

## Markers for Subclinical Inflammation in Egyptian Children with Familial Mediterranean Fever: Splenomegaly and Mean Platelet Volume

Talaat HS<sup>1</sup>, Sheba MF<sup>1</sup>, Mohammed RH<sup>2</sup>, Ibrahim MFM<sup>1\*</sup>

<sup>1</sup>Department of Pediatrics, Cairo University, Cairo, Egypt; <sup>2</sup>Ministry of Health, Cairo, Egypt

### ABSTRACT

**Background:** Familial Mediterranean fever (FMF) is an auto-inflammatory systemic disease, of an autosomal recessive inheritance, that is characterized by recurrent attacks of fever, peritonitis, pleuritis, pericarditis, and/or arthritis; MEFV is the responsible gene.

**Aim:** To detect the correlation of mean platelet volume (MPV) and splenomegaly as subclinical inflammatory markers in children with FMF at the attack-free periods.

**Methods:** This cross-sectional study included 40 pediatric patients diagnosed clinically and according to gene mutations already with FMF and were following-up at the Rheumatology Outpatient Clinic, Children's Hospital, Cairo University. Abdominal ultrasonography was done for all patients to detect splenomegaly; MPV was also measured.

**Results:** Patients were classified in two groups; group 1 (n=13) patients with splenomegaly and group 2 (n=27) patients with no splenomegaly. The MPV were significantly higher in group 1 ( $8.9 \pm 0.9$ fl) than in group 2 ( $8.3 \pm 0.5$ fl) ( $p < 0.05$ ).

**Conclusion:** MPV and splenomegaly could serve as markers of chronic inflammatory activity in FMF patients even during the attack-free period; these may be applied for chronic inflammatory markers that may be related to the prognosis and the possibility of development of amyloidosis.

**Keywords:** Familial Mediterranean fever; MEFV; Splenomegaly; Mean platelet volume

### INTRODUCTION

Familial Mediterranean fever (FMF) is an auto-inflammatory disease, inherited in an autosomal recessive pattern; however, many patients with only one mutation were clinically diagnosed with FMF and responded well to colchicine therapy [1,2]. FMF is characterized by recurrent attacks of fever, peritonitis, pleuritis, pericarditis, arthritis, and sometimes an erysipelas-like erythema (ELE) [3]. The acute inflammatory attack is usually short and lasts 1 to 3 days and then subsides spontaneously. In some occasions, the attacks are prolonged, last more than 1 week and present with arthritis, sacroiliitis or persistent febrile myalgia. Most children with FMF remain symptom-free in-between the attacks [4]. In about 30% of patients, the inflammation persists even in the attack-free periods with subtle clinical inflammatory signs (e.g. chronic normocytic normochromic anemia,

splenomegaly, persistently elevated erythrocyte sedimentation rate (ESR), and growth retardation) reflecting persistent subclinical inflammation and chronic immune activation [5]. Interleukin-6 (IL-6) has been reported to be higher in FMF patients than controls during the attack-free periods. IL-6 promotes megakaryocyte maturation and possibly stimulates megakaryocyte proliferation [6]. The spleen acts as a reservoir for platelets and about one third of the circulating platelet is temporarily sequestered within a normal sized spleen, and up to 90% may be found within a markedly enlarged spleen [7]. Changes of peripheral platelet volume depend on the rate of splenic sequestration and bone marrow production; MPV is increased if the rate of platelets destruction is equal to or higher than the rate of their production, as a result of increased peripheral immature platelets [8]. The aim of this study was to

**Correspondence to:** Mohamed Farouk M Ibrahim, Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt, Tel: + 002-01097515771; E-mail: m.farouk76@gmail.com

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detect the correlation of MPV and splenomegaly as subclinical inflammatory markers in children with FMF during the attack-free periods.

## PATIENTS AND METHODS

This cross-sectional study included 40 children with FMF, during their regular follow-up at the Rheumatology Clinic, Specialized Pediatric Hospital, Cairo University. FMF was diagnosed according to Tel Hashomer criteria [9].

