic effects gastric emptying delays, intestinal motility slows down so that they are easily absorbed by the intestines and undergo enterohepatic recirculation. This may lead to delayed absorption of the drug and, hence, longer duration of signs and symptoms. Because TCAs have high solubility in lipids, they have wide distribution width in the body and their half-lives are long.[2]

Intravenous lipid emulsions (ILE) have been recently used for poisonings with fat-soluble drugs, although they have been used for parenteral nutrition for years.[3] ILE was used for the first time by Rosenblatt et al.[4] to treat asystole caused by bupivacaine, a local anesthetic.

In this manuscript, we aimed to share our experience of ILE treatment in addition to basic treatment steps in cases of high-dose TCA poisoning and discuss the effectiveness of this treatment.

Material and Method

From the patients under 18 years of age who admitted to pediatric emergency department due to drug intoxication between January 2014 and December 2019; those who had history of exposure to TCAs were included in our study. Following obtaining an Ethics Committee Approval, patients' information, files and data in the hospital's automation system were examined and recorded retrospectively (Ethics Committee Approval number: 2020/2580). Those with missing data were excluded from the study. Information regarding patients' age, gender, age group, time to admission to emergency department, clinical and electrocardiographic (ECG) findings and treatments given, as well as whether the case was an intoxication or suicide were recorded.

According to our pediatric emergency department's treatment protocol for TCA poisonings, once a secure airway is assured, all patients are monitored. Gastric lavage is performed only for those who admitted within an hour after drug intake, while all patients undergo repeat-dose application of activated charcoal. If hypotension occurs during the follow-up, the intervention is fluid loading with normal saline. Patients with seizure are managed with an antiepileptic drug other than phenytoin, as it may enhance the cardiotoxic effect. If a conduction disorder, dysrhythmia or widened QRS develops, a bolus of sodium bicarbonate at a dose of 1-2 mEq/kg is administered and, if needed, it is repeated to achieve pH<7.55 in blood gas analysis. Patients with hypotension, tachycardia and ECG changes which are refractory to these basic treatment steps undergo ILE treatment. %20 ILE lipid solution is administered at a bolus dose of 1-1.5 mL/kg given over 5-10 minutes, followed by 0.25-0.5 mL/kg/min infusion until hemodynamic improvement is achieved for 30-60 minute infusion, with a total maximum dose not exceeding 10 mL/kg/hour.

Statistical Analysis

Statistical analysis of the study was performed by using the Statistical Package for the Social Sciences for Windows ver. 20.0 package program. While the expression n (%) is used for categorical variables, for continuous variables mean ± SD (standard deviation) was used in case of suitability for normal distribution and median (lower-upper limit) values in case of unsuitability for normal distribution. Kolmogorov Smirnov test was used for normality analysis. For analyses of data's distribution and frequency, descriptive analyses were used and for frequency data, Pearson Chi-Square tests were used for comparison of two independent groups. For comparison of means of two independent groups, the independent t-test was used. For all statistical analyses, the level of significance was considered <0.05.

Results

Examination of six-year patient records revealed that there were a total of 619 intoxication cases and 108 (17.4%) of these were TCA poisoning. While mean age of all patients was 7.46±2.67, mean age was 9.38±4.22 for girls and 5.32±2.36 for boys. Of these patients; 57 (52.8%) were determined to be girl and 51 (47.2%) boy. When their causes of admission to emergency department were reviewed, it was observed that 66 (61.1%) admitted with intoxication, 11 (10.2%) with suspected intoxication and 31 (28.7%) with suicide. When the time to admission to emergency department was reviewed, it was determined that 41 (38%) patients had admitted within an hour after drug intake and 67 (62%) more than an hour. Of the drugs they exposured 97 (89.8%) of the patients had taken drug of another adult and 11 (10.2%) their own drug. When the treatment approaches were reviewed, it was determined that all (n=41, 38%) patients who admitted within an hour after drug intake underwent gastric lavage and all (n=108, 100%) treated with activated charcoal. During their clinical follow-ups, it was determined that 25 (23.1%) of the patients developed hypotension, 32 (29.6%) conduction disorder, dysrhythmia or widened QRS and 2 (1.8%) seizures. Distribution of treatments given by gender and age are represented in **Tables 1** and **2**.

Table 1
Distributions of Treatments Given By Gender

	Girls 57 (52.8%)	Boys 51(47.2%)	Total 108 (100%)	p
Gastric lavage	19 (33.3%)	22 (43.1%)	41 (38%)	>0.32
Activated charcoal	57 (52.8%)	57 (52.8%)	108 (100%)	N/A
Loading with normal saline	21 (36.8%)	4 (7.8%)	25 (23.1%)	<0.001
Sodium bicarbonate	24 (42.1%)	8 (15.7%)	32 (29.6%)	0.003
ILE treatment	19 (33.3%)	2 (3.9%)	21 (19.9%)	<0.001

ILE: Intravenous lipid emulsion
N/A: No statistics are computed because activated charcoal is a constant.

Table 2
Distribution of Treatments Given By Age Groups

	<5 yr of age 63 (58.3%)	5-10 yr of age 8 (7.4%)	10-15 yr of age 13 (12%)	>15 yr of age 24 (22.2%)	p
Gastric lavage	33 (52.4%)	2 (25%)	1 (7.7%)	5 (20.8%)	0.003
Activated charcoal	63 (58.3%)	8 (7.4%)	13 (12%)	24 (22.2%)	N/A
Loading with normal saline	6 (9.5%)	2 (25%)	4 (30.8%)	13 (54.2%)	<0.001
Sodium bicarbonate	11 (17.5%)	5 (62.5%)	6 (46.2%)	10 (41.7%)	0.007
ILE treatment	7 (11.1%)	2 (25%)	4 (30.8%)	8 (33.3%)	0.07

ILE: Intravenous lipid emulsion
N/A: No statistics are computed because activated charcoal is a constant.

When the association of gender was examined, 24 (77.4%) of 31 suicide cases were girls which was statistically significant (p=0.004). When their clinical courses were examined, 21 (84%) of 25 patients who developed hypotension were statistically significantly determined to be girls (p<0.001). Examination of ECG findings revealed that 24 of 32 patients who were found to have conduction disorder, dysrhythmia or widened QRS on ECG were statistically significantly determined to be girls (p=0.003).

21 (19.4%) patients who had hypotension, tachycardia and ECG changes which were refractory to all basic treatment steps were administered ILE. After ILE treatment, a marked improvement was observed in patients' clinical and ECG findings, as well as vital signs. Only one (0.9%) patient required monitoring in intensive care unit, who was then discharged with cure. None of the patients developed a complication related to ILE treatment.

Discussion

Marked improvement in clinical and ECG findings and vital signs was observed after ILE treatment in 21 (19.4%) patients who admitted to our emergency department with TCA poisoning and were refractory to all basic treatment steps.

One of the common causes of admissions to pediatric emergency departments is drug intoxications. According to American Association of Poison Control Centers National Poison Data System 2018 data, poisonings with antidepressants rank fifth, with an incidence of 5.22%.[5] In our country, based on the data of Poison Helpline datas, most common agents of poisoning are drugs containing paracetamol (acetaminophen), followed by combined upper respiratory airway drugs and amitriptyline.[6] Again, in a study from our country on forensic case admissions to pediatric emergency departments, patients who admitted with drug intoxication were poisoned most commonly with non-steroid anti-inflammatory drugs with a rate of 25%, followed by antipsychotic and antidepressant drugs with a rate of 19.3%.[7]

In case of exposure to TCA drugs at high doses, toxicity may develop within a duration as short as approximately 30 minutes.[8] Cardiotoxicity is the most important cause of mortality in TCA poisoning. Hypotension and cardiovascular collapse largely result from ventricular arrhythmias and reduced myocardial contractility secondary to sodium channel blockage. Sodium channel blockage prolongs potential of cardiac effect and the refractory period, as well as delays atrioventricular node conduction. This prolongs QRS, QTc and PR intervals, respectively. Toxicity-related acidosis promotes myocardial irritation and dysarhythmogenesis.[9,10] Due to lack of an antidote in poisonings with TCA, gastric lavage and activated carbon are used to minimize drug toxicity, and sodium bicarbonate is used to reduce cardiogenic toxicity.[1] As in our study, there are cases refractory to treatment despite of all these basic treatment methods. This, therefore, has led to search of new treatment methods like ILE treatment.

ILE has arisen as a promising treatment for severe toxicity of lipophilic drugs. Although there are reports for its use in poisonings caused by local anesthetics, anti-arrhythmic drugs, calcium channel blockers, β-blockers, neuroleptics, tricyclic antidepressants, serotonin reuptake inhibitors and phenothiazines,[11-13] there is no sufficient data for its use and dose in pediatric age group. Although by which mechanism ILE acts has not been exactly known, there are some assumptions suggesting that it is multifactorial. The "Lipid-sink" theory postulates that insertion of an expanded lipid phase within intravascular space drains the lipophilic agents from the watery plasma phase, reducing the bioavailability.[14,15] An alternative theory demonstrates that the lipid emulsion enhance presence of myocardial free fatty acids and

reverses the switching from lipid to glucose metabolism in myocardium. Additionally, it is thought that lipid emulsion may oppose to prevention of oxidative phosphorylation in toxic myocardium.[16]

There are some limitations to the current study, which presented the observational data from a single-center with a limited sample size. Therefore, the limited sample size might have prevented drawing definitive conclusions in some analyses. Despite these limitations, this study is significant as one of the first reports of ILE treatment in the pediatric population. Data from more extensive multicenter studies are required to improve the diagnosis, follow-up, and treatment approaches.

Conclusion

TCA poisonings cause high mortality and morbidity because of the fact that they cause toxicity on central nervous system and cardiovascular system. Lack of a known antidote and the fact that there is only a supportive treatment cause challenges in management. ILE is the leading one of promising treatment methods for this issue. Early administration of ILE treatment in emergency departments for cases with hypotension, conduction disorder, dysrhythmia or widened QRS which are refractory to sodium bicarbonate is thought to prevent potential cardiovascular complications. In the literature, there is limited data on ILE treatment in pediatric age group. Larger prospective studies on this issue are required.

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A Comparison of Leak Synchronized Nasal SIMV Methods and Leak Compensated Nasal SIMV in Newborns with Respiratory Distress Syndrome

Author (s)

Ahmet Özdemir[1], Mustafa Ali Akın[2], Osman Baştuğ[1], Tamer Güneş[3]

Affiliation (s)

[1]University of Health Sciences, Kayseri City Hospital, Neonatal Unit, Kayseri, Turkey
[2]Ondokuz Mayis University Medical Faculty, Department of Neonatology, Samsun, Turkey
[3]Erciyes University Medical Faculty, Department of Neonatology, Kayseri, Turkey

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Abstract

The aim of the present study was to compare the efficacy of leak compensated nasal SIMV (LCnSIMV) and leak synchronized nasal SIMV (LSnSIMV) modes in order to reduce the need for endotracheal intubation and associated complications in newborns with respiratory distress. This randomized, prospective study was conducted on 50 infants (25 per group) with gestational age below 34 weeks and/or below 2000 grams who have been admitted to NICU of Erciyes University Hospital because of respiratory distress syndrome (RDS) and need for mechanical ventilation. Infants with congenital heart disease, nasopharyngeal pathology (coanal atresia and cleft palate-lip) were excluded. Infants monitored on mechanical ventilator after surfactant were randomly assigned to LCnSIMV and LSnSIMV groups before extubation. SPO_2/FiO_2 (S/F), peak heart rate (PHR), respiration rate per minute (RRM), and arterial blood pressure (aBP) values of patients were recorded. Gestational age, birth weight, gender, RDS, patent ductus arteriosus (PDA) requiring treatment, presence of intraventricular bleeding (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) were recorded. The patients enrolled in the study were female by 48% and male by 52%. There was not any statistically significant difference between groups for gender, postnatal age and birth weight. There was detected statistically significant difference between LCnSIMV and LSnSIMV groups for non-invasive ventilation period and re-intubation rate (p=0.04 and p=0.03, respectively). There was detected statistically significant difference between LCnSIMV and LSnSIMV groups for SpO_2 and S/F rates at 60 minutes (p=0.03 and p=0.01, respectively). There was not any difference between groups for blood pressure, PDA, IVH, ROP, BPD, NEC, sepsis and air leak. It may be appropriate to prefer the LSnSIMV method in patients with respiratory distress syndrome who need non-invasive ventilation in the pre-extubation period by considering the patient-ventilator compliance for positive effect in terms of mechanical clinical variables.

