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Articular manifestations in Egyptian children with familial Mediterranean fever

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Abstract

Background: Familial Mediterranean fever (FMF) is an autosomal recessive auto-inflammatory disease. Arthritis in early-onset FMF is a common finding. The aim of this study was to assess frequency of arthritis in 200 Egyptian children with FMF and also to detect its clinical characteristics, response to colchicine treatment, its effect on disease severity, and the most common MEFV gene mutations in patients with arthritis.

Results: We studied 200 children with FMF. We analyzed joint involvement in FMF attacks regarding its clinical characteristics, its effect on the disease severity, and response to colchicine treatment. We found arthritis in 20.5% of the studied population. Most of the children with arthritis had mono-articularjoint involvement during the FMF attack (73.1%), followed by oligo-articularjoint (22%). The knees and ankles were the most commonly affected joints. Arthritis was the presenting symptom in only 4%. We observed redness of the affected joints in 70.7%, and persistence of swelling after the attacks only in 17.1%. The majority of patients (85.4%) had a 75–100% decrease in the frequency of arthritic attacks after colchicine treatment. We did not find any joint disability in all studied patients, and arthritis was only present during attacks. The most frequent MEFV gene mutations in arthritic patients wereV726A and E148Q, each occurring in 28.6%. We observed an earlier age of disease onset and a more disease severity in patients with arthritis ($p = 0.031$ and $p \leq 0.001$, respectively). We also observed that chest pain, erysipelas-like-erythema, and testicular affection were more observed in patients with arthritis (p values 0.001, 0.001, and 0.006, respectively).

Conclusion: This study showed that around 20% of Egyptian children with FMF can develop arthritis during the attacks, which usually runs a benign course. The presence of arthritis can denote a more severe disease course.

Keywords: FMF, Arthritis, MEFV gene mutation

Keypoints

Articular manifestations in FMF children, severity, and scoring of FMF in FMF children with arthritis

Background

Familial Mediterranean fever is an autosomal recessive disorder recently considered as one of the monogenic auto-inflammatory diseases [1]. It is caused by mutation in MEFV gene [2], one of the genes encrypting proteins important for regulation of innate immune system [3–6].

It is a periodic fever syndrome characterized by recurrent attacks of fever with healthy interval in-between episodes [4]; these episodes are also associated with inflammation in different parts of the body as pleuritis, arthritis, pericarditis, peritonitis, and orchitis. Attacks last for 2 or 3 days and complete recovery is usual but with recurring episodes of arthritis [1].

The classical presentation is of acute joint involvement precipitated by minor trauma or effort. It is usually self-limiting mono arthritis affecting the shoulders, hips, knees, temporomandibular, or sternoclavicular joints [1, 5, 7]. The articular involvement usually starts at an early age and is usually short in duration. The joint becomes red, hot, and swollen with a limitation of movement.

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Complete resolution of symptoms usually occurs with resolution of the attack [8]. These symptoms occur due to influx of neutrophils into the affected tissue due to uninhibited pyrin activity resulting in uncontrolled production of interleukin-1 [9–11].

It was observed that articular attacks affect up to three quarters of patients with FMF, and sometimes it is the sole manifestation in up to 15% of patients [12–14]. Sometimes patients are misdiagnosed as juvenile idiopathic arthritis or acute rheumatic fever due to an early age of onset and high frequency of arthritis or arthralgia [12–14]. Careful and accurate assessment of signs and symptoms is essential for early detection and differential diagnosis of FMF.

Musculoskeletal involvement in FMF, mostly in the form of arthritis or arthralgia, is the third common manifestation, following periodic fever and abdominal pain [15]. The frequency of arthritis in FMF has been reported to range from 21 to 77% in different ethnic groups [15–17]. Classically, the presentation is recurrent mono-articular joint involvementat early age, usually between 1 and 5 years [15, 16]. Arthritis in FMF usually responds to colchocine. Resistent cases can be given methotrexate and anti-tumor necrosis factor biologics (etanercept and infliximab) [18].

The purpose of this study was to assess frequency of arthritis in 200 Egyptian children with FMF and also to detect its clinical characteristics, response to colchicine treatment, its effect on disease severity, and the most common MEFV gene mutations in patients with arthritis.

Methods

This was a retrospective study, and 200 children were included who were diagnosed as FMF according to the new pediatric FMF criteria [19]. They were being followed in our pediatric rheumatology clinic, from March 2017 to September 2019. All included patients were diagnosed with FMF before age of 18 years, and we included FMF patients whether in attack or in between attacks (at least 2 weeks after the last attack). Children with any associated autoimmune disease were excluded.

