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Research

Erysipelas-like Erythema: A Pathognomonic Rash in Children with Familial Mediterranean Fever

Erizipel Benzeri Eritem: Ailevi Akdeniz Ateşi Tanılı Çocuklarda Patognomonik Bir Döküntü

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is the most common genetic autoinflammatory disease presenting as recurrent fever episodes, and inflammation of serosal surfaces, joints, and skin. During attacks, erysipelas-like erythema (ELE) may occur on the dorsum of the foot, ankle, or lower leg. Although the skin involvement is less common, ELE is pathognomonic. We aimed to review the frequency and characteristics of ELE in children diagnosed with FMF and to identify genotypic and phenotypic differences between patients with and without ELE, if any.

Methods: This study included children aged 0-18 years diagnosed with FMF followed up by two tertiary pediatric rheumatology units. The data were collected by two pediatric rheumatology fellows from the patients' files and electronic records. We divided the cohort into two groups according to whether they had ELE. Those with ELE were included in group 1 and those without ELE were in group 2.

Results: Two thousand-three patients participated in the study. There were 197 (9.8%) patients with ELE in group 1 and 1806 (90.1%) patients without ELE in group 2. The mean age of onset of symptoms in group 1 was significantly lower than in group 2 [4.85 (minimum-maximum: 0.1-17) vs. 5.98 (minimum-maximum: 0.1-17) years, p<0.001]. The median age at diagnosis was significantly higher in group 1 [8 (0.6-18) vs. 6 (0.5-18) p<0.001]. The diagnostic delay time was 24 months in group 1, 13 months in group 2, and the duration was significantly longer in group 1 [24 (0-150) vs. 13 (0-192) p<0.001]. M694V homozygosity was more frequent in group 1 [n=116 (58.9%), n=484 (26.8%), p<0.001].

Conclusion: Because ELE is an uncommon clinical presentation, clinicians should be alert. The clinical course of patients presenting with ELE may have a more severe disease course.

Keywords: Familial Mediterranean fever, erysipelas-like erythema, genotype

ÖZ

Amaç: Ailevi Akdeniz ateşi (AAA), periyodik ateş atakları ile karakterize, ataklarda serozal yüzeyler, eklemler ve deride enflamasyonun görüldüğü, en yaygın monogenik otoenflamatuvar hastalıktır. Ataklar sırasında ayak sırtında, ayak bileğinde veya alt bacakta erizipel benzeri eritem (ELE) oluşabilir. Deri bulguları daha nadir görülmekle birlikte, ELE AAA atağı için patognomonik bir bulgudur. Bu çalışma ile, pediatrik AAA hastalarından oluşan geniş bir kohortta ELE'nin sıklığını ve özelliklerini gözden geçirmeyi, ELE bulgusu olan ve olmayan hastalar arasındaki genotipik ve fenotipik farklılıkları belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya iki üçüncü basamak pediatrik romatoloji ünitesinde izlenen AAA tanısı ile takip edilen, 0-18 yaş aralığındaki çocuklar dahil edildi. Veriler, iki pediatrik romatoloji uzmanı tarafından hasta dosyalarından ve elektronik kayıtlardan toplandı. Hastalar ELE bulgusu olan ve olmayanlar şeklinde iki ana gruba ayrılarak değerlendirildi.

Bulgular: İki bin üç hasta çalışmaya dahil edildi. Grup 1'de ELE bulgusu olan 197 (%9,8) hasta varken grup 2'de ELE bulgusu olmayan 1806 (%90,1) hasta vardı. Grup 1'de ortalama semptom başlama yaşı daha küçük iken, ortanca tanı yaşı anlamlı olarak daha büyüktü [4,85 (minimum-maksimum: 0,1-17) vs. 5,98 (minimum-maksimum: 0,1-17) yaş, p<0,001; 8'e (0,6-18) karşı 6 (0,5-18) p<0,001]. Tanı gecikme süresi grup 1'de 24 ay, grup 2'de 13 ay ve grup 1'de anlamlı olarak daha uzundu [24 (0-150) vs. 13 (0-192) p<0,001]. Gruplar genotip açısından karşılaştırıldığında M694V homozigotluğu grup 1'de anlamlı olarak daha fazlaydı [n=116 (%58,9), n=484 (%26,8), p<0,001].