Keywords: Prematurity, respiratory distress syndrome, surfactant, mechanical ventilation, leak compensation, leak synchronization

Correspondence: Ahmet Özdemir, University of Health Sciences, Kayseri City Hospital, Neonatal Unit, Kayseri, Turkey
E-mail: dr.ozdemir@yahoo.com

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Introduction

Mechanical ventilation (MV) is associated with increased survival in preterm babies; however, it may also play a role in the development of bronchopulmonary dysplasia (BPD) in living babies. Non-invasive ventilation (NIV) both reduces the need for invasive MV and decreases the incidence of BPD in preterm babies with RDS.[1-5]

Different ventilators differ significantly in their ability to compensate for leaks and achieve patient synchronization for patient-ventilator compliance. Ventilator performance, ventilator settings, and leak size play an important role in determining trigger and respiratory compliance. The aim of the study was to compare the efficacy of leak compensated nasal SIMV (LC nSIMV) and leak synchronized nasal SIMV (LS nSIMV) in order to prevent complications associated with invasive mechanical ventilation in preterm infants with RDS since there are limited and conflicting data about use of NIV methods in infants with RDS.

Highlights

- The adverse effects of invasive mechanical ventilation in infants are known, especially premature babies with respiratory distress syndrome.
- Considering patient-ventilator compatibility in premature infants, providing non-invasive ventilation is extremely important for patient comfort.
- In patients diagnosed with respiratory distress, it would be more appropriate to prefer non-invasive ventilation method with leak synchronization to leak-compensated method.

Material and Method

Approval of Erciyes University Faculty of Medicine Ethics Committee was obtained for this study (date:19.06.2015, number:2015/303), and the informed consent form was filled out by parents and their consents were obtained. Our study was supported by Scientific Research Projects unit of Erciyes University by project code TSG-2015-5873.

This prospective and randomized study included 50 preterm infants (25 per group) with gestational age below 34 weeks and/or body weight below 2000 grams who were admitted because of RSD and connected to a mechanic ventilator after consents of the parents; infants were randomly assigned to LC nSIMV and LS nSIMV groups. Exclusion Criteria were congenital heart disease, respiratory and nervous system malformation and nasopharyngeal pathology (coanal atresia and cleft palate-lip), and major congenital/chromosomal abnormality. Surfactan was administered to preterm infants enrolled due to RDS. Before extubation, intravenous caffeine was started in all patients according to our clinic's protocol, and noninvasive respiratory support was provided using short binasal prongs. LC nSIMV ventilation support was performed through Nellcor Puritan Bennett™ 840 Ventilatory System; LS nSIMV ventilator support was provided by Nellcor Puritan Bennett™ 980 Ventilatory System. Blood gas parameters, SPO_2/FiO_2 (S/F) rate, peak heart rate of the patients, respiration count per minute and duration for separation from mechanical ventilator at 1st hour following extubation and at 4 to 6-hour intervals were recorded. Maternal variables, delivery type, antenatal steroid use, gestational age, birth weight, gender, extubation failure and the status of premature babies in terms of common comorbid problems such as PDA, IVH, ROP, BPD, Pneumothorax, and NEC were followed. Reintubation criteria included respiratory acidosis in the blood gas (pH <7.25, PCO_2> 60 mm Hg); frequent apnea (<100/min heart rate along with respiratory arrest for >10 sec or >20 sec), FiO>0.6 to preserve SpO_2 at 90% to 95% and occurrence of frequent desaturation.

Statistical Analysis

Statistical analyses were performed by SPSS ver 22.0. Shapiro-Wilk test was used to review if data distributed normally; values were expressed in mean±standard deviation. Chi-square test was used for comparison of categorical data. In comparison of LC NSIMV and LS NSIMV groups, the difference between dependent samples was determined by paired t sample test. Any p value below 0.05 ($p<0.05$) was accepted as statistically significant. Statistical analysis between repeated measurements was done by repeated measure method.

Results

24 (48%) females and 26 (52%) males were enrolled in the study. There was not any statistically significant difference between LCnSIMV and LSnSIMV groups for gender, postnatal age and birth weight (**Table 1**). There was not any statistically significant difference between LCnSIMV and LSnSIMV groups for APGAR score minutes 1 and 5 (**Table 1**). There was detected statistically significant difference between LCnSIMV and LSnSIMV groups for non-invasive ventilation period and re-intubation rate (p=0.04 and p=0.03, respectively) (**Table 1**).

Table 1.
Demographic characteristics and primary neonatal outcomes between groups

Demographic characteristics and primary neonatal outcomes	Groups		p value
	LC nSIMV	LS nSIMV	
Gestational age, weeks	29.6±1.8	29.4±1.7	0.72
Birth weight, g	1355±220	1370±231	0.96
Cesarean section, n (%)	12 (48)	13 (52)	0.83
Male gender, n (%)	14 (56)	15 (60)	0.92
Antenatal steroid, n (%)	8 (32)	9 (36)	0.79
APGAR score minute 1	6.8±1.5	7.3±1.5	0.65
APGAR score minute 5	8.6±0.7	8.7±0.9	0.98
NIV period, hours	48.1±10	40.2±8.1	0.04
Re-intubation, n (%)	5 (20)	2 (8)	0.03

NIV: Non-invasive ventilation, LC nSIMV: Leak compensated nasal SIMV, LS nSIMV: Leak synchronized nasal SIMV

There was detected statistically significant difference between LCnSIMV and LSnSIMV groups for SpO_2 and S/F rates at 60 minutes (p=0.03 and p=0.01, respectively) (**Table 2**). There was not any statistically significant difference between LCnSIMV and LSnSIMV groups for respiratory rate per minute, heart rate and PCO_2 (**Table 2**).

Table 2.
Clinical and laboratory data in NIV process

Variables	Time			
	Min. 15	Min. 30	Min. 60	Hour 6
SpO_2	91.5±1.2 90.6±1.4	92.7±1.5 92.3±1.3	95.6±0.8 93.0±0.5	94.3±0.7 94.2±0.4
p value	0.41	0.64	0.03	0.1
S/F rate	240±7 236±6	258±5.4 255±4.6	276±6.9 260±7.2	290±5.3 288±4.4
p value	0.74	0.56	0.01	0.1
RRM (/min)	50.4±2.2 50.1±2.0	48±1.5 48.3±0.9	44±1.1 43.6±1.0	40.2±1.2 41.3±0.8
p value	0.82	0.87	0.59	0.63
HR (/min)	146±5 144±4	140±6 141±5	135±4 136±3	131±3 130±4
p value	0.54	0.58	0.61	0.47
PCO_2 (mmHg)	- -	- -	40±5 40±4	40±4 39±4
p value			0.52	0.18

* Upper line LS nSIMV, lower line LC nSIMV, S/F rate: Saturation / FiO_2 rate, RRM: Respiratory rate per minute, HR: Heart rate

There was not any statistically significant difference between LCnSIMV and LSnSIMV groups for pneumothorax, patent ductus arteriosus, intraventricular bleeding, necrotizing enterocolitis, prematurity retinopathy, bronchopulmonary dysplasia rates and hospitalization periods (**Table 3**).

Table 3.
Evaluation of groups for secondary neonatal outcomes

Secondary neonatal outcomes	Groups		p value
	LC nSIMV	LS nSIMV	
Pneumothorax, n (%)	2 (8)	1 (4)	0.12
Patent ductus arteriosus, n (%)	1 (4)	2 (8)	0.18
Intraventricular bleeding, n (%)	3 (12)	4 (16)	0.36
Necrotizing enterocolitis, n (%)	2 (8)	1 (4)	0.15
Prematurity retinopathy, n (%)	2 (8)	3 (12)	0.27
Bronchopulmonary dysplasia, n (%)	3 (12)	2 (8)	0.46
Hospitalization period	41.2±4.2	40.5±4.6	0.59

LC nSIMV: Leak compensated nasal SIMV, LS nSIMV: Leak synchronized nasal SIMV

Discussion

Our study is the first study evaluating the effectiveness of LC nSIMV and LS nSIMV modes in preterm babies with RDS.

Gas leakage is inevitable in non-invasive positive pressure ventilation when compared to invasive positive pressure ventilation. The space between the mask/cannula and nose and/or mouth is the main factor of air leakage. NIPPV (Nasal Intermittent Positive Pressure Ventilation) is a non-invasive ventilation method which has similar effects with invasive ventilation with pressures applied in addition to CPAP (Continious Positive Airway Pressure). NIPPV facilitates ventilation (CO_2 excretion) and oxygenization. It may be synchronized or non-synchronized. Mechanical ventilators providing effective synchronization using flow sensors are not very common and difficult due to large leaks during CPAP, and it is not clear whether unsynchronized NIPPV is effective. Synchronized NIPPV may reduce extubation failure if delivered via a ventilator rather than a two-stage CPAP device, but may not provide long-term benefits such as reduction in BPD.[6,7] In our study, we compared leak compensation and leak synchronization in patients with RDS. Our results revealed the importance of leak synchronization of which we have shown the superiority for patient compliance.

When compared with NIPPV and CPAP in the initial treatment of RDS; NIPPV appears to be superior to CPAP in terms of the need for intubation and reducing the rate of respiratory failure. Many studies indicating the superiority of NIPPV to other NIV methods performed synchronization. When synchronized NIPPV and CPAP are compared, it was emphasized that synchronized NIPPV is superior to CPAP in terms of extubation failure, need for oxygen support, and the risk of BPD development.[8-10] It was emphasized in a meta-analysis on avoiding endotracheal intubation for protection from BPD that this strategy has significantly lower mortality and BPD (p=0.01).[11,12] In our study, high-level mechanical ventilators were used as the mechanical ventilation mode in which the compensation and synchronization features of the NSIMV mode were tested in non-invasive ventilation. We did not detect any difference between groups for BPD which is one of the secondary diseases when compared with the study conducted by Jasani et al.[8] This may be explained with limited number of patients.

The results of the meta-analysis investigating whether synchronization is a necessary factor in premature infants indicated that synchronized CMV (Continuous mandatory ventilation) NIPPV is more beneficial in terms of extubation failure. Furthermore, small clinical studies have emphasized that although it has been observed to reduce the symptoms of prematurity apnea in infants treated with sNIPPV, there is little evidence of the effect of synchronization on important outcomes such as BPD and mortality.[13] Another study evaluating the effect of synchronization of NCPAP vs NIMV (Non-invasive Mechanic Ventilation) vs S-NIMV (Infant Star 950; Infrasonics, Inc., San Diego, CA) in clinically stable premature infants showed that groups were similar for ventilation and gas exchange; however, synchronized nasal ventilation has a positive effect on ventilation effort.[14] Another recent meta-analysis including 10 studies and 1061 preterm infants reported that although a significant decrease was found in respiratory failure and intubation need with NIPPV, there was not any significant decrease in the development of chronic lung disease, BPD, and further studies were needed.[15] Positive effect of synchronization was also demonstrated in our study with clinical parameters. However, in parallel with the cochrane database, no positive effect was found in terms of BPD development. An important study comparing the leak compensation in pediatric NIV simulation through 7 top-quality ventilators (Maquet Servo-i, Drager V500, Drager Carina, Covidien PB840, Respironics V60, Respironics Vision, GE Healthcare/Engstrom Carestation, CareFusion Avea, Hamilton C3, Hamilton G5) stated that compensations of ventilators would change depending on patient weights and pulmonary mechanics. PB840 and C3 have compensation rates of over 90% on all body weights, whole lung mechanics

profiles and all leak levels; however, although PB840 and C3 show better triggering and compensation than other ventilators, the clinical significance of these differences is uncertain.[16] Although the compensation of Covidien PB840 that we have used in our study was good, more positive results were obtained in terms of patient compliance with Covidien PB980 synchronization in the other study group.

The main limitation of our study was limited number of patients in groups. Studies with larger numbers of patients comparing noninvasive compensation and synchronization in preterm babies are needed.

Conclusion

Consequently, in consideration of the positive effect on clinical parameters in patients with RDS who need noninvasive ventilation in the pre-extubation period and patient-ventilator compliance, we believe that it would be more appropriate to prefer the LS nSIMV method to the LC nSIMV method.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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

Ethics Committee Approval: Ethical approval of Erciyes University Faculty of Medicine Ethics Committee was obtained for this study (date:19.06.2015, number:2015/303).