Informed consents were taken from the parents or the patient's guardians.

Demographic data was collected from patients' files (age, sex, and consanguinity; family history of FMF; and family history of autoimmune diseases). Clinical history including age at onset and at diagnosis, disease duration, number of attacks/year, and duration of attack before starting treatment and at the time of study was recorded. Disease symptoms (fever, abdominal pain, chest pain, arthritis, erysipelas-like rash, orchitis, and vasculitis) were reported. Also dose of colchicine at the time of the study was reported. We also recruited investigations done at disease onset as follows: complete blood count, erythrocyte sedimentation rate, C-reactive protein, proteinuria, and results of MEFV gene mutations. Plain X-ray was done for all patients with arthritis to detect anyerosion.

Disease severity was measured by severity score[1 = 1 site in single attack, 2 = 2 sites in disease course, 3 = 2 mg of colchicine to achieve remission, 4 = 2 pleuritic attacks in disease course, 5 = 2 erysiple-like erythemaattacks in disease course, 6 = age of onset < 10 years "interpretation" severe disease = 3 criteria, intermediate = 2 criteria, mild = 1 criterion] [20] and response to colchicine therapy assessed by FMF-50 score [which assess the response to treatment using the following**:** 1-change in frequency of attacks, 2-change in duration, 3-patients/parents global assessment, 4-physician global assessment, 5-change in arthritis attack, and 6-change in inflammatory markers. At least 50% improvement in five out of six criteria by 3 to 6 months means FMF 50 response [2].

Analysis of joint involvement was done regarding (age at onset, arthritis as presenting symptom, duration of attack of arthritis/hour, and number of swollen joint either monoarticular (1 joint), oligoarticular (2–4 joints), or polyarticular (> 4 joints), type of affected joint, clinical picture (redness, limitation of movement, relation to fever, persistence of swelling after the attack, complete resolution or chronic limitation, response of arthritis after 6 months of colchicine treatment, and use of other DMARDS). Then patients were divided into 2 groups according to the presence of arthritis [group 1: patients with arthritis (N = 41) and group 2: patients without arthritis (n = 159)]; the two groups were statistically compared regarding previous data collected.

Statistical methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using the mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test [21]. For comparing categorical data, chi-square (χ^2) test was performed. Fisher's exact test was used instead when the expected frequency is less than 5 [22]. P values ≤ 0.05 were considered as statistically significant.

Results

Two hundred patients were included in this study; 96 were males (48%) and 104 were females (52%). Demographic features of the studied FMF patients were summarized in Table 1.

Table 1 Demographic features of studied FMF patients according to age, family history, consanguinity , disease duration and arthritis

Patients' characteristics	Frequency (n = 200)/ (mean ± SD)
Consanguinity	68 (34%)
Family history of FMF*	76 (38%)
Family historyof autoimmune diseases	26 (13%)
Age at time of study (years)	9.98 ± 3.48
Age at onset of disease (years)	4.44 ± 2.86
Age at diagnosis (years)	6.25 ± 3.07
Disease duration (years)	5.54 ± 3.19
Arthritis as a presenting symptom	8 (4%)

***FMF* familial Meditarranean fever**

Observing the genotypic features of studied FMF patients revealed that 127patients (63.5%) had heterozygous gene mutation, 27 patients (13.5%) had homozygous gene mutation, and 30 patients (15%) had compound heterozygous gene mutation, while negative gene mutation was recorded in 16 patients (8%). The type of MEFV gene mutation of included FMF patients was summarized in Table 2. All X-rays that were done did not show any erosions.

Patients were divided into two groups according to the presence of arthritis in their disease course. Group 1: FMF patients having arthritis (n = 41) and group 2: FMF patients without arthritis (n = 159). Table 3 showed the comparison between group 1 and group 2 patients as regards demographic features. We found that the mean age of the patients at the time of the study in the arthritic group was statistically significantly higher, while the mean age of FMF onset was significantly lower in the arthritic group and the mean disease duration was significantly longer in the arthritic group (p = 0.023, 0.031, < 0.001, respectively) (Table 3).

Table 4 showed the comparison between the previous two groups regarding clinical manifestations of FMF attacks, laboratory parameters at time of disease, and colchicine dosage at the time of the study. We observed that chest pain, erysipelas-like erythema, and testicular affection more in patients were arthritis, with a statistical significance difference (p values 0.001, 0.001, and 0.006, respectively). Also, ESR was higher in patients with arthritis (p value 0.02).