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Sonuç: ELE nadir görülen bir klinik bulgu olduğu için, klinisyenlerin farkındalığının yüksek olması önemlidir. ELE ile başvuran hastalar daha şiddetli bir hastalık seyrine sahip olabilir ve erken tanı önem arz etmektedir.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, erizipel benzeri eritem, genotip

INTRODUCTION

Familial Mediterranean fever (FMF) is one of the most common inherited periodic fever syndromes among people of Mediterranean and Middle Eastern descent. The main features of the disease are fever, abdominal pain, and arthritis or erysipelas-like skin disease (1). The major features of FMF are recurrent fever, abdominal pain, and arthritis or erysipelas-like skin disease (2). Abdominal pain may occur abruptly before the fever, mimic appendicitis, and is accompanied by diarrhea. Monoarthritis is asymmetrical, comprises the ankle, knee, or wrist joint, and usually resolves within 5 to 14 days. An erysipelas-like erythema (ELE) is found on approximately 25% of the affected joint, and sometimes clinicians misdiagnose it as septic arthritis. The rash is especially unilateral and disappears in almost 2 to 3 days (3).

Various cutaneous manifestations have been noted in the literature in 25% to 47% of cases during attacks (4). Several types of skin lesions were associated with FMF, although ELE is an unusual but well-known pathognomonic and characteristic finding of FMF. Lesions are characterized by erythematous, tender, and warm plaques with bounded borders, usually triggered by physical effort. They may be mainly located on the dorsum of the foot, lower legs, and the medial malleolus (5). Fever and leukocytosis may accompany ELE and spontaneously subsides within 48 to 72 hours of bed rest. Apart from ELE, several skin manifestations have been described. These include diffuse erythema, urticaria, angioneurotic edema, mild desquamation, pyoderma, Raynaud phenomenon, subcutaneous nodules, and vasculitic skin lesions (6).

There is a remarkable lack of information about the characteristics of ELE in children with FMF. Since it is a pathognomonic skin lesion, it is crucial to define it in clinical practice and diagnostic approaches. We aimed to review the frequency and characteristics of ELE in a large pediatric FMF cohort and to identify genotypic and phenotypic differences between patients with and without ELE, if any.

METHODS

The study included children 0-18 years of age diagnosed with FMF who met at least one Tel-Hashomer or Eurofever/PRINTO 2019 diagnostic criteria and carried at least one mutation in exon 2, 3, 5, or 10 in the MEFV gene (7). We obtained data from the archives of two tertiary pediatric rheumatology units.

Patients' files and electronic records were evaluated by two pediatric rheumatology fellows. Clinical manifestations and laboratory features during attacks, attack-free periods, attack frequency, colchicine dose, family history of FMF and amyloidosis, parental consanguinity, genetic test results, treatments used, and presence of colchicine resistance were evaluated in detail.

All patients were receiving colchicine treatment. The dose of the colchicine regimen was 0.5 mg/day in patients <5 years, 1 mg/day in patients >5, <10 years, and 1.5 mg/day in patients >10 years. Children with prior complications (e.g., amyloidosis) or higher disease activity were given 2 mg of colchicine daily. Patients with subclinical inflammation and having one or more attacks per month (for at least three months) despite treatment with the maximum tolerable colchicine dose (for at least six months) were defined as colchicine-resistant (8). In colchicine-resistant children, anti-IL1 (anakinra, canakinumab) treatments were added to the existing treatment.

In the cohort, group 1 had patients who had experienced ELE during attacks and group 2 had patients who had never experienced ELE.

The study was approved by the Local Ethical Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 19, date: 21.08.2020).

Statistical Analysis

Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS 28.0 (IBM, Armonk, NY) were used while collecting and analyzing the data. Visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were used to determine whether the variables were normally distributed. Descriptive analysis was presented using proportions, medians, minimum (min), and maximum (max) values. Categorical data were statistically analyzed by chi-square analysis. Mann-Whitney U test was used to compare the non-normally distributed variables between the two independent groups. P values <0.05 were considered statistically significant.

RESULTS

A total of 2003 children were enrolled in the study. Nine hundred eighty-seven (49.2%) patients were male and 1016 (50.7%) were female. The median age at symptom onset was 4 (min-max: 0.1-17) years and the median age of diagnosis was 6 (0.5-18) years. Six hundred fifty (32.5%) patients had parental consanguinity. A family history of FMF was present in 1216 (60.6%) patients and a history of amyloidosis in 153 (7.6%) patients.