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Solitary Rectal Ulcer Syndrome in Children

Author (s)

Duran Arslan, Buket Daldaban Sarıca

Affiliation (s)

Department of Pediatric Gastroenterology, Hepatology and Nutrition Erciyes University Faculty of Medicine, Kayseri, Turkey

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Abstract

To describe clinical features, demographic data, and complications of the patients with SRUS, which is a rare cause of rectal bleeding in children. Eleven patients diagnosed with Solitary Rectal Ulcer Syndrome (SRUS) were evaluated. The patients assessed by colonoscopy and the biopsies were investigated. The data evaluated in SPSS Program. The exact Method of the Chi-square test was used to compare groups according to qualitative variables. P <0.05 value was considered statistically significant. The most common symptom of the patients was rectal bleeding followed by abdominal pain and constipation. Lesions were mostly ulcerative in the endoscopic examination. There was a statistically significant relationship between the admission symptom and the response to treatment. Patients with abdominal pain and rectal bleeding had poor responses to treatment. In conclusion, SRUS is not uncommon than is thought in pediatric patients with the symptoms of rectal bleeding and constipation. SRUS should be considered in patients with or without rectal prolapse, with any complaints of any lesions in the rectum, hematochezia, and tenesmus.

Keywords: Solitary rectal ulcer, rectal bleeding, constipation

Correspondence: Buket Daldaban Sarıca, Department of Pediatric Gastroenterology, Hepatology and Nutrition Erciyes University Faculty of Medicine, Kayseri, Turkey
E-mail: buketdaldaban@gmail.com

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Introduction

Solitary Rectal Ulcer Syndrome (SRUS) is a rare condition that manifests with rectal pain and bleeding described mostly in young adults.[1] Generally, the presentation complaints are rectal bleeding with pain, constipation, and sometimes diarrhea. Cruveilhier first described it in 1830; later, in 1969, clinical and pathological features were revealed by Madigan and Morson. The underlying pathophysiology is multifactorial, and its annual prevalence is estimated to be 1/100.000.[4] Although the etiology of SRUS is not fully clear, direct trauma (self-digitation) and ischemia are two main mechanisms held responsible in pathogenesis.[3] The most annoying course of SRUS is the difficulty in treatment; experiences have demonstrated that numerous treatment options are inadequate. There are little data on treatment and outcome in children with SRUS. Enema, laxatives, and surgical options have been used in the literature.[4]

Highlights

- Constipation is common in children.
- Solitary Rectal Ulcer Syndrome is a clinicopathological abnormality.
- Solitary Rectal Ulcer Syndrome should be considered in pediatric patients with the symptoms of rectal bleeding and constipation.
- Enema, laxatives, and surgical options are used in the treatment of SRUS.

The present study, aimed to contribute to the literature by evaluating the clinical features, demographic data, and complications of our patients with SRUS, which is a rare cause of rectal bleeding in children.

Material and Method

In this study, SRUS was diagnosed in 16 cases, 11 of which were evaluated in the determination of clinical findings and demographic features. The study was conducted in Erciyes University in 2010 and the enrolled patients had been followed between 1998 and 2007. All the patients were male. There was a fresh blood story on the patients' stools' surface or mixed with the stool. The growth of all patients was average. None had a problem explained by bleeding diathesis, bacterial or parasitic infection, and any systemic disease. A pathologist evaluated biopsies taken from the colon in all patients. The data were assessed on SPSS Program. Average, standard deviation, median, minimum and maximum values were given as descriptive statistics. The Exact Method of Fisher's Exact test was used to compare groups according to qualitative variables. P<0.05 value was considered statistically significant.

Results

The patients' mean age was 12.02±4.57 years (Min-Max: 16 months - 18 years), and all were male. The most common symptom seen in patients was rectal bleeding (100%) followed by abdominal pain (45.5%), constipation (27.3%), and mucus (27.3%) (**Table 1**).

Table 1
Symptoms observed in patients

Symptom	Number (n)	Frequency (%)
Rectal bleeding	11	100.0
Abdominal pain	5	45.5
Constipation	3	27.3
Mucus	3	27.3
Diarrhea	0	0.0

Bleeding tests of all patients were normal. The mean hemoglobin level of patients at the time of admission was 11.31±1.08 (min-max: 9.50-12.80) gr/ dl, MCV value 74.64±8.09 fl (min-max: 58.70-83.30). Iron deficiency anemia was detected in four of the patients (36.4%). In the follow-up, one patient (9.1%) received a blood transfusion.

In the endoscopic examination, 63.6% of the lesions were multiple. Macroscopically, 72.7% were ulcerative, and 27.3% were polypoidal/nodular. Lesions were detected at a distance of 2-10 cm from the anal edge (**Table 2**). All of the biopsies were compatible with SRUS, and none developed malignancy.

There was a statistically significant relationship between the admission symptom and treatment response (p=0.027). Patients with abdominal pain and rectal bleeding had an inadequate response to treatment (**Table 3**).

In the treatment, constipation therapy was used with local sucralfate, local steroid (oral or rectal). Rectal bleeding continued in seven patients receiving treatment, and two patients required surgery for bleeding. Endoscopy was not repeated routinely, except in four patients with ongoing rectal bleeding. Factors affecting the response to treatment in patients are shown in **Table 4**.

Table 3.
Initial symptom - Response to treatment

Symptom	Clinical Answer		P*
	Yes	No	
Rectal bleeding	5	0	0,027
Rectal bleeding + constipation	1	0	
Rectal bleeding + abdominal pain	0	2	
Rectal bleeding + mucus	1	2	

* According to Fisher's Exact test

Table 4.
Factors affecting clinical response in patients

Variables		Clinical Answer		P*
		Yes	No	
Number of lesions	Single	3	1	1
	Multiple	4	3	
Lesion type	Ulcerated	5	3	1
	Ulcer inflammatory / polypoid	2	1	
Treatment	Sucralfate	0	1	0,727
	Mesalazine	1	0	
	Sucralfate, mesalazine	0	1	
	Laxative	1	2	
	Sucralfate, mesalazine, emptying enema	0	1	
	Laxative, emptying enema	2	2	
Iron deficiency	Yes	3	1	1
	No	4	3	

* According to Fisher's Exact test

Table 2.
Endoscopic findings of the patients and the treatments applied

Patient Number	Rectoscopy Findings	Number of Lesions	Lesion Type	Treatment	Surgical	Number of Recurrent Biopsies	Clinical Answer
1	Nonspecific Proctitis	Multiple	Ulcerated	Sucralfate, Mesalazine	NO	-	YES
2	Nonspecific Proctitis	Single	Ulcerated	Laxative	NO	-	YES
3	Nonspecific Proctitis	Single	Ulcerated	Laxative, Emptying enema	NO	-	YES
4	Ulcerated areas at 7-8 cm	Multiple	Ulcerated	Sucralfate	NO	-	NO /EXITUS
5	Active bleeding	Multiple	Ulcerated inflammatory polyp	Laxative, Emptying enema	NO	-	YES
6	Mutual hyperemia, minor erasions	Multiple	Ulcerated inflammatory polyp	Laxative, Emptying enema	NO	-	NO
7	2 cm proximal anterior localized ulcer	Single	Ulcerated	Laxative, Emptying enema	YES	-	NO SURGICAL
8	Ulcer lesion at 7-8cm and 1cm	Single	Ulcerated	Laxative	NO	2	NO
9	3-4 ulcers at 10 cm	Multiple	Ulcerated	Laxative	NO	2	NO
10	Ulcers at 8 cm	Multiple	Ulcerated	Mesalazine	NO	2	NO
11	Hyperemic edema, 5-10 cm edema, some covered with white exudate, one polypoid lesion	Multiple	Ulcerated inflammatory polyp	Sucralfate Mesalazine Emptying enema	YES	3	NO SURGICAL

Discussion

Solitary Rectal Ulcer Syndrome is a collection of clinicopathological abnormalities that express a solitary ulcer or rectal wall thickening in the rectum and is characterized by rectal bleeding, stool with mucous, prolonged straining, tenesmus, and local pain in the perineum. The actual pathogenetic mechanism is not fully understood and is likely multifactorial. However, it is known that there is a defecation defect in patients, and this is thought to occur with two main mechanisms:[5,6] (i) Relaxation defect of the puborectal muscles during defecation (or paradoxical contraction) and (ii) rectal prolapse. SRUS is seen mostly in young adults, and the incidence in women and men is almost equal. SRUS is seen mainly in older children (>10 years of age).[7-9]

The diagnosis of SRUS is based on the findings of manometer and electromyography, clinical features, rectal examination, proctosigmoidoscopy, histological examination, nutritional habits, defecation habit, dynamic MRI, and anorectal functional studies.[4,6] While no symptoms are found in 1/4 of the disease, symptomatic cases typically complain of the feeling of straining during defecation, being in the toilet for a long time, but still not fully emptying.[10] The predominant presentation is rectal bleeding (as in the present study), in a study reported in Iran (the most extensive pediatric series in the literature with 256 rectal bleeding cases), and in another study in which 140 SRUS cases were examined in 2020.[4,7] In our study, the relationship between presentation symptoms and response to treatment was found to be significant. Patients with rectal bleeding alone, constipation with rectal bleeding, and rectal bleeding with mucus-containing defecation responded positively to the treatment. Mucus discharge, tenesmus, perineal/abdominal pain, incomplete defecation sensation, and fecal incontinence are also among the symptoms. While there was no difference between genders in previous studies, the disease was significantly higher in boys.[1,4]

Histologically, in laminated propria, fibromuscular obliteration is characterized by disorientation in muscle fibers. This condition is thought to develop secondary to chronic mechanical and ischemic trauma with intussusception in the rectal mucosa. Although this syndrome is well defined in adults, its pediatric forms are generally not well defined, misidentified, or limited in number.[9,12]

Treatment can be divided into two groups, conservative or surgical.[13,14] In the absence of overt rectal prolapse, high-fluid and high-fiber diet, laxative, and avoiding difficult defecation are the basis of conservative treatment. Sucralfate, salicylate, corticosteroid, sulfasalazine, mesalazine, and topical fibrin concealing agents, are used in medical treatment.[15] Surgical treatment should be considered in the presence of rectal prolapse. We found that the number of lesions, lesion type, treatment type, and iron deficiency presence did not affect the clinical response.

In pediatric case series, laxatives, enemas, and surgical approaches were used more often than behavioral modification as biofeedback therapy teaches how to relax pelvic floor muscles and the external anal sphincter during bowel movements, especially in adults.[16,17] As shown in many other studies, good results cannot be obtained with the disease's current treatment options. In some patient groups, the disease is treated with only fibrin glues, while in others, the patient goes to surgery. Also, there are patients in whom rectal bleeding continues despite surgery. For this reason, it is suggested that some patients can recover on their own.

A study conducted by Dehghani et al.[4] on 12 children recommended avoiding difficulty in defecation, excess fluid, and fiber diet to all patients. They observed that all symptoms improved in seven patients (58.3%) with sucralfate enema. Salicylate enema (50 mg/kg/day six weeks) and corticosteroids were given to those

who did not respond to sucralfate. Three patients were treated with corticosteroids injected around the ulcer during medical treatment and colonoscopy; two were asymptomatic, and one underwent surgery. Two of our seven cases that could not respond to medical therapy were operated on, and these patients were asymptomatic after surgery. In their pediatric SRUS study of 140 cases, Poddar et al.[7] noted that approximately 60 percent of children without significant rectal prolapse showed a clinical response to behavioral change with a corticosteroid enema.

Kırıştıoğlu et al.[1] reported a series of four cases. They used defecation training, laxative, sulfasalazine, and rectal sucralfate in medical treatment. Ertem et al.[6] reported a series of two cases, and one patient who did not respond to medical therapy underwent rectopexy. The patient was asymptomatic 1.5 years after the operation. In our study, patients who underwent surgery were asymptomatic two years after the operation.

Adaptation to treatment is difficult in younger patients, so follow-up of these patients is more critical, and therapy should be more aggressive. Most pediatric patients with SRUS have a satisfying outcome using a simple behavioral modification approach. Continuity of follow-up is vital to reinforce behavioral modifications and can prevent prolonged, treatment-resistant illness into adulthood.[4] Special studies cannot be conducted in many centers, and biofeedback or large intestine training programs cannot be performed in treatment. Treatment success is likely to increase with the use of these treatment options.[14,18] Keshtgar et al.[19] have developed a treatment method by injecting botulinum toxin into the internal anal sphincter of children with chronic idiopathic constipation. In the SRUS cases, external anal sphincter botulinum toxin injection may have a therapeutic role.[20] Due to our hospital's limited treatment options, it was impossible to compare different treatments in our study.

In patients with abdominal pain and stool of eccentric character (soft or hard), the symptoms last longer. In our study, patients with abdominal pain and rectal bleeding had more prolonged symptoms and did not respond to treatment. Constipation is significant, especially for the persistence of the disease.