Table 2 Type of MEFV gene mutation of included FMF patients (n-230), pattern, and type of gene mutation according to gene alleles

Gene mutation				**Frequency (n = 230)**
V726A				56 (24.35%)
E148Q				48 (20.87%)
M694I				47 (20.43%)
M680I				29 (12.61%)
M694V				24 (10.43%)
A7445				7 (3.04%)
K695R				1 (0.43%)
I692de1				1 (0.43%)
S650F				1 (0.43%)
	Type of mutation			**Total (n = 400)**
	Heterozygous	**Homozygous**	**Compound heterozygous**	
	Count (%)	**Count (%)**	**Count (%)**	
V726A	37 (9.25%)	6 (1.50%)	16 (4.00%)	59 (14.75%)
E148Q	38 (9.50%)	2 (0.50%)	9 (2.25%)	49 (12.25%)
M694I	18 (4.50%)	28 (7.00%)	15 (3.75%)	61 (15.25%)
M680I	16 (4.00%)	14 (3.50%)	6 (1.50%)	36 (9.00%)
M694V	11 (2.75%)	4 (1.00%)	11 (2.75%)	26 (6.50%)
A7445	5 (1.25%)	0 (0%)	2 (0.50%)	7 (1.75%)
K695R	1 (0.25%)	0 (0%)	0 (0%)	1 (0.25%)
I692de1	0 (0%)	0 (0%)	1 (0.25%)	1 (0.25%)
S650F	1 (0.25%)	0 (0%)	0 (0.%)	1 (0.25%)
Total	127 (31.75%)	54 (13.5%)	60 (15 %)	241 (60.25%)

N number

Table 3 Comparison between group 1 and group 2 patients as regard to age, gender, consanguinity, disease duration, and family history showing results as *p* value

		Group 1 (*n* = 41)	Group 2 (*n* = 159)	*P* value
Gender[a]	F	18 (43.9%)	86 (54.1%)	0.244
	M	23 (56.1%)	73 (45.9%)	
Consanguinity[a]		14 (34.1%)	54 (34.0%)	0.982
Age at time of study (years)[c]	Mean ± SD	10.95 ± 3.11	9.73 ± 3.53	**0.023**
Age at onset of FMF (years)[c]	Mean ± SD	3.48 ± 2.27	4.69 ± 2.95	**0.031**
Age at diagnosis(years)[c]	Mean ± SD	5.46 ± 2.65	6.45 ± 3.15	0.113
Disease duration(years)[c]	Mean ± SD	7.48 ± 2.88	5.04 ± 3.08	**< 0.001**
Family history of FMF[a]		15 (36.6%)	61 (38.4%)	0.834
Family history of other autoimmune disease[b]		4 (9.8%)	22 (13.8%)	0.488
Type of autoimmune disease in the family history[b]	SLE	0 (0.0%)	6 (27.3%)	0.788
	Rheumatoid arthritis	1 (25.0%)	5 (22.7%)	
	Rheumatic fever	3 (75.0%)	8 (36.4%)	
	Type 1 DM	0 (0.0%)	3 (13.6%)	

N number, *SD* standard deviation, *FMF* familial Mediterranean fever, *SLE* systemic lupus erythematosus, *DM* diabetes mellitus
[a]Chi-squared test
[b]Fisher's exact test
[c]Mann-Whitney test

All our patients were on colchicine treatment only. Colchicine dosage was significantly higher in patients with arthritis.

Regarding severity score, severe disease was found in 53 patients (26.5%), moderate disease was found in 35 patients (17.5%), and mild disease severity was found in 112 patients (56%). Regarding FMF-50 score for assessing response to colchicine treatment in FMF patients, it was found that139 patients (69.5%) had a good response to treatment while 61 patients (30.5%) had a poor response to treatment. We increased the colchicine dosage to patients with poor response.

As regards joint involvement, it was monoarticular in 30 patients (73.1%), oligoarticular in 9 patients (22%), and polyarticular in only 2 patients (4.9%); the knees were the most commonly affected and were found in 32 patients (78%), followed by the ankles in 30 patients (73.2%), wrist in 7 patients (17.1%), hips in 4 patients

Table 4 Comparison between group 1 and group 2 patients as regards clinical features at the time of the study, laboratory parameters at the time of the disease diagnosis and colchicine dosage

