Erysipelas-like erythema in children with familial Mediterranean fever

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ABSTRACT

Objective. *Erysipelas-like erythema (ELE) is a well-known pathognomonic skin lesion associated with familial Mediterranean fever (FMF). The aim of this study was to describe the clinical and demographic features and phenotypic differences between paediatric FMF patients with and without ELE.*

Methods. *We retrospectively collected the medical charts of paediatric patients who had been diagnosed with FMF and followed by the Paediatric Rheumatology Department of Gazi University, Turkey, from 2006 to 2016.*

Results. *Among 782 FMF patients, 59 (33 males and 26 females; median age, 11.1±5.1) were found to have ELE. More patients had arthritis in the ELE group than in the other group (p=0.011). Arthritis occurred in the ankle (77.4%), knee (19.3%) and hip (3.2%) joints. The coexistence of arthritis and ELE was seen in 12 (20.3%) patients. All ELE plaques were located on the lower legs and dorsum of the feet. Eleven patients (18.6%) presented with ELE as the initial symptom and were diagnosed with FMF, and 48 (81.4%) patients experienced ELE attacks while receiving colchicine therapy. The median dose of colchicine at last visit, PRAS activity score and M694V homozygous mutation status were significantly higher in the ELE group than in the other group (p=0.041, p=0.001 and p=0.023, respectively).*

Conclusion. *ELE is an uncommon but important feature of FMF. In patients with ELE, arthritis is more frequently encountered, and M694V homozygous mutation is more frequently found. FMF patients with ELE have more severe disease activity, and they use higher doses of colchicine in relation to this severe disease course.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive inherited autoinflammatory disorder that is characterised by recurrent episodes of fever, pleuritis, pericarditis, peritonitis, arthritis or erysipelas-like erythema (ELE). The attacks are self-limiting and typically resolve within 24-72 hours (1). ELE is a well-known pathognomonic skin lesion associated with FMF, characterised by erythematous, warm and tender plaques sized 10–15 cm^2 that are usually located on the lower legs and the extensor surfaces of the feet. ELE may be triggered by physical activity and fades within 48–72 hours with bed rest. The histopathological features of ELE include sparse superficial perivascular and interstitial lymphocytic and neutrophilic infiltrations with mild papillary dermal oedema but no vasculitis (2).

ELE has rarely been reported, especially in the paediatric population of FMF patients. The aim of this study was to describe the clinical and demographic features and phenotypic differences between paediatric FMF patients with and without ELE. The study also aimed to analyse the frequency and characteristics of ELE in children who have FMF.

Material and methods

We retrospectively collected the medical charts of 782 paediatric FMF patients (aged ≤16 years), who had been diagnosed with FMF according to the clinical criteria (3) and followed at Gazi University's Department of Paediatric Rheumatology, Turkey, from 2006 to 2016. Fifty-nine (7.5%) of these patients had experienced an ELE attack. We recorded the following for each patient: age, gender, birthplace, age of onset of symptoms, age of diagnosis,

delay time between onset of symptoms and diagnosis, Mediterranean fever (MEFV) gene analysis, and dose of colchicine at last visit; the presence of fever, peritonitis, pleuritis, pericarditis, arthralgia, arthritis, ELE, amyloidosis, or accompanying vasculitis; the duration and the frequency of attacks; and the Pras activity scores (4). The Pras activity score evaluates the severity of the disease with scores of 2-5 for those having mild activity, 6–10 for moderate activity, and >10 for severe activity. All patients received colchicine therapy. The starting dose of colchicine was 0.25-0.5 mg/day for children ≤5 years of age and 1.0 mg/day for children >6 years of age. The colchicine dose was gradually increased (0.25 or 0.5 mg/step) up to a maximum of 2.0 mg/day to control disease in patients who did not clinically respond to the starting dose. ELE was treated with non-steroidal anti-inflammatory drugs (NSAIDs) and bed rest.