Conclusion

Contrary to what is stated in the literature, the frequency of SRUS is not low in children who present with fresh rectal bleeding. The reason for this is not known precisely. However, the most common pathogenetic factor is thought to be mucosal injuries associated with rectal prolapse. It requires a good clinician and an experienced pathologist for early diagnosis. Therefore, patients with rectal bleeding should be questioned in terms of SRUS, and SRUS should be considered in the differential diagnosis. SRUS also should be considered in patients with or without rectal prolapse, with any complaints of any non-natural-looking lesions in the rectum, hematochezia, or tenesmus.

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Conflict of Interest: All the authors declare that they have not received any financial support or other benefits from commercial sources for the work described in this paper. They also declare that they have no other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with about this work.

Ethics Committee Approval: The study was conducted in Erciyes University in 2010 and the enrolled patients had been followed between 1998 and 2007. An ethical approval was not necessary for retrospective studies at the time of this study.

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Rare Autoinflammatory Diseases: A Single Center Experience of 47 Patients

Author (s)

Sema Nur Taşkın[1], Ayşenur Paç Kısaarslan[1], Sümeyra Özdemir Çiçek[2], Nihal Şahin[3], Şeyda Doğantan[1], M. Hakan Poyrazoğlu[1], Ruhan Düşünsel[4]

Affiliation (s)

[1]Erciyes University, Faculty of Medicine, Department of Pediatric Rheumatology, Kayseri, Turkey
[2]Kayseri City Hospital, Department of Pediatric Rheumatology, Kayseri, Turkey
[3]Bursa City Hospital, Department of Pediatric Rheumatology, Bursa, Turkey
[4]Yeditepe University, Faculty of Medicine, Department of Pediatric Nephrology-Rheumatology, İstanbul, Turkey

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Abstract

Autoinflammatory diseases include a group disease characterized by recurrent systemic inflammatory attacks due to failure in the regulation of the innate immune system. The beginning time of autoinflammatory disease are the most commonly in childhood. Autoinflammatory disease which having different clinical forms are rare, therefore diagnosis is often delayed. To determine the clinical, laboratory and radiological characteristics of children with rare autoinflammatory diseases and in which patients to consider autoinflammatory disease. Forty seven patients diagnosed with rare autoinflammatory diseases between 2010 and 2020 were analyzed retrospectively. Demographic characteristics, clinical courses, laboratory and imaging findings of the patients were recorded. Forty-seven with rare autoinflammatory patients evaluated. Twenty-three patients had Chronic Nonbacterial Osteomyelitis (CNO), seven patients had Mevalonate Kinase Deficiency (MKD), six patients had Blau Syndrome / Early-Onset Sarcoidosis (BS/EOS) Syndrome, three patients had Cryopyrin-associated periodic fever syndrome (CAPS), three patients had Autoinflammatory Vasculitis, one patient had Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD) syndrome, one patient had Neonatal Onset Pancytopenia, Autoinflammation, Rash and Episodic HLH (NOARCH) syndrome. Three of our patients were being followed up with a diagnosis of undiferantiated systemic autoinflammatory disease (uSAID).Autoinflammatory diseases may have different presentations. Steril and recurrent inflammation should be warning clinicians.

Keywords: Rare autoinflammatory diseasea, fever, sterile inflammation, genetics

Correspondence: Muammer Hakan Poyrazoğlu, Division of Pediatric Rheumatology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey
E-mail: drpoyrazoglu@yahoo.com

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Introduction

Autoinflammatory disorders are characterized by recurrent episodes of apparently unprovoked inflammation that, unlike autoimmune disorders, lack the production of high-titer autoantibodies or antigen-specific T cells.[1] In 1999, the term "Autoinflammatory" was used to denote such a family of clinical disorders. This proposed nomenclature was inspired by the discovery of dominantly-inherited missense mutations in TNFRSF1A, encoding the 55 kDa tumor necrosis factor receptor.[2] More than 50 new monogenic systemic autoinflammatory diseases (SAID) have been discovered in the last decade with advances in genetics and continues to be discovered.[3]

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease, particularly in the Mediterranean.[4] FMF is characterized by recurrent systemic inflammatory attacks with fever and serositis. Periyodik Ateş, Aftöz Stomatit, Farenjit, Servikal Adenit Sendromu (PFAPA), which not known genetic defect still is another SAID wide range of worldwide. Other SAIDs are defined as rare diseases, and more data are need to be shared for a better understanding of rare autoinflammatory diseases.

This study evaluated the demographic, clinical, and laboratory of patients with rare SAIDs in the pediatric rheumatology clinic.

Highlights

- Autoinflammatory diseases should come to mind in recurrent fever and sterile inflammations. Diagnosis may be difficult in rare autoinflammatory diseases because of the overlapping clinical findings. The diagnosis is based on genetic investigation. Early diagnosis can shape treatment more accurately and prevent morbidity and mortality.

Material and Method

Patients with autoinflammatory diseases in Erciyes University of Pediatric Rheumatology clinic between January 2010 and January 2020 were evaluated retrospectively. All of the patients were under 18 years of age. Patients with FMF and PFAPA patients were excluded. Demographic, clinic and laboratory data were collected from patients' records with the approval of the local ethics committee of Erciyes University (date:02.12.2020, number: 611).

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 21.0. NY). Continuous variables were shown as mean standard deviation or median [minimum (min)– maximum(max)] and categorical variables are shown using frequency (percentage).

Results

Forty-seven with rare autoinflammatory patients evaluated. Twenty-three patients had Chronic Nonbacterial Osteomyelitis (CNO), seven patients had Mevalonate Kinase Deficiency (MKD), six patients had Blau Syndrome / Early-Onset Sarcoidosis (BS/EOS) Syndrome, three patients had Cryopyrin-associated periodic fever syndrome (CAPS), three patients had Autoinflammatory Vasculitis, one patient had Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD) syndrome, one patient had Neonatal Onset Pancytopenia, Autoinflammation, Rash and Episodic HLH (NOARCH) syndrome. Three of our patients were being followed up with a diagnosis of undiferantiated systemic autoinflammatory disease (uSAID).

Chronic Nonbacterial Osteomyelitis

The data of some of the patients included in this study have been published before.[5] We had 23 CNO patients. Twelve patients (52.2%) were male. The mean±SD age of patients was 12.8±4.52 years. The mean±SD age of symptoms onset and diagnosis were 9.5±4.17, and 10.4±4.1 years, respectively

All patients had musculoskeletal system complaints. Thirteen patients (56.5%) had arthralgias, six patients (26.1%) had limping, or abnormal gait, three patients (13.1%) had local swelling of the bones.

Eleven patients (47.8%) had constitutional symptoms, which included fever in 9 (81.8%), malaise in 4 (36.4%), weight loss in 2 patients (18.2%), and night sweats in 1 patient (9.1%). Skin involvement was detected in 5 patients (21.7%). None of the patients had a family history of CNO.

Thirteen patients (56.5%) had concomitant diseases including FMF in 8, jSpA in 4 patients, psoriatic arthritis in 1, and IBD in 1 patient. All FMF-CNO patients had at least one M694V variant. Besides, 5 patients had recurrent aphthous stomatitis. But they did not the fulfillment of pediatric Beçet Disease diagnostic criteria. On admission, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were high in 16 (69.6%) and 13 (56.5%) patients, respectively. Five patients (21.7%) had an elevated white blood cell count. Of 18 patients, 3 (16.7%) were positive for human leukocyte antigen (HLA)-B27. Two of these patients had spondyloarthropathy as a concomitant disease.

Regional Magnetic Resonance Imaging (MRI) detected bone lesions in 13, whole-body MRI in 10, and whole-body bone scintigraphy in 8 patients. Regional MRI suggested CNO in 13 patients. This diagnosis was confirmed by whole-body bone scintigraphy in 5 of these 13 patients and whole-body MRI in 3 patients. The most frequently affected areas were femur (74%), tibia/fibula (74%), and pelvis (52.2%) (**Figure 1**). Bone biopsy was performed in seven patients (30.4%). Biopsy findings showed lymphoplasmacytic cell infiltration consistent with chronic inflammatory osteomyelitis.

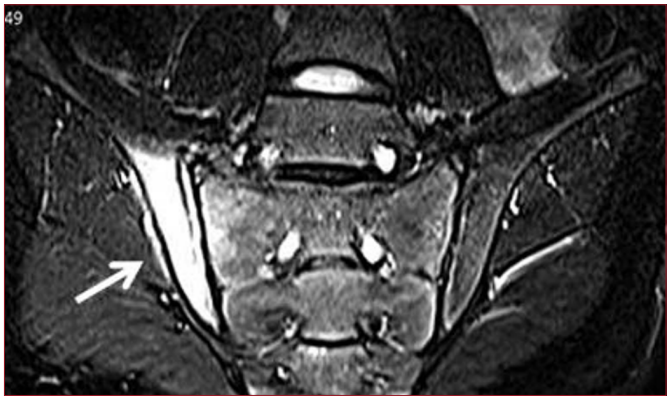

Figure 1. Pelvic MRI of one patient at the diagnosis; T2-weighted turbo spin echo image with fat suppression showing hyperintensity of the right iliac wing.

One patient who was not treated by medication encountered spontaneous complete remission, and radiological findings had disappeared within seven months. Nonsteroidal anti-inflammatory drugs (NSAIDs) were used in 6 (26.1%), disease-modifying antirheumatic drugs (DMARDs) (methotrexate or sulfasalazine) were used in 13 (56.5%), biological agents (anti-TNF, IL-1 blocker) were used in 8 (34.8%) patients.

Mevalonate Kinase Deficiency

We had seven patients diagnosed with MKD. Six (85.7%) of them were male. The mean±SD age of the patients was 12.1±5,6 years. The median age of symptoms onset was 5.0 (min:0.3-max:6,1) and the mean diagnosis age was 6.8 (±3.4) years, respectively.

All patients had a fever, rash, lymphadenopathy (LAP), gastrointestinal system involvement, and high acute phase reactants during the attack. One (14.2%) patient with amyloidosis had growth retardation.

Arthritis were in 4 (57.1%), arthralgia was in 6 (85.7%), oral aphthae was in 4(57.1%) and conjunctivitis was in 2 (28.5%) patients. Splenomegaly was detected in 3, hepatomegaly was detected in 1 patient. One of our patients had kidney transplantation as a result of amyloid deposition. In genetic analysis, 5 (71.4%) of 7 patients had V377I mutation. Others had not any mutations.

One patient was treated with steroids during attacks. Six of 7 patients were treated with IL-1 blocker, 3 of them were also treated with colchicine.

Blau Syndrome and Early-Onset Sarcoidosis

The data of some of the patients included in this study have been published before.[6] There were six patients with the diagnosis of Blau Syndrome / Early Onset Sarcoidosis, including four patients (two men, two women) with EOS and two siblings (one male, one female) with BS. Three (50%) of 6 patients were male. The mean ± SD age of the patients was 12.0±2.3 years. The median age of symptoms onset was 1.0 (min:0.3-max:5.0) and the mean diagnosis age was 6.6 (±3.2) years, respectively.

Five (83.3%) of six patients had arthritis, tenosynovitis, camptodactyly, three patients had the rash, two patients had uveitis (**Figure 2**). Fever was observed in one (16.6%) patient. Renal, liver, lung, cranial nervous system involvement, and lymphadenopathy developed in one patient.

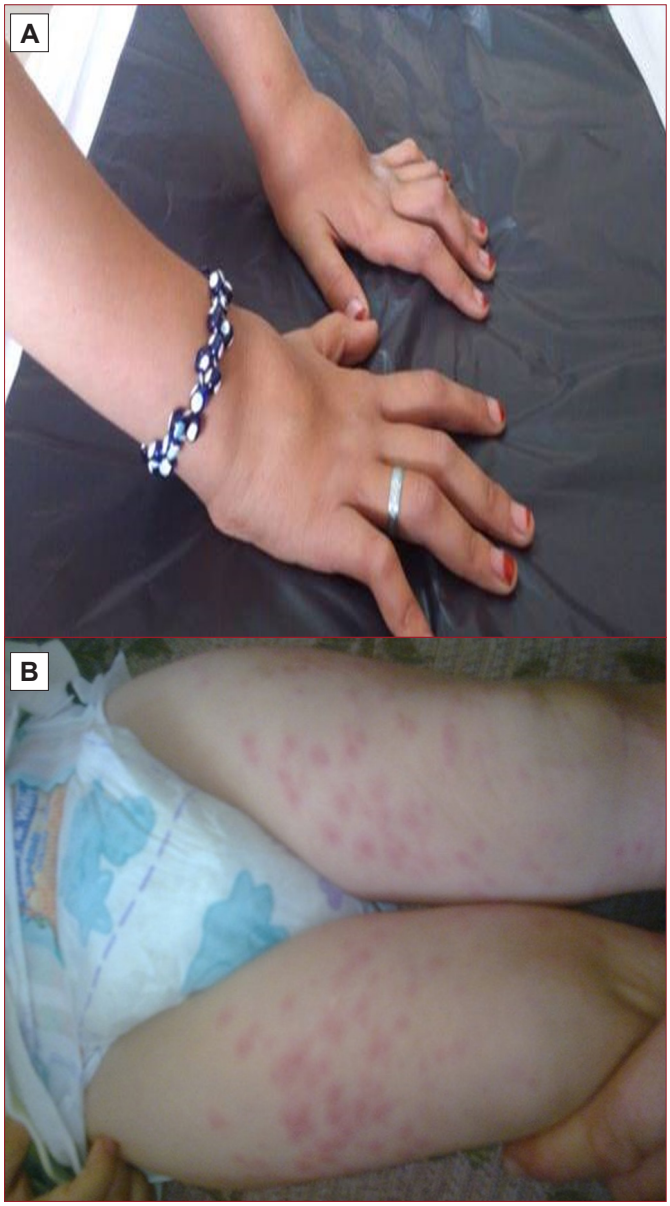

Figure 2. In patients followed up with the diagnosis of Early-Onset Sarcoidosis **2A:** Boggy synovid and camptodactyly **2B:** Rash

Acute-phase reactant elevation was present in 3 (50%) patients, and angiotensin-converting enzyme level was elevated in one (16.6%) patient.