	Group 1 (*n* = 41)	Group 2 (*n* = 159)	*p* value
Fever[a]	40 (97.6%)	144 (90.6%)	0.201
Chest pain[a]	23 (56.1%)	47 (29.6%)	0.001
Abdominal pain[a]	40 (97.6%)	154 (96.9%)	1
Erythematous-like erythema[a]	9 (22.0%)	7 (4.4%)	0.001
Testicular affection[b]	6 (26%)	4 (5.5%)	0.006
HSP[a]	3 (7.3%)	12 (7.5%)	1
Hb(mg/dl)[c]	11.30 ± 1.31	11.67 ± 1.29	0.098
TLC(*1000)[c]	8.66 ± 3.54	8.56 ± 3.57	0.643
PLT(*1000)[c]	360.20 ± 92.51	344.81 ± 120.20	0.206
ESR[c]	45.10 ± 29.35	35.36 ± 27.17	0.028
CRP[c]	26.72 ± 17.50	27.51 ± 27.77	0.591
Persistant proteinuria (frequency %)[b]	0 (0.0%)	1 (0.6%)	1
Colchicine dosage at time of study (g)[c]	1.46 ± 0.53	1.13 ± 0.45	< 0.001

N number, *HSP* Henoch-Schonlein Purpura, *Hb* hemoglobin, *TLC* total leucocytic count, *PLT* platelet, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *g* gram
[a]Chi-squared test
[b]Fisher's exact test
[c]Mann-Whitney test

(9.8%), elbows in 4 patients (9.8%), small joints of the feet in 2 patents (4.9%), and small joints of the hands in 1 patient (2.4%). No arthritis was observed outside the FMF attacks.

Clinical characteristics of the arthritic attacks in FMF arthritis patients were summarized in Table 5. The persistence of swelling after the attacks for 1–2 days was observed in 7 patients (17.1%), and complete resolution without chronic limitation was observed in all our arthritic patients (100%).

In our study, disease severity was found to be statistically significant higher in patients with arthritis (p = 0.001), while no statistical difference as regards FMF 50% score (Table 6).

The type of gene mutation of FMF patients with arthritis was summarized in Table 7.

Discussion

We found that 20% of the studied group had arthritis during their FMF attacks. Joint involvement was mostly mono-articular and non-erosive, affecting predominantly the large joints of the lower limbs. Disease severity was higher in patients with arthritis.

We found that the mean age of FMF disease onset was significantly lower in arthritic group, and the mean disease duration was significantly longer in arthritic group. This comes lower than the mean age of onset of FMF reported by Ince et al. 2002 and Jarjour and Dodaki 2011, and similar to Majeed and Rawashdeh 1997 [16, 23, 24]. Arthritis and early disease onset were linked together in other studies [18, 25].

When we analyzed the clinical presentation, we found that abdominal pain was the most common followed by fever, chest pain, and arthritis. This is similar to the results of another Egyptian study [26], while Duşunsel et al. [27] reported that fever was the most common followed by abdominal pain. It seems that different genetic patterns of the disease among different populations affect the clinical picture of the attacks.

Heterozygous mutation was the most frequent genetic pattern, followed by compound heterozygous and homozygous mutation. The Lebanese study by Mneimneh et al. [28] reported similar results. High rate of simple heterozygosity in an autosomal dominant disease may suggest the presence of one or more modifying alleles or other environmental factors [diet, temperature, oxygen levels, humidity, light cycles, and presence of mutagens can impact on which gene is expressed] which eventually affect phenotype [29].

The most frequent MEFV gene mutations were V726A (24.35%), E148Q (20.87%), M694I (20.43%), M680I (12.61%), M694V (10.43%), and A7445 (3.04%). This is nearly similar to many studies [26, 27] while in the study by Mneimneh et al. [28], M694V (37.2%) and E148Q (27.4%) were the commonest. These differences may be due to the effect of different genetic backgrounds that affect the genetic pattern of the disease.

According to Mor et al. 2005's severity score [20], nearly half of the patients (56%) had mild disease, 17.5% had moderate, and 26.5% had severe disease. This is nearly similar to the Turkish studies [30, 31]. On the other hand, Lotfy et al. [32] used Pras severity score [33] and reported more severe courses (63.5% severe cases). These differences may be due to the use of different severity scores.

On following response to colchicine, 69.5% were good responders and 30.5% were poor responders. In other studies, Mneimneh et al. [28] reported a complete response in 33.3%, incomplete response in 52.2%, and no response in 14.5%. Barutet al [34]. reported a complete response in 79%. Different response to treatment may be affected by the genetic background of the disease.

We observed arthritis in 41 patients (20.5%). This is nearly similar to some Egyptian studies [32, 35]. However, other studies as Salah et al. [36], El-Garf et al. [23], Yilmaz et al. [31], and Barut et al. [34] reported a higher frequency of arthritis (ranging from 42 to 57%).