MEFV gene analysis had been performed on all of the patients. Evaluations of the MEFV genes were analysed from ethylenediaminetetraacetic (EDTA) tubes at the Nephrology and Tissue Laboratory at Gazi University Medical Faculty. Polymerase chain reaction (PCR) work-ups, which are shown with the pyrosequencing DNA analysis system, demonstrated the 2, 3, 5 and 10 exons of the MEFV gene. The 12 MEFV mutations were all analysed, including A744S, E148Q, F479L, I640M, K695R, M680I (G/C), M680I (G/A), M694I, M694V, P369S, R761H and V726A.

The statistical data were evaluated using the SPSS program version 15.0. Descriptive values were specified as "number" and "percent". Variables were defined as mean ± standard deviation or median (minimum-maximum) according to the distribution of the data. The *t*-test was applied to evaluate the parametric distribution of the data, while Mann-Whitney U-test was applied to evaluate the non-parametric distribution of the data. Comparison of the categorical variables was done using the chi-square test. $p<0.05$ was considered to be statistically significant. The present study was approved by the Gazi University Medical Faculty of Local Ethics Committee (13.02.2017, approval number: 12).

Results

Table I displays the characteristics and demographic features of the FMF patients who had ELE and those who did not. The male to female ratios were 33:26 in patients with ELE and 334:389 in those without ELE. The family history in patients with and without ELE were similar ($p=0.47$). There were no significant differences between the two groups in the frequencies of attacks, which included abdominal pain ($p=0.093$), chest pain ($p=0.42$) and arthralgia ($p=0.076$). However, significantly more patients in the ELE group had arthritis than in the other group ($p=0.011$). Arthritis was essentially oligoarticular and occurred in the ankle (77.4%), knee (19.3%) and hip (3.2%) joints in the ELE group. The coexistence of arthritis and ELE, known as 'red arthritis', was seen in 12 (20.3%) patients. All ELE plaques were located on the lower legs and dorsum of the feet. Unilateral ELE lesions were seen in 57 (96.5%) patients, and bilateral lesions were seen in two (3.5%) patients. Eleven patients (18.6%) presented with ELE as the initial symptom and were then diagnosed with FMF, while 48 (81.4%) patients experienced ELE attacks while receiving colchicine therapy. The prevalence of fever in patients with ELE was significantly lower than in the other group ($p=0.044$). The median dose of colchicine at last visit was higher in the ELE group than in the other group ($p=0.041$). The Pras activity score was significantly higher in the ELE group than in the other group ($p=0.001$). Only two (0.3%) patients had renal amyloidosis, and they had not experienced an ELE attack. Table II provides a comparison of the data for the MEFV analysis; and M694V homozygous mutation status was significantly higher in the ELE group than in the other group ($p=0.023$).

Discussion

This study established that ELE is an uncommon but important feature of FMF. Arthritis was frequently encountered in patients with ELE, and M694V homozygous mutation was more frequently found in patients with ELE. Furthermore, our data showed that severe disease activity was more common in patients with ELE than in those without ELE and that FMF patients with ELE were using higher doses of colchicine as a result of this severe disease course.

ELE is mostly seen on the anterior side of the ankle and the dorsum of the foot (2). Koné-Paut *et al*. described multiple ELE lesions over the face, trunk and limbs of FMF patients (5). Lidar *et al*. reported adult FMF patients whose ELE lesions were located on the ankle, distal shin, and dorsum of the feet of the lower extremities (6). In our cohort, all the ELE plaques were located on the lower legs and dorsum of the feet. We observed bilateral ELE lesions in only two (3.5%) patients; in the remaining patients, the ELE lesions were located unilaterally. In several studies, the frequency of ELE among FMF cohorts was reported as varying from 3%-46% (7-9). In our cohort, ELE was determined in 7.5% of the patients, which is compatible with the literature. This study is also the first to investigate gender in a paediatric ELE group; the male to female ratio was found to be 1.3 among 59 FMF patients. Lidar *et al*. reported a male to female ratio of 1.6 among eight adult FMF patients with ELE (6). Family histories should be examined for the presence of FMF. Our study was the first to investigate the presence family histories for FMF in patients with and without ELE, but no differences were found.