The mutations were detected as P268S (Exon4), M513T (Exon4), R702W (Exon4), H343Y (Exon4), V955I (Exon4), M491L (Exon4) in patients.

Five patients were treated with methotrexate. Three patients were treated with Tumor necrosis factor α (TNF-α) inhibitors, one patient was treated with Interleukin-6 Inhibitor, and one of them was treated with tofacitinib.

Cryopyrin-Related Periodic Syndrome

We had three patients with CAPS. Two (66.6%) of them were boys. The mean±SD age of the patients was 9.4±2.4 years. The median age of symptoms onset was 4 (min:1.0-max:4.0) and the mean diagnosis age was 7.3 (±3.9) years, respectively.

All patients had a fever, urticaria-like rash, and high acute phase reactant values at the time of the attack. Two (66.6 %) patients had arthritis/arthralgia, 2 (66.6 %) patients had oral aft, 2 (66.6 %) patients had gastrointestinal

involvement, 1 (33.3 %) patient had eye involvement, 1 (33.3 %) patient had papilledema, and 1 (33.3 %) patient had hepatosplenomegaly (**Figure 3**).

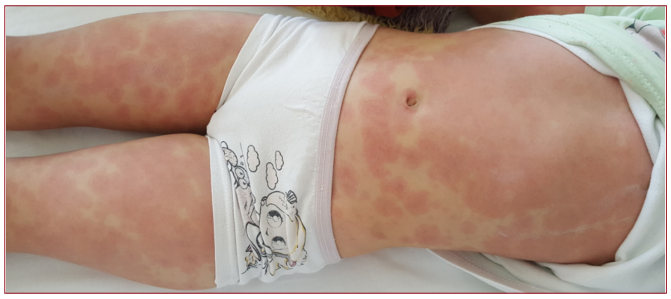

Figure 3. Urticaria-like rash seen in a patient followed up with the diagnosis of Cryopyrin-Related Periodic Syndrome

Two other patients had mutation in the NLRP 3 ((Val198Met(592G>A)) and NLRP12 (p.Thr260Met(c.779C>T)) gene.

Two patients were treated with IL-1 blocker; 1 of them did not receive any medications.

Autoinflammatory Vasculitis

Three patients were followed up with a diagnosis of autoinflammatory vasculitis. All of the patients were female. The mean±SD age of the patients was 11.4±7.0 years. The median age of symptoms onset was 2.4 (min:2.4-max:8.0) and the mean diagnosis age was 10.5 (±6.8) years, respectively.

The symptoms of the first patient started at the age of 2.5 years. Fever and seizure were developed during the attacks. Her magnetic resonance imagine findings were appropriated as vasculitis. Hemophagocytic lymphohistiocytosis developed in the follow-up. Her diagnosis was ADA2 deficiency at first, but CECR1 mutation was not detected in the genetic analysis. Her attacks were controlled with Etanercept and steroid therapy.

The attacks of our second patient, whose symptoms started at the age of 2, had a fever, arthritis/arthralgia, and rash. The patient was diagnosed with systemic JIA. During the follow-up, renal involvement and cranial vasculitis were developed. CECR1 mutation was not detected in genetic analysis. This patient also benefited from etanercept and steroid therapy.

The girl who followed by pre-diagnosis of Fanconi anemia had a fever, widespread arthritis, erythema nodosum, and lipodystrophy (**Figure**). Skin biopsy was compatible with septal panniculitis. The homozygous FANCA mutation (P.Gly1009Asp) was detected with the whole-exome sequencing. Joint and skin findings improved with etanercept treatment. Bone marrow transplantation was planned for the patient.

Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay

Patient's symptoms started when she was four months old. The patient was diagnosed at the age of 2. She had periodic febrile attacks, anemia, hypogammaglobulinemia, severe growth, and developmental delay. During the attack periods, she had diarrhea and high acute phase reactants. In genetic analysis TRNT1 gene (Exon 6, p.I233fs (c.679 del A, Exon 8 p.K416E (c.126 A>G)) mutation was found. The patient was treated with etanercept and IVIG. Unfortunately, the patient died due to trauma.

Neonatal Onset Pancytopenia, Autoinflammation, Rash and Episodic HLH

A five-year-old male patient was admitted to the neonatal intensive care unit on the 20th day of age due to anemia, thrombocytopenia, neutropenia, and high acute phase reactants. The patient was diagnosed with septicemia. On the 40th day of age, persistent fever, rash, and hepatosplenomegaly developed. The patient was diagnosed with hemophagocytic lymphohistiocytosis. Anemia, thrombocytopenia, neutropenia, and high acute phase reactants recurred at six months. The patient suffered from mucosal and intracranial bleeding. Anemia and thrombocytopenia regressed, but neutropenia continued in the following years. The patient had hypotonia, mental, motor retardation, and osteoporosis. CDC42 (LRG_1326t1:c556C>T;p Arg186Cys) was detected with whole exon sequencing. The patient was treated with canakinumab and steroid therapy, was also treated with pamidronate therapy for osteoporosis.

Undifferentiated Autoinflammatory Diseases

There were three patients with a diagnosis of Undifferentiated Autoinflammatory Diseases. 2 (66.6 %) of them were male. The mean±SD age of the patients was 9.3±8.9 years. The median age of symptoms onset was 4 (min:0.2-max:17.5) and the mean diagnosis age was 8.4 (±8.7) years, respectively.

The fever and diarrhea started at seven days old. The patient had lymphadenopathy, psoriatic rashes, and nail dystrophy. His attacks period was longer than a month. STAT5B (p.Arg566Gln(c.1697 G>A)) / TLR6 (Pro740Leu(c.2219 C>T)) mutation was detected in the genetic analysis Interleukin 1 inhibitor, cyclosporine, acitretin treatment was not under controlled the attacks. He was dependent on steroid therapy. Unfortunately, the patient recently died due to Covid 19 at sixteen months.

Our second patient was male, and his symptoms started at the age of 17. Fever, gastrointestinal symptoms, myalgia, massive pericardial/pleural / peritoneal effusion were observed along with high acute phase reactants during the attack. The familial HLH3 Type 3 related mutation (P.Val731Met(c.2191 G>A) in the UNC13D gene was detected. IL-1 blockade was not effective. His disease was under control with steroid, colchicine, and etanercept therapy.

Six year old female patient's symptoms started at the age of 4. Fever, gastrointestinal symptoms, myalgia, arthritis/arthralgia, periorbital edema were observed along with high acute phase reactants during the attacks. NLRP1(p.Met1184Val(c.3550A>G)) mutation was detected .The patient benefited from colchicine and steroid therapy.

The demographic, clinical characteristics, diagnostic methods and treatments of the patients are summarized in **Table 1**.

Table 1

Disease Name	N	F/M	The mean±SD age of patients (year)	The mean±SD age of symptoms onset (year)	The mean±SD age of symptoms diagnosis (year)	Prominent clinical features	The main tests to help diagnose	Treatment
CRMO	23	11/12	12.8±4.52	9.5± 4.17	10.4± 4.1	Localizing bone pain	MRI, scintigraphy, bone biopsy	NSAIDs, DMARDs or biological agents (anti-TNF, IL-1 blocker)
MKD	7	1/6	12.1±5.6	The median age:5.0 (min:0.3-max:6.1)	6.8±3.4	Fever, rash, vomiting, diarrea, LAP, arthritis/ arthralgia, oral aphthae, HSM, conjunctivitis,	High AFR during the attack, genetic analysis	Steroid, colchicine, biological agents (IL-1 blocker)
BLAU Syndrome /EOS	6	3/3	12.0±2.3	The median age:1.0 (min:0.3-max:5.0)	6.6 (±3.2)	Arthritis, tenosynovitis, camptodactyly, uveitis, LAP,fever, rash ,renal, liver, lung, cranial nervous system involvement	High AFR during the attack, genetic analysis	DMARDs or biological agents (anti-TNF, Interleukin-1 and 6 Inhibitor, Tofacitinib)
CAPS	3	1/2	9.4±2.4	The median age:4.0 (min:1.0-max:4.0)	7.3 (±3.9)	Fever, urticaria-like rash, arthritis/arthralgia, oral aft, papill edema	High AFR during the attack, genetic analysis	Biological agents (IL-1 blocker)
Autoinflammatory Vasculitis	3	3/-	11.4±7.0	The median age:2.4 (min:2.4-max:8.0)	10.5 (±6.8)	Fever, seizure, vasculitis, rash, arthritis/ arthralgia, erythema nodosum, lipodystrophy, septal panniculitis	High AFR during the attack, genetic analysis, MRI, BMA,skin Bx	Steroid, biological agents (anti-TNF)
SIFD	1	1/-	2.5	4 months	2	Fever, GIS involvement, hypogammaglobulinemia, severe growth, and developmental delay.	High AFR during the attack, genetic analysis	Biological agents (anti-TNF), IVIG
NOARCH	1	-/1	5	*Neonatal*	6 months	Fever, rash, pancytopenia, HLH, HSM, hypotonia, mental, motor retardation, osteoporosis	High AFR during the attack, genetic analysis, BMA	Steroid, biological agents (IL-1 blocker), pamidronate
Undifferentiated Autoinflammatory Diseases	3	1/2	9.3±8.9	The median age:4 (min: 0.2-max:17.5)	8.4 (±8.7)	Fever,rasch, GIS involvement,LAP, miyalgia, serositis, arthritis/ arthralgia, periorbital edema	High AFR during the attack, genetic analysis,	Steroid, biological agents (IL-1 blocker, anti-TNF), cyclosporine, colchicine

AFR:Acute phase reactants, BMA: Bone marrow aspiration, Bx: Biopsy, DMARDs: Disease modifying antirheumatic drugs, F: Female, GIS: Gastrointestinal system, HSM: Hepatosplenomagaly, IVIG: intravenous immunoglobulin, LAP: lymphadenopathy, M: Male, MRI: Magnetic resonance imaging, N: Number of patients, NSAIDs: Nonsteroidal, anti-inflammatory drugs, SD: standard deviation

Discussion

Chronic Nonbacterial Osteomyelitis

Chronic nonbacterial osteomyelitis is characterized by noninfectious bone inflammation.[7] It is often referred to as "chronic recurrent osteomyelitis" in cases where multifocal or recurrent features are seen during the clinical course.[8]

It is known that CNO is an autoinflammatory disease and may occur as a result of monogenic diseases such as Majeed syndrome,[9] deficiency of the IL-1 receptor antagonist (DIRA),[10] and pyogenic arthritis, Pyoderma gangrenosum, and acne(PAPA syndrome.[11,12] In most sporadic cases, responsible genes were not found.

Concomitant inflammatory diseases were reported in 30% of patients with CNO. These diseases mainly involve the skin and intestine. Psoriasis, palmoplantar pustulosis, Crohn disease, ulcerative colitis, celiac disease, and sypondiloarthritis were reported with CNO patients.[13] In our observation reported before, FMF was the most common concomitant disease with a rate of 34.8%. All of our FMF-CNO patients had at least one M694V variant. In our experience, the M694V variant may be a predisposing factor of CRMO.[5]

In contrast to a previous report,[14] the incidence of aphthous stomatitis was higher in our cohort (21.7% vs 1%). None of our patients had uveitis or symptoms related to Behçet disease. Of 18 patients, 3 (16.7%) were positive for human leukocyte antigen (HLA)-B27, which is not as high as seen in jSpA in Turkish children.[15,16]

Other clinical, laboratory and radiologic findings in our patients were consistent with the literature.[13,14,17,18]

Patients with non-specific musculoskeletal complaints and have localizing bone pain should be evaluated for CRMO.