We found the mean age at arthritis onset to be 5.72 ± 2.67 years. This is similar to Majeed and Rawashdeh [23], but lower than Ince et al.'s [24]. The mean duration of the attacks of arthritis in this study was 110.05 ± 50.9 h. The duration of the attacks of arthritis reported by Ince et al. [24] ranged from 12 h to 6 weeks.

Arthritis was the presenting symptom in 4%. This is nearly similar to Karakayalı et al. [37]. Monoarticular arthritis was the commonest type, followed by oligoarticular and polyarticular types. This is nearly similar to most of the studies done [24, 38], except for Jarjour and

Table 5 Clinical characteristics of the arthritic attacks in FMF arthritis patients and response to colchicines treatment

Arthritis characteristics	Frequency (n = 41)%
Fever	31 (75.6%)
Redness	29 (70.7%)
Limitation of joint movement during the attack	41 (100%)
Persistence of joint swelling for 2 days after the attack	7 (17.1%)
Resolution without chronic limitation	41 (100%)
Response of arthritis attacks to colchicine	
75–100% decrease in the frequency	85.4%
50% decrease in the frequency	9.8%
25% decrease in the frequency	4.8%

N number

Table 6 Comparison between group 1 and group 2 patients as regards severity score, FMF 50% score

		Group 1 (*n* = 41)	Group 2 (*n* = 159)	*p* value
Severity score[a]	**Mild**	11 (26.8%)	101 (63.5%)	**< 0.001**
	Moderate	9 (22.0%)	26 (16.4%)	
	Severe	21 (51.2%)	32 (20.1%)	
FMF 50% score[a]	**Good responders**	30 (73.2%)	109 (68.6%)	0.567
	Poor responders	11 (26.8%)	50 (31.4%)	

N number
[a]Chi-squared test

Dodaki [16], who found a more prevalence to di-arthritis pattern.

We observed that the knees were the most affected joint, followed by the ankles, wrists, hips, and elbows. We did not find axial or tempromandibular joint affection. This is nearly similar to the study done by Jarjour and Dodaki [16].

We found that fever, redness, and limitation of movement of the affected joint, joint swelling for 1–2 days followed by a complete resolution of arthritis were common findings in arthritis attacks. This is nearly similar to all studies as Ince et al. [24]. None of the patients developed irreversible joint damage.

We found that the most frequent MEFV gene mutations were V726A, E148Q, M694I, M680I, and M694V. In Jarjour and Dodaki [16] study, the most frequent mutations were M694V followed by M694I. This difference suggests a unique genetic background for each population.

Disease severity was found to be higher in patients with arthritis (p = 0.001). Also, arthritis was more prevalent in patients with higher disease severity (p = 0.0004). This was a common finding with Eshed et al. [10].

The frequency of erysipelas-like erythema in patients with arthritis was 22% in the present study, with a statistical significance difference. This comes in agreement with Ince et al., who reported that ELE was an associated finding to arthritis in the lower limbs [31]. Also, chest pain and testicular affection were statistically higher in patients with arthritis, together with ESR at time of diagnosis. These findings may be linked to a higher disease severity with these symptoms.

The limitation of the study was the relatively small number of patients included in the study and the need for the cooperation of more than one center in data collection.

Table 7 Type of gene mutation of FMF patients with arthritis (*n* = 49)

Frequency (*n* = 49)	Gene mutation
V726A	14 (28.6%)
E148Q	14 (28.6%)
M694I	10 (20.4%)
M680I	5 (10.2%)
M694V	4 (8.2%)
Negative gene mutation	2(4.0%)

N number

Conclusion

Frequency of arthritis in Egyptian children with FMF can be estimated to be around 20%. Joint affection was mostly mono-articular and non-erosive, affecting predominantly the large joints of the lower limbs. Disease severity was higher in patients with arthritis. Studies with a larger number of patients are recommended to verify these findings.

Abbreviations

FMF: Familial Mediterranean fever; MEFV: Mediterranean fever gene

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Authors' contributions

All authors have contributed significantly and all authors are in agreement with the content of the manuscript. YM contributed to the searching of literature, writing and editing the manuscript, and being the corresponding author. HT contributed to following the results and writing the manuscript. NMS contributed to the idea of the research, following the results, and writing the manuscript. DF contributed to the searching of literature, collecting the data, performing the statistical part of the research, and writing the manuscript. HM contributed to following the results and writing the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

The dataset used and/or analyzed during the current study are available with the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethical scientific committee of the Faculty of Medicine, Cairo University (reference number: I-210317). Written informed consents to participate were taken from the parents or the patient's legal guardian.

Consent for publication

Written informed consents to publish the data contained within this study were taken from the parents or the patient's legal guardians.

Competing interests
The authors declare that they have no competing interests.

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