In the cohort, 197 (9.8%) patients were in group 1 and 1806 (90.1%) patients were in group 2. Demographic and clinical data of the groups were depicted in Table 1. There were 112 (56.9%) females in group 1 and 904 (50.1%) females in group 2, and the gender distribution was similar in both groups (female n=56.9 vs. 50.1%; male n=43.1 vs. 49.9% p=0.07). The mean age at onset of symptoms in group 1 was significantly lower than in group 2 [4.85 (min-max: 0.1-17) vs. 5.98 (min-max: 0.1-17) years, p<0.001]. The median age at diagnosis was significantly higher in group 1 [8 (0.6-18) vs. 6 (0.5-18) p<0.001]. The diagnostic delay duration was 24 months in group 1 and 13 months in group 2, and the duration was significantly longer in group 1 [24 (0-150) vs. 13 (0-192) p<0.001]. The prevalence of family history of amyloidosis and FMF was similar between the groups.

The annual number of attacks was evaluated and it was similar in both groups (12 vs. 12, p=0.76). When attack symptoms were evaluated; fever and abdominal pain were more frequent in group 2 [n=149 (75.6%) vs. n=1663 (92.1%), p<0.001; n=1153 (77.7%) vs. n=1672 (92.6%), p<0.001 respectively]. Chest pain, arthralgia, arthritis, persistent febrile myalgia, exercise-induced leg pain, and myalgia were significantly more frequent in group 1 [n=47 (23.9%) vs. n=318 (17.6%), p=0.03; n=164 (83.2%) vs. n=639 (35.4%), p<0.001;

Table 1. The demograhic and clinical characteristics of the patients

		Patients with erysipelas-like erythema (n=197)	Patients without erysipelas-like erythema (n=1806)	p-value
Demographic features				
Gender Female Male		112 (56.9) 85 (43.1)	904 (50.1) 902 (49.9)	0.07
Age of onset (years)	Min-max (mean)	0.1-17 (4.85)	0.1-17 (5.98)	<0.001
Age of diagnosis (years)	Min-max (median)	0.6-18 (8)	0.5-18 (6)	<0.001
Delay in diagnosis (months)	Min-max (median)	0-150 (24)	0-192 (13)	<0.001
Diagnosis of FMF in family	n (%)	118 (59.9)	1096 (60.7)	0.83
Diagnosis of amyloidosis in family	n (%)	21 (10.7)	132 (7.3)	0.93
Clinical features				
The annual number of attacks	Min-max (median)	0-48 (12)	0-48 (12)	0.76
Fever	n (%)	149 (75.6)	1663 (92.1)	<0.001
Abdominal pain	n (%)	153 (77.7)	1672 (92.6)	<0.001
Chest pain	n (%)	47 (23.9)	318 (17.6)	0.031
Arthralgia	n (%)	164 (83.2)	639 (35.4)	<0.001
Arthritis	n (%)	142 (72.1)	296 (16.4)	<0.001
Persistant febril myalgia	n (%)	9 (4.6)	24 (1.3)	0.01
Pericarditis	n (%)	4 (2)	11 (0.6)	0.052
Exertional leg pain	n (%)	81 (41.1)	288 (15.9)	<0.001
Myalgia	n (%)	81 (41.1)	366 (20.3)	<0.001
Amyloidosis	n (%)	1 (0.5)	5 (0.3)	0.46
Colchicine resistance	n (%)	18 (9.1%)	89 (4.9%)	0.013

FMF: Familial Mediterranean fever, Min-max: Minimum-maximum

n=142 (72.1%) vs. n=296 (16.4%), p<0.001; n=9 (4.6%), n=24 (1.3%) p=0.01; n=81 (41.1%), n=288 (15.9%), p<0.001; n=81 (41.1%), n=366 (20.3%), p<0.001; respectively]. Pericarditis was observed with similar frequency in both groups [n=4 (2%) vs. n=11 (0.6%), p=0.052].

All patients received colchicine therapy, and colchicine resistance was significantly more common in group 1 [n=18 (9.1%) vs. n=89 (4.9%), p=0.013]. When the genotype of patients was compared, M694V homozygosity was more common in group 1 [n=116 (58.9%), n= 484 (26.8%), p<0.001].