Mevalonate Kinase Deficiency

Mevalonate Kinase Deficiency is an autosomal recessive autoinflammatory disease. It is caused by loss-of-function mutations in the MVK gene that encode mevalonate kinase, a critical enzyme involved in cholesterol biosynthesis.[19] V377I and I268T are the most common pathogenic mutations.[20,21] These two mutations are located in highly conserved positions of orthologous gene products in human[22] Most MKD patients are heterozygous for two different variants.[21] Five (%71.4) of the 7 patients had V377I mutation in their genetic analysis. The mutation was not detected in two patients.

MKD is characterized by a variable clinical progression, with an episodic-recurrent or chronic pattern, and usually presents with early childhood onset, mostly within the first year of life, but can manifest during the first five years. The occurrence of symptoms after five years of age excludes the diagnosis.[23] The mean age of onset of symptoms was at 3.5 years. Conversely to the literature, the symptoms started later in our patients.

Acute episodes generally occur every 4–6 weeks and last about 3–7 days on average, with asymptomatic periods between attacks.[23] Disease severity highly correlates with the mevalonate kinase enzymatic function.[24] Patients suffer from the episodic high-grade fever that may be accompanied by oral ulcers, cervical lymphadenopathy, gastrointestinal symptoms, skin rashes, arthritis, or headache.[23,25] All of our patients had an episodic high-grade fever, rash, lymphadenopathy, gastrointestinal system involvement, and high acute phase reactants during the attack.

Amyloidosis can be seen in about 3% of cases.[23] One of our patients had kidney transplantation as a result of amyloid deposition. To our knowledge, it is the first reported case of renal AA amyloidosis, which caused severe nephrotic disease in a Turkish child due to MKD.[26] His attacks repeated after renal transplantation. The attacks were controled with canakinumab treatment. We considered canakinumab treatment is safe in renal transplantation.[27]

MKD should be considered in fever, cervical lymphadenopathy, abdominal pain, and diarrhea despite symptoms started after the infancy period.

Blau Syndrome and Early-Onset Sarcoidosis

The clinical triads are granulomatous dermatitis, symmetrical arthritis, and recurrent uveitis that began before four years old.[28] Blau syndrome is a hereditary form, EOS is a sporodic form of the disease. Two forms of the disease associate with NOD2 mutation.[29] Our sibling patients and their mother were assessed as BS because of the familial form of the disease.

The disease begins typically before four years of age.[29] However, symptoms sometimes appear after the age of 10.[30] Our patients' initial symptoms started at about two years in accordance with the literature.

Two main types of symptomatic eruptions are reported: rash and multiple subcutaneous nodules.[31] Histology of the lesions demonstrates non-caseating granulomas with multinucleated giant cells.[32] Our patients' biopsies were shown noncaseating granulomatous inflammation on the kidney, hepatic, lymph node, and dermal biopsy.

Joint manifestations usually appear such as symmetric polyarthritis, and contractures often develop in the PIP joints in the early disease course. These early deformities are described as camptodactyly.[33] Granulomatous inflammation in the periarticular structures leads to marked periarticular swelling and tenosynovial cysts, which significantly affect the hands' wrists and dorsa.[31] Rosé et al. reported that the characteristics of arthritis in BS, comprising boggy synovitis and tenosynovitis, are distinct from those observed in JIA.[34] Our patients' most common manifestations were boggy synovitis and camptodactyly. These clinical findings allowed us to establish an early diagnosis.

Eye symptoms generally appear later at around the age of 12.[33] Chorioretinitis, cataracts, glaucoma, and retinal detachment can lead to significant visual impairment and blindness.[31] As a result of regular eye examinations, uveitis was detected in two of our patients, and it was controlled with early treatment.

The most commonly detected NOD2 mutations are R334W and R334Q.[35] BS / EOS penetration associated with NOD2 mutations is very high, but asymptomatic family members with NOD2 mutations have also been described in the literature.[36-38] The father of family patients had a V955I mutation and did not have any symptoms.

BLAU/EOS Syndrome should be considered when joint deformity, bogy synovitis develop at a young age.

Cryopyrin-Associated Periodic Fever Syndrome

CAPS is an autosomal dominantly inherited disease characterized by attacks of fever, urticaria, arthritis, bone deformity, deafness, and CNS involvement. The mutations in the C1AS1 gene, known as NLRP3, on chromosome 1 are lead to the disease.[39,40]

CAPS is the spectrum disease. The mild form is called familial cold autoinflammatory syndrome (FCAS). The moderate form is called Muckle-Wells syndrome. The severe forms of the spectrum represent chronic infantile neurological cutaneous and articular syndrome (CINCA) or neonatal-onset multisystem inflammatory disease (NOMID).[41] Two of our three patients were diagnosed with FCAS. One of the patients was diagnosed with FCAS2. FCAS2 develop in patients with NLRP12 variants (FCAS2, OMIM # 611762). This autosomal-dominant disease with a clinical phenotype between FCAS and MWS was reported in several families.[42] Approximately 62 patients with NLRP12 variants have been reported in the literature so far.[43]

The age of onset of symptoms is expected to be under one year of age. The symptoms onset age is our patients was 4.3 (years).[39] Diagnostic delay can be seen in patients with the mild phenotype.[44]

Levy et al. reported that the most common symptoms were fever, skin rash, and musculoskeletal involvement (although deforming arthritis is rare) observed in 84%, 97%, and 86% of patients, respectively.[45] The clinics

of our patient, who had cold / stress-triggered attacks, were compatible with the literature.

Papilledema, deafness, seizures, and developmental delay may develop during follow-up.[46,47] All CAPS patients should evaluated eye and ear examinations regularly. None of the patients had sensorineural hearing loss. One of them had papilla edema during the attack period. It regressed with steroid therapy and not recurred. Eye involvements that threaten vision at any level from the cornea to the optic nerve are common findings.[48-50]

CAPS should be considered in the case of patients with fever, urticarial rash, and high acute phase reactants.

Autoinflammatory Vasculitis

Vasculitis can also be either one of an autoinflammatory disease's characteristics or highly associated with an autoinflammatory disease.[49,50] It is known that FMF is accompanied by vasculitides such as IgA vasculitis, polyarteritis nodosa, and Behçet's disease.[51]

The Autoinflammatory vasculitides were listed as Deficiency of Adenosine Deaminase 2 (DADA2), STING-associated vasculopathy with onset in infancy (SAVI), and COPA Syndrome. DADA2 usually manifests as a PAN-like disease with recurrent stroke, livedoid skin rash, and immunodeficiency features. SAVI is an autoinflammatory vasculopathy with causing severe skin lesions that cause ulceration, necrosis, and in some cases amputation. Copa Syndrome features include erosive polyarthritis, an interstitial lung disease with or without pulmonary hemorrhage, and kidney disease with autoantibodies (ANA, ANCA, RF, and others).[52,53]

Our first two patients were compatible with the DADA2 clinic. It is known that etanercept treatment is effective in patients with a vasculitic form of DADA2. Both patients are under control with etanercept treatment. We follow these patients with genetically negative DADA2 diagnosis. The last patient was also evaluated as DADA2 with hematological involvement, but homozygous FANCA mutation was detected in WES analysis. The sweet syndrome was reported in FA with malignancy.[54,55] In our patient, malignancy was not detected in the 1.5-year follow-up, and bone marrow transplantation was planned.

Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay Syndrome

Mutations in the gene encoding transfer RNA (tRNA) nucleotidyltransferase (TRNT1) are associated with SIFD syndrome. Knockdown of TRNT1 results in significant cytotoxicity and apoptosis.[56] Approximately 30 patients with TRNT1 deficiency have been identified in the literature with significant heterogeneity in the clinical phenotype and underlying immunological defects.[57] Our patient's anemia was not sideroblastic anemia. Other findings were consistent with classical SIFD findings. The diagnosis of the patient was made by whole-exome sequencing (WES). The importance of WES in undifferentiated autoinflammatory diseases is increasingly accepted.[58]

Neonatal Onset Pancytopenia, Autoinflammation, Rash and Episodic HLH

Hemophagocytic lymphohistiocytosis (HLH) has characterized by hyperinflammation due to overactivation and expansion of macrophages and CD8+ T lymphocytes.[59,60] Cell division cycle 42 (CDC42) is a member of the Ras- homologous (Rho) GTPase family functioning as a signaling node controlling several cellular processes, including adhesion, migration, polarity, cell cycle, and proliferation.[61] NOARCH syndrome, which developed due to aberrant CDC42 function, was newly described in 4 patients in 2019 as neonatal-onset pancytopenia, autoinflammation, rash, and episodic HLH.[62] Our patient was diagnosed with WES at the age of 5. This shows once again the importance of genetic analysis.

Undifferentiated Autoinflammatory Diseases

The number of innate immune system disorders classified as systemic autoinflammatory diseases (SAID) has increased in recent years. More than 70-80 % of patients with clinical signs of SAID did not receive a molecular diagnosis and were therefore classified as undifferentiated SAID.[58]

In 2019, the Euro fever Project described the characteristics of 187 patients with uSAIDs, concluding a need for new classification criteria for monogenic SAIDs. It was stated that more research is needed to provide insight into the genetic and clinical relationship and the genotype-phenotype connection.[63]

Our first patient was diagnosed with DITRA. But bone pathology was not detected. Beyond this, genetic analysis was not appropriate with the DITRA. It has been determined that STAT5B deficiency affects growth, especially T regulatory cell deficiency.[64] Toll-like receptors (TLRs) have been shown to play a role in the innate immune response, and constitutively active TLR6 activates both NF-kB and c-Jun N-terminal kinase (JNK).[65] Both two mutations could be affected by the severe disease course in our patients.

HLH3 mutation was detected in the second patient. Feldmann et al. identified a Familial Hemophagocytic Lymphohistiocytosis (FHL) subtype, FHL3, in 10 patients from 7 unrelated families.[66] We diagnosed the patient as uSAID, because clinical and laboratory findings did not appropriate the HLH.

NLRP1 inflammasome is effective in converting interleukin-1β and interleukin-18 into the active forms.[67] The patient's clinic was not compatible with a specific autoinflammatory disease. But he responded to colchicine therapy. We reported this patient at ISSAID congress in 2019.[68]

Conclusion

Autoinflammatory diseases may have different presentations. Steril and recurrent inflammation should be a warning to clinicians. New developments in genetics facilitate the diagnosis of autoinflammatory diseases.

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Ethics Committee Approval: Ethical approval of Erciyes University Faculty of Medicine Ethics Committee was obtained for this study (date:02.12.2020, number: 611).

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Staphylococcal Pyomyositis Within Initial Course of Juvenile Dermatomyositis Patient

Author(s)

Ayşenur Paç Kısaarslan[1], Hülya Nalçacıoğlu[2], Taylan Çelik[3], Gonca Koç[4]

Affiliation(s)

[1]Erciyes University Faculty of Medicine, Pediatric Rheumatology,Kayseri, Turkey
[2]Ondokuz Mayıs University Faculty of Medicine, Pediatric Nephrology, Samsun,Turkey
[3]Çanakkale University Faculty of Medicine, Pediatric Infectious Disease, Çanakkale, Turkey
[4]Ege University Faculty of Medicine, Pediatric Radiology; İzmir, Turkey

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Abstract

Infectious complications are increasingly reported in patients with connective tissue diseases. These complications are both related to using immunosuppressive drugs and organ dysfunctions caused by diseases. Pyomyositis is a pyogenic infection of skeletal muscle associated with immunocompromised conditions, especially human immunodeficiency virus (HIV) infection, diabetes mellitus, malignancy, immunosuppressive drugs, and rheumatic diseases. We presented a patient with juvenile dermatomyositis complicated by staphylococcal pyomyositis initial disease course. The patient did not respond to drainage and appropriate antibiotic therapy. Abscess formation successfully regressed with IVIG. Muscle inflammation and corticosteroids are possible predisposing factors for pyomyositis.