The M694V homozygous mutation is responsible for the most severe clinical phenotype of FMF (9). The association between ELE and M694V homozygosity, which was previously reported, is consistent with the present study (5). We established no relationship in the MEFV mutations other than the M694V homozygosity between patients with and without ELE. ELE is, therefore, an important feature of FMF that is commonly seen with M694V homozygosity, which shows a severe clinical presentation. This result suggests that M694V homozygous muta-

Table I. Comparison of FMF patients with and without ELE.

Variable	FMF patients with ELE		FMF patients without ELE		*p*-value
	n (%)	median (min–max) mean ± SD	n (%)	median (min–max) mean ± SD	
Total	59 (100%)		723 (100%)		
Males	33 (56%)		334 (46%)		0.15
Females	26 (44%)		389 (54%)		
Median age of present time (years)		11.1 ± 5.1		11.3 ± 4.5	0.67
Median age of onset symptoms (months)		55.9 ± 4.4		58.4 ± 1.1	0.54
Median age of diagnosis (years)		7.8 ± 4.6		8.2 ± 3.9	0.56
Median age of delay time to diagnosis (months)		23.0 ± 3.6		21.3 ± 0.7	0.55
Family history positivity on 1st, 2nd or 3rd relatives	27 (46%)		341 (47%)		0.47
Attack frequency at diagnosis					
<2 attacks per year	24 (41%)		319 (44%)		0.35
>2 attacks per year	35 (59%)		404 (56%)		
Median duration time of attacks					
<24 hours	12 (20%)		156 (21%)		0.75
24-48 hours	23 (39%)		308 (43%)		
>48 hours	24 (41%)		259 (36%)		
FMF symptoms					
Abdominal pain	45 (76%)		607 (84%)		0.093
Fever	38 (64.4%)		551 (76.2%)		**0.044**
Arthralgia	39 (66.1%)		391 (54%)		0.076
Arthritis	31 (52.5%)		260 (35.9%)		**0.011**
Chest pain	7 (12%)		75 (10%)		0.42
Median dose of colchicine (mg/day)		1.5 (0.5-2)		1 (0.25-2)	**0.041**
Median of PRAS activity score		7.4 ± 1.6		5.1 ± 1.3	**0.001**
Co-existent diseases (%)					
IgA vasculitis	3 (5%)		18 (2.4%)		0.78
JIA	1 (1.6%)		9 (1.2%)		
PAN	0 (0%)		2 (0.02%)		
Kawasaki disease	0 (0%)		1 (0.01%)		

FMF: familial Mediterranean fever; ELE: erysipelas-like erythema; IgA: immunoglobulin A; JIA: juvenile idiopathic arthritis; PAN: polyarteritis nodosa.

tion might be played an additional factor for the development of ELE in FMF patients.

Previous reports noted lower fevers associated with ELE (6), and we found remarkably lower fevers in patients with ELE than in those without ELE. Lower fever could be an effect of colchicine, since doses are higher in this group. Cefle *et al*. reported higher rates of ELE lesions in FMF patients with amyloidosis than without amyloidosis (10). It was not appropriate to assess the relationship between amyloidosis and ELE in our study because of the small number of patients who had amyloidosis. Findings already exist in terms of ELE and ankle arthritis, and a greater frequency of arthritis was seen in our ELE group, which is compatible with the literature (5). We observed oligoarticular type arthritis in the ankle (77.4%), knee (19.3%) and hip (3.2%) joints. However, there were no differences between patients with and without ELE in terms of the presence of abdominal pain and chest pain.

Table II. The comparison of MEFV analysis of patients with and without ELE.