DISCUSSION

In this study, ELE was detected as a relatively uncommon finding in a large cohort of FMF, but it was a distinctive presentation. While the most common findings in typical FMF attacks were abdominal pain and fever, they were less frequent in those with ELE compared with others. The age of the onset of symptoms was lower and the age of diagnosis was higher in the ELE group. Since the diagnostic delay is longer, we can assume that it is more challenging to diagnose FMF in the ELE group. Exertional leg pain, arthralgia, myalgia, and persistent febrile myalgia, which are not among the classification criteria, were more common in the ELE group. The reason for the delay in diagnosis may be attributed to the fact that the patients presenting with these findings did not fulfill the diagnostic criteria. Since M694V homozygosity is more common in the ELE group, a delay in diagnosis is definitely not desired because homozygous cases have a more severe clinical course (9). It is crucial to reveal the phenotypic and genotypic characteristics of patients with ELE in terms of difficulty in diagnosis, delay in diagnosis, and prevention of morbidity.

In previous reports, ELE is notably associated with a more severe FMF clinical phenotype, M694V homozygosity, and even amyloidosis (6,10,11). Avar-Aydın et al. (10) revealed higher frequencies of biallelic exon 10 and homozygous M694V mutations in patients with ELE. They also reported that subclinical inflammation was more common in the ELE group and that patients presenting with ELE received higher doses of colchicine (10). Gezgin Yildirim et al. (12) evaluated the genotype in both groups with or without ELE and reported that M694V homozygosity was more common in the ELE group, similar to our study. They also revealed that the median colchicine dose and PRAS activity scores were higher at the final visit in patients with ELE (12). The fact that genotypic correlations associated with severe clinical courses are more common in patients presenting with ELE indicates that this patient group is a candidate for a more severe disease course. For this reason, it is essential to be vigilant in the diagnosis and follow-up of these patients. In a recent study, a novel model was built, and ELE was scored as 2 points in the scoring system to predict colchicine resistance in children with FMF (13).

ELE is an unusual but well-known pathognomonic skin manifestation of FMF (5). ELE is more common in the Turkish population and in the early phase of the disease course (11). In our cohort, the median age at diagnosis was 8 years in patients with ELE. Lesions resemble erysipelas or cellulitis, and differential diagnosis may be difficult in patients without unique clinical findings during an attack. Some features that distinguish ELE from other infectious diseases are as follows; the duration is shorter (average 4 days), it is not always accompanied by fever, it can be seen in both feet at the same time and heals spontaneously (14). When the lesion can not be distinguished from a lesion of infectious origin erysipelas, family history of FMF, detailed history of the patient, and recurrent course of the disease gain importance. In our cohort, nearly 60% of patients presenting with ELE had a family history of FMF. Being able to recognize clues during follow-up enables an early diagnosis and appropriate treatment. The delay in diagnosis was longer in the group presenting with ELE in our cohort. If we raise the awareness of pediatricians, it may influence timely diagnosis.

In this cohort, we found a similar rate of ELE (9.8%) compared to pediatric studies in our country (9,10,12,15). Öztürk et al. (15) reported abdominal pain and fever as the most common attack symptoms in their cohort. In our cohort, the rates of these symptoms were slightly higher in patients not presenting with ELE and lower in patients presenting with ELE. As reported in the literature, arthritis was more common in patients presenting with ELE in our study (10,12). In addition, arthralgia, myalgia, and prolonged febrile myalgia were also more common in the ELE group in the current study.

The retrospective design was the major limitation. There were missing data on disease severity assessment tools and acute phase reactants. Despite these, it was the largest cohort of pediatric FMF patients assessed for the presence of ELE.

CONCLUSION

ELE is an uncommon clinical presentation, and patients presenting with ELE may have different phenotypic and genotypic characteristics. We should be alert and keep in mind that the clinical course of patients presenting with ELE may have a more severe disease course. A detailed history and comprehensive physical examination are required for an accurate and timely diagnosis.

ETHICS

Ethics Committee Approval: The study was approved by the Local Ethical Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 19, date: 21.08.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: F.Ç., S.D.A., G.K.K., Ş.Ç., K.U., T.C., A.T., B.S., N.A.A., Concept: F.Ç., B.S., N.A.A., Design: F.Ç., N.A.A., Data Collection or Processing: F.Ç., S.D.A., G.K.K., Ş.Ç., K.U., T.C., A.T., Analysis or Interpretation: F.Ç., S.D.A., G.K.K., Ş.Ç., K.U., T.C., Literature Search: F.Ç., Writing: F.Ç., N.A.A.

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