Keywords: Dermatomyositis, pyomyositis, treatment

Introduction

Pyomyositis is a pyogenic infection of skeletal muscle that rises from the hematogenous spread and usually presents with localized abscess.[1] It is associated with immunocompromised conditions, especially human immunodeficiency virus (HIV) infection, diabetes mellitus, malignancy, immunosuppressive drugs, and rheumatic diseases.[2,3]

Dermatomyositis (DM)/Polymyositis (PM) are systemic inflammatory disorders affecting skeletal muscles and other organs.[4] Juvenile DM diagnosis is based on the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria.[5] This classification system involves age, symmetric proximal muscle weakness, characteristic skin changes:

Correspondence: Ayşenur Paç Kısaarslan, Erciyes University Faculty of Medicine, Pediatric Rheumatology,Kayseri, Turkey
E-mail: aysenurkisaarslan@hotmail.com

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heliotrope rash, Gottron sign and papules, elevation muscle enzymes, electromyographic changes, magnetic resonance, and muscle biopsy findings.[5,6] Polymyositis is uncommon in children and is defined by the absence of characteristic skin changes.[5,6] DM/PM is considered to be associated with high morbidity and mortality rates, in some cases as high as 50%, primarily related to life-threatening muscle weakness, cardiac and lung impairment, as well as infectious manifestations. Infectious complications that involved pyogenic and opportunistic infections have been described in 26-37.3% of DM/PM patients.[4] Several factors may be implicated in this apparent such as increased frequency of infections in DM/PM patients, particularly immunosuppressive medications. Due to DM/PM itself, immune system dysfunction may lead to elevated susceptibility to opportunistic infections. Three cases of pyomyositis with DM were reported in the literature since 1990's.[7-9]

Here we presented a patient with juvenile dermatomyositis complicated of staphylococcal pyomyositis after the initial disease course.

Case

A four-year-old girl was admitted to the hospital because of severe pain on extremities after an upper airway infection. She was diagnosed with post-infectious myositis and prescribed ibuprofen therapy. After ten days, her pain persisted, and she was referred to our rheumatology clinic with the chief complaint of severe pain, edema on extremities, and disabling walking. Upon presentation, she was afebrile with no other constitutional symptoms. On the physical examination, malar and heliotropic rash on her face, vasculitic rash on plantar faces of hands and feet, severe nonpitting edema on extremities were detected. Muscle strength was not determined because of the severe pain. Haemogram and blood smear were normal, CRP: 12.5 g/L, Erythrocyte Sedimentation Rate: 19 mm/h, AST: 42 IU/L, ALT: 80 IU/L; LDH:1007 IU/L, CK: 500 IU/L, immunoglobulins, C3, and C4 were normal, ANA:-, ANA subgroups:-, vWFAg: 183.7 (high level) were detected. EBV, CMV, Parvovirus, HIV, and hepatitis B, C serology were negative. A severe hyperintense signal at all of the girdle muscle on T2 weighted images was detected (**Figure 1**). Our patient was diagnosed with JDM based on the heliotrope rash, symmetric proximal muscle weakness, elevated muscle enzymes, and MRI findings. Her total diagnostic score was 9.4 according to the 2017 EULAR/ACR classification critera.[5] She was started prednisolone 2 mg/kg/d and methotrexate 15 mg/m^2/w. The CMAS (Childhood Myositis Assessment Scale, an assessment of muscle strength and the total score is 52), was detected 28 on the therapy's 5th day. After ten days of immunosuppressive therapy, we noticed localized tenderness, erythema, and swelling on the left gluteal side. An abscess formation was determined as 24*37*45 mm, and it was lied down posterior to the inferior of gluteus maximus muscle by repeated MRI (**Figure 2**). The pus was drained through guided needle aspiration on the first day of hospitalisation. A gram-stained preparation showed gram-positive cocci in clusters. The culture of the pus yielded methicillin-sensitive *S. aureus*. After 2 days later, clindamycin and gentamycin were added to ceftriaxone. The abscess formation was not regressed through a drainage tube and appropriate antibiotic therapy on the 14th day. IVIG, which was recommended for dermatomyositis therapy also, was infused as 1 gr/kg. The patient improved two days later, steroid and methotrexate therapies were continued. The abscess formation did not repeat.

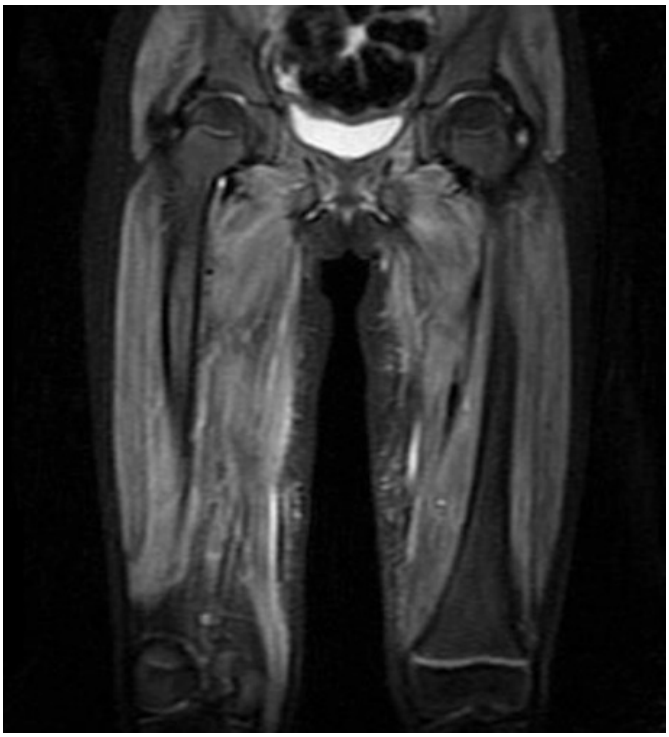

Figure 1. Hyperintense signal at all of the girdle muscle on T2 weighted images on MRI.

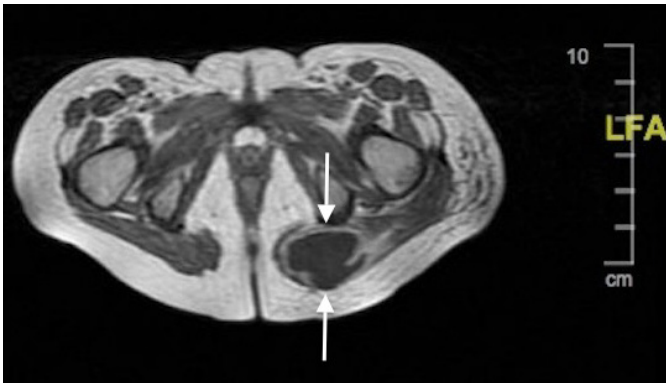

Figure 2. An abscess formation were determined as 24*37*45mm, and it was lied down posterior to inferior of gluteus maximus muscle by MRI.

Discussion

We presented a patient with dermatomyositis complicated of staphylococcal pyomyositis initial course of the disease.

Infectious complications are increasingly reported in connective tissue diseases. These are related to using immunosuppressive drugs and is related to organ dysfunctions caused by diseases. Marie et al.[4] reported that infectious complications had been described 37.3% in 279 DM/PM patients. The most common pyogenic infections are aspiration pneumonia and calcinosis cutis infections.[4]

Most of the reports on pyomyositis were in the 1990s and mostly reported from tropical areas, named ''Tropical myositis''. In recent years, PM has been more frequently diagnosed in immunocompetent children presenting with limping, even in temperate countries.[10] Infectious myopathies are mostly associated with immunocompromised conditions, especially HIV infection, diabetes mellitus, malignancy, immunosuppressive drugs, and rheumatic diseases.[11]

The clinical presentation of pyomyositis can be divided into three stages. The first stage is typically subacute, occurring over 1 to 3 weeks, with local swelling and ''woody'' texture, mild pain, and variable fevers. The diagnosis is often confused with thrombosis, hematoma, contusion, muscle strain, or osteomyelitis because the purulent collection has not yet developed. During the second or suppurative stage, which occurs at 10 to 21 days, tenderness and fevers become more pronounced. The diagnosis of pyomyositis is usually established in this stage. If the infection remains undiagnosed and untreated, intense local pain and fluctuance, systemic findings, sepsis will develop as part of the third stage of pyomyositis.[12]

In our patient, abscess formation was detected approximately 25 days after the onset of generalize muscle pain and ten days after immunosuppressive treatment. In the first MRI findings did not show abscess (**Figure 1**). Attempts to create pyomyositis in animal muscles challenged with intravenous injection of *S. aureus* failed to initiate the infection unless the muscles were traumatized by electric shock, pinching, or ischemia. These experiments confirm the skeletal muscle's high intrinsic resistance to bacterial infection and suggest that underlying muscle damage facilitates its onset.[13] Although there was no injection or trauma history, muscle inflammation and immunosuppressive therapy may have facilitated abscess formation in our patient.

The majority of cultures with infectious myositis were yielded *S. aureus*. Increased staphylococcal infections in childhood dermatomyositis were previously reported associated with calcinosis. We founded staphylococcal pyomyositis in one patient, streptococcal pyomyositis in two patients with DM in the literature[7-9] At last, Tuberculous pyomyositis was reported in SLE and DM patients in 2014.[14]

We present a patient with pyomyositis involved in the differential diagnosis of JDM. We think that pyomyositis developed as a complication in this case. JDM presents with clinically symmetrical proximal muscle weakness and muscle pain. However, pyomyositis should be kept in mind in the presence of local pain and other signs of inflammation.

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Late Diagnosed Argininemia

Author(s)

Sezai Arslan[1], Ümmü Alakuş Sarı[1], Banu Kadıoğlu Yılmaz[1], Fatih Kardaş[1], Füsun Ferda Erdoğan[2], Mustafa Kendirci[1]

Affiliation(s)

[1]Erciyes University Faculty of Medicine, Division of Pediatric Nutrition and Metabolic Diseases, Kayseri, Turkey
[2]Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkey

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Abstract

Ammonia; It is a toxic molecule for the central nervous system resulting from the catabolism of proteins. Its excretion is provided with the urea cycle. Argininemia is a rare subtype of urea cycle disorders. Arginase enzyme catalyzes the last stage of the urea cycle, arginine; urea and ornithine are broken down. The decrease in arginase 1 (ARG1) enzyme activity is responsible for argininemia. The most common presenting symptoms of patients diagnosed with argininemia are progressive spastic diplegia, regression in developmental stages, choreoathetosis, hepatomegaly and seizures. The diagnosis of the disease can be made by detecting the elevation of arginine in body fluids together with the increase in serum ammonia. Neurological findings of these patients can be confused with cerebral palsy. In this case report, we wanted to present a patient with argininemia who was followed up with a diagnosis of cerebral palsy for a long time. Early diagnosis, restricted protein and arginine diet are life-saving in this disease. Argininemia should be kept in mind in patients with unexplained neuromotor retardation.

Keywords: Argininemia, urea cycle disorders, cerebral palsy

Introduction

Cerebral palsy (CP) is the most common lifelong developmental disorder of childhood affecting movement and posture. CP is a non-progressive, permanent loss of motor function, posture and movement disorder which develops as a result of a developing fetus and lesion or injury in the brain in the first months of life. Motor retardation can often be accompanied by sensory, cognitive, behavioral disorders, epilepsy, and secondary musculoskeletal problems.[1,2]

Genetic and metabolic diseases may present with clinical features similar to the CP phenotype.[3] It is especially important to screen for treatable metabolic diseases. Some

Correspondence: Sezai Arslan, Mustafa Eraslan and Fevzi Mercan Children's Hospital, Köşk Mah. Prof. Dr. Turhan Feyzioğlu Cad. No:42 Melikgazi, Kayseri 38039, Turkey
E-mail: drsezai955@gmail.com

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of these metabolic diseases are urea cycle disorders (UCD), Glucose transporter 1 deficiency syndrome, monoamine neurotransmitter deficiency, biotinidase deficiency, mitochondrial diseases and organic aciduria. Ammonia, lactate, plasma/urine amino acid analysis, tandem mass spectrometry, urine organic acid analysis, cerebrospinal fluid examination are important in screening these diseases.

Ammonia is a toxic substance that occurs as a result of the catabolism of proteins in living things. Hyperammonemia can be mentioned when the plasma ammonia level is> 50 µmol/L (in newborns>100 µmol/L). Regardless of the underlying cause, if hyperammonaemia is not treated early and effectively, irreversible brain damage occurs.[4,5] The most common genetic cause of hyperammonemia in infants is UCD.

The removal of ammonia from the body by converting it into urea with various enzymes in the liver is called the urea cycle. It was first described by Krebsand Henseleit in 1932. Deficiencies of enzymes involved in the urea cycle cause hyperammonemia. Decreased Arginase 1 (ARG1) enzyme activity is blamed for argininemia. This enzyme takes part in the last step of the cycle and provides the conversion of arginine to urea and ornithine.[6,7]

The estimated prevalence of UCD is 1: 35000 live births. UCD are inherited autosomal recessively, except for ornithine transcarbamylase deficiency (x-linked). Urea cycle enzyme deficiencies usually show symptoms in the first days of life with the intake of protein foods. The main symptoms and signs of hyperammonemia in the neonatal period; refusal to feed, vomiting, tachypnea, convulsion, marked lethargy, stupor and coma. If appropriate treatment is not initiated, patients will rapidly deteriorate and will be lost with cardiovascular collapse, respiratory failure and renal failure.[5,8-10]

This case was presented to draw attention to the case of argininemia, which was followed up with a diagnosis of cerebral palsy for a long time and lost the chance of early diagnosis.