MEFV mutation of patients with ELE n=59	(100%)	MEFV mutation of patients without ELE n=723	(100%)	*p*-value
M694V/M694V	14 (23.7%)	M694V/M694V	95 (13.1%)	**0.023**
M680I/M680I	1 (1.6%)	M680I/M680I	19 (2.6%)	0.662
M694V/-	17 (28.8%)	M694V/-	227 (30.9%)	0.680
M680I/-	6 (10.1%)	M680I/-	68 (9.4%)	0.909
M694V/M680I	3 (5%)	M694V/M680I	34 (4.7%)	0.894
E148Q/E148Q	1 (1.6%)	E148Q/E148Q	9 (1.2%)	0.767
E148Q/-	4 (6.7%)	E148Q/-	60 (8.2%)	0.682
E148Q/V726A	1 (1.6%)	E148Q/V726A	11 (1.5%)	0.917
E148Q/P369S	1 (1.6%)	E148Q/P369S	14 (1.9%)	0.896
E148Q/M680I	1 (1.6%)	E148Q/M680I	4 (0.6%)	0.290
V726A/-	2 (3.3%)	V726A/-	35 (4.8%)	0.613
F479L/-	1 (1.6%)	F479L/-	4 (0.6%)	0.290
M694V/V726A	1 (1.6%)	M694V/V726A	35 (4.8%)	0.267
M694V/E148Q	1 (1.6%)	M694V/E148Q	15 (2%)	0.842
No mutation	5 (8.4%)	No mutation	30 (4.1%)	0.122
		Other mutations	63 (8.7%)	

MEFV: Mediterranean fever; ELE: erysipelas-like erythema.

Lidar *et al*. demonstrated a less severe disease phenotype in an older age group with delayed diagnoses and also found lower frequencies of M694V homozygosity among the FMF patients who had ELE as the first disease presentation (6). When ELE is the only initial manifestation of FMF in a patient, a diagnosis of FMF can be difficult. Kavukcu *et al*. reported that two pediatric FMF patients who presented with ELE and were later diagnosed

as having FMF had M694V homozygous mutations (11). In our cohort, 11 patients (18.6%) presented with ELE as the initial symptom and were diagnosed with FMF, and 48 (81.4%) patients experienced ELE attacks while receiving colchicine therapy. Therefore, patients who present with ELE as the initial symptom should be investigated in terms of clinical, medical and family history for early diagnosis with FMF. Evaluation of the severity of the disease in our ELE patients revealed a more severe phenotype than among other FMF patients, and this result suggests that more disease severity might be associated with ELE in FMF. The necessity for clinicians to recognise ELE early is important for early diagnosis of FMF to prevent long-term complications such as amyloidosis. FMF frequently coexists with other autoinflammatory disorders, such as IgA vasculitis, polyarteritis nodosa (PAN), juvenile idiopathic arthritis and Kawasaki disease (12). However, we found no differences in patients with and without ELE for the presence of additional coexisting diseases.

The primary treatment for FMF is colchicine, which effectively suppresses inflammatory attacks and prevents the development of amyloidosis (1). In recent years, anti-interleukin-1 (IL-1) treatments, including anakinra and canakinumab, have been used as alternative treatments for colchicine-resistant patients and have suppressed inflammation (13). Tezcan *et al*. reported that a more effective treatment for FMF patients with ELE could be the use of colchicine and anakinra together rather than colchicine alone (14). All the patients in our study were receiving colchicine therapy; those in the ELE group were using higher doses of colchicine than those in the other group for suppress the inflammation. There are no specific therapies for ELE treatment, and ELE attacks were treated with NSAIDs and bed rest in our cohort.

The retrospective nature of this study is its main limitation. Further studies that include a large number of patients could present more information about the features of ELE in FMF patients.

In conclusion, physicians who meet FMF attacks accompanied by ELE lesion should be alert to the need to make a correct diagnosis of systemic diseases such as FMF. ELE may be a valuable finding for the diagnosis of FMF. Arthritis is also frequently encountered in patients with ELE, and M694V homozygous mutation is more frequently found in patients with ELE. Furthermore, a severe disease course is more common in patients with ELE, and FMF patients with ELE use higher doses of colchicine in relation to this severe disease course. Our study should increase physicians' awareness of ELE, which could present as the sole manifestation of FMF.

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