Case

Thirty two years old male patient presented with complaints of inability to walk, speak, and seizures. He was referred to our outpatient clinic by the adult neurology department with a pre-diagnosis of metabolic disease. The patient, whose neuromotor development was compatible with his peers until the age of seven, was impaired in walking and then speaking from this age. When the patient was fourteen years old, his speech stopped completely. He was wheelchair dependent when he applied to our outpatient clinic. It was also learned that the patient used valproic acid for epileptic seizures that started three years ago.

Although the birthweight of the patient was unknown, it was learned that he was born at term, cried and had no cyanosis. It was reported that his walking and talking were on time. There was no consanguinity between the parents. It was learned that there was no family member with similar complaints.

The weight: 26 kg (<3p), height: 125 cm (<3p) percentiles of the patient were found to be extremely low. His head circumfrence: 56 cm (16p) was normal. Vital signs were stable. In the physical examination of the patient, he was conscious and non-cooperative. Generalized hypertonicity was noted, along with an extremely weak body structure. There were flexion contractures affecting all four extremities (**Figure 1**). Therefore, deep tendon reflexes, clonus and babinski could not be evaluated clearly. No hepatomegaly was detected in the abdominal examination. It was normal in other system examinations.

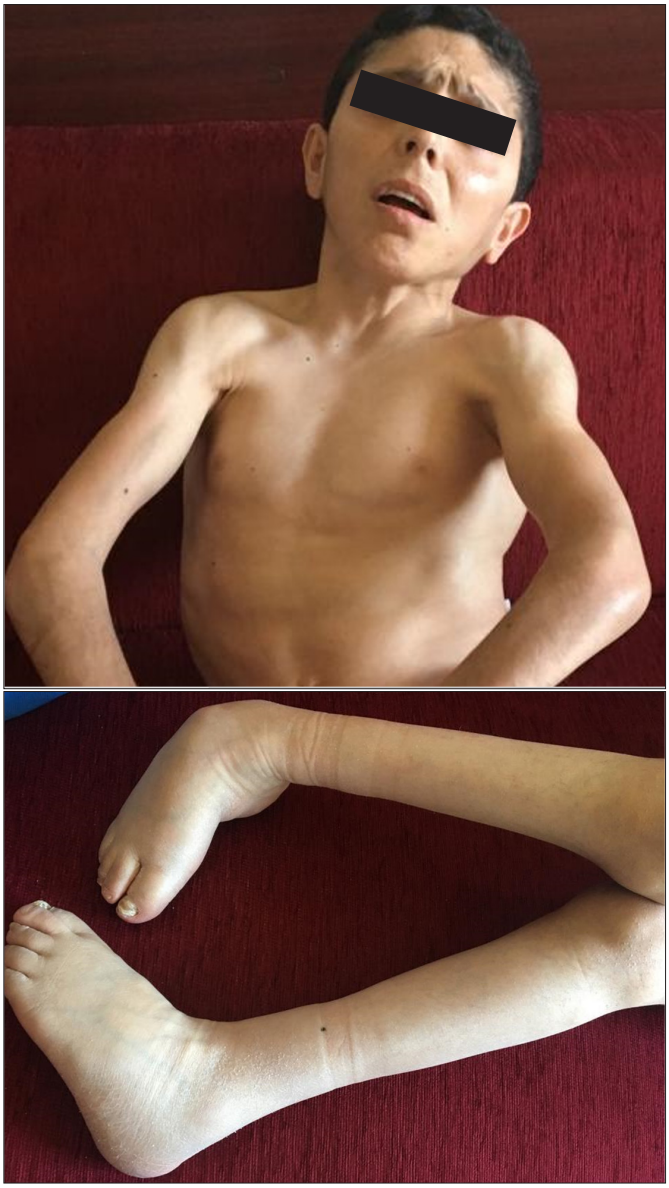


Figure 1. Bilateral spastic paraplegia view of the patient with argininemia

In the basal laboratory tests of the patient, hemogram, thyroid function tests, vitamin B12 and folic acid levels were normal. In other biochemical tests, increased ALT: 115 U/L (0-41) level and normal range AST: 37 U/L (0-40) and CK: 162 U/L (40-170) were detected. Serum valproate level was not measured. In the metabolic tests of the patient, ammonia: 154 µmol/L (N: 50-80) level was found to be high. It was also observed that arginine levels were significantly increased in plasma and urine amino acid analysis (**Table 1**).

Table 1.
His metabolic test results show high levels of arginine in tandem MS and plasma/urine amino acid analysis.

Tandem MS (umol/l)	Arginine 477 (6-60)
Tandem Acyl Carnitine analysis	Normal
Plasma amino acid analysis (nmol/ml)	Alanine 141 (200-483), Proline 66 (104-383), Isoleucine 15 (34-98), Threonine 43 (67-198), Leucine 35 (73-182), Tryptophan 23 (40-91), Lysine 59 (119-233), Tyrosine 30 (38-96), Phenylalanine 28 (40-74), Valine 56 (132-313), Arginine 650 (43-407)
Urine amino acid analysis (mmol/molkre)	Sitrulin 4 (0-2), Ornitin 13 (0-4), Arginine 55 (0-5)
Urine organic acid analysis	Normal

In the cranial magnetic resonance imaging of the patient, dilatation in the third and lateral ventricles with frontoparietal region were detected in atrophic appearance (**Figure 2**). A left-facing scoliosis deformity was observed on chest tomography, other structures were normal. There was extremely scoliosis in the direct X-ray (**Figure 3**). Multifocal epileptic activity disorder was observed in the electroencephalogram examination. Eye examination was normal.

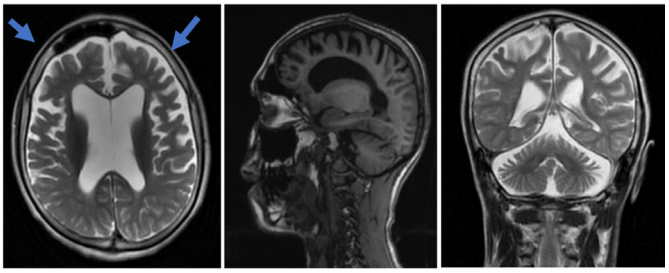


Figure 2. Cranial MR images of the patient with argininemia; significant atrophy in frontoparietal regions of the brain

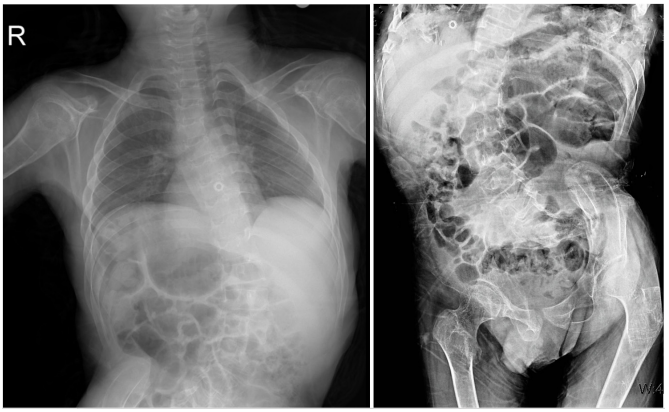
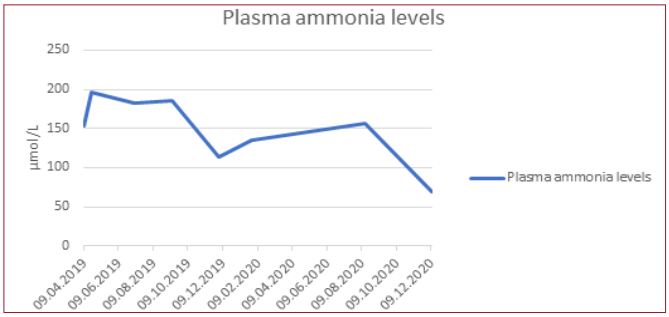


Figure 3. Excessive scoliosis appearance was detected in the X-ray image of the patient

A homozygous mutation in the ARG1 gene c.703_707del (p.Gly235ArgfsTer20) was detected in the genetic examination requested to confirm the diagnosis of argininemia. It was reported that this mutation was considered a pathogenic variant due to the frame shift and early stop codon that was previously described and reported to be associated with the disease.

As a result, our patient was diagnosed with arginemia. Protein and arginine restricted diet was started. Sodium benzoate and sodium phenylbutyrate were initiated for hyperammonemia. In addition, the valproic acid used by the patient for epileptic seizures was replaced with levatiracetam. With the treatment, the patient's liver function tests (AST, ALT) returned to normal. A significant decrease was observed in serum ammonia level (**Graphic 1**). In the 20-month follow-up, the agitation of our patient decreased significantly and he seemed happier in the control examinations.



Graphic 1. Ammonia measurements in the argininemia patient's follow-up

Discussion

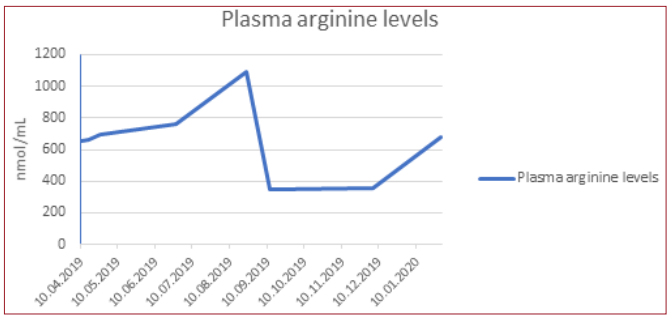
The clinical manifestations of UCD can occur at any age, with hyperammonemic crises being frequently triggered by catabolic events, protein overload or certain drugs. Most symptoms are neurological but nonspecific.[8] Arginase deficiency, which is among this group of diseases, has been reported much less frequently (1:950000).[9] Rapid-onset hyperammoniemia attacks are not characteristic for argininemia, they follow a slower clinical course. It may often present with growth retardation and pronounced progressive spasticity in the lower extremities. Seizures, loss of intellectual gains, irritability, growth retardation, vomiting and anorexia can be observed.[11] The arginase enzyme activity of our patient could not be measured, but it was thought that the reason for the slow clinical course may be related with the partial enzyme deficiency.

In the literature, cases with CP findings and diagnosed with argininemia have been reported. In 2020, four years old boy of a Turkish family with psychomotor retardation and walking difficulties were referred to our clinic with the diagnosis of cerebral palsy. In the genetic analysis, the diagnosis of argininemia was confirmed by detecting the homozygous novel mutation in the ARG1 gene.[12] A Korean case presented with attention deficit hyperactivity symtomps and progressive fingertip walking and was diagnosed at the age of eleven.[13] In arginase deficiency, arginine and its metabolites (such as guanidoacetate) as well as ammonia are considered to be toxic.[8] In our case, both ammonia and plasma arginine levels were found to be high (**Graphic 1, Graphic 2**).

The urea cycle disorder argininemia is caused by a defective ARG1 enzyme resulting from mutations in the ARG1 gene. Brazil, China and Turkey, the most common mutations are clustered geographically (p. Thr134Ileu, p. Gly235Arg and p. Arg21) have been identified. An even more severe effect was observed for the mutation

p. Gly235Arg.[15] In our patient, in accordance with the literature, homozygous deletion has been detected affecting the p. Gly235Arg region.[16]

In 1979, Synderman et al. reported an argininemia case diagnosed in the neonatal period due to the diagnosis of metabolic disease in one of siblings. Arginine and protein restricted diet was started in the early period. When the age of the patient was 32 months, it was evaluated as physically, neurologically and mentally normal.[14] In our case, it is seen that the delay in diagnosis is quite long. It is obvious that the neuromotor development of our patient will be better with the chance of diagnosis at an earlier age. However, despite the presence of significant psychomotor retardation, ourpatient's agitation decreased significantly after a protein and arginine restricted diet.



Graphic 2. Arginine measurements in the argininemia patient's follow-up

Conclusion

It is important to keep in mind argininemia, especially in cases of unexplained neuromotor retardation and spastic diplegia that occur with age. Favorable results can be obtained in patients who use arginine-restricted diet and ammonia-lowering drugs in the early period of their lives.

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