Children with established diagnosis of FMF were included in the study. However, children with other rheumatic diseases and those with suspected FMF but the diagnosis was not yet established were excluded.

A detailed history and thorough clinical examination were provided for all included patients, and their medical records were reviewed, focusing on: consanguinity, family history of FMF, age of onset of the disease, time interval between the onset and the diagnosis, number of attacks per year, clinical manifestations, severity of the disease according to FMF disease severity score (10), and the colchicine dose to control the attacks and the response to treatment: attack free, incomplete (decline more than 50% in frequency of attacks) and unresponsive.

Results of mutation analysis were collected from records. A panel of 12 common MEFV gene mutations was tested; DNA was extracted from patients whole blood using conventional phenol-chloroform extraction method, then using a reverse hybridization, test strip-based assay (FMF StripAssay; ViennaLab Labordiagnostika, Vienna, Austria). Patients were classified as homozygous: gene mutation on both alleles, or heterozygous: gene mutation on only one allele, or gene negative: no mutations could be identified.

Complete blood count (CBC), ESR, C-reactive protein (CRP), and liver and kidney function tests were done. MPV was measured in a blood sample collected in citrate (1:1 v/v) in order to avoid the platelet swelling induced by EDTA, and analyzed within 1 hour. A Cell-Dyn 3700 was used for whole blood counts. Normal range of mean platelet volume was used. Results of urine analysis were collected to detect the presence of any abnormalities especially proteinuria or hematuria.

Abdominal ultrasonography was done for all patients to detect the presence of splenomegaly using Toshiba and General electric apparatus equipped with multi-frequency convex linear transducer and splenic span was measured; we used age and sex dependent standard for splenomegaly [11]. Consents were obtained from parent of patients.

Data confidentiality was preserved. The Scientific Research Committee of the Pediatrics Department, Cairo University approved the study protocol. Data were statistically described in terms of mean  $\pm$  SD, median and range, or frequencies (number of cases) and percentages when appropriate.

For comparing numerical variables between the study groups, Mann Whitney U test for independent samples was used, and for comparing categorical data, Chi square test was performed. P-values less than 0.05 were considered statistically significant. Statistical calculations were done using Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA version 16 for Microsoft Windows.

## RESULTS

This study included 40 children with FMF. Out of them, 26 (65%) were females, and 14 (35%) were males with a female to male ratio of 1.8:1. According to the results of abdominal ultrasound, our patients were divided into two groups; group 1: patients with splenomegaly (n=13), and group 2: patients with no splenomegaly (n=27). Group 1 included 13 patients, 6 females (46.2%) and 7 males (53.8%), F:M=1:1.1, and group 2 included 27 patients, 20 females (74%) and 7 males (26%) with F:M=2.8:1.

The mean age of onset and the mean of diagnosis for group 1 were  $4.19 \pm 2.07$  years and  $6.65 \pm 2.78$  years, respectively. For group 2, the mean age of onset and the mean age of diagnosis were  $4.09 \pm 2.19$  years and  $6.38 \pm 2.87$  years, respectively. Out of 40 FMF patients, consanguinity was detected in 15 (37.5%) children. And a positive family history for FMF was found in 10 patients (25.0%) (Table 1).

**Table 1:** Comparing the study groups regarding age of onset and diagnosis, time interval between disease onset and diagnosis.

Item	Group 1 (n=13)	Group 2 (n=27)	p value
Male/Female	7/6	7/20	0.15
Consanguinity n (%)	4 (30.8%)	11 (40.7%)	0.4
Family history n (%)	4 (30.8%)	6 (22.2%)	0.41
Age (years) mean $\pm$ SD	$8.31 \pm 2.92$	$9.00 \pm 3.61$	0.48
Age of onset (years), mean $\pm$ SD	$4.19 \pm 2.07$	$4.09 \pm 2.19$	0.95

Age at diagnosis (years), mean $\pm$ SD	6.65 $\pm$ 2.78	6.38 $\pm$ 2.87	0.93
Time interval between disease onset and diagnosis (years), mean $\pm$ SD	2.32 $\pm$ 2.13	3.28 $\pm$ 2.14	0.17
Duration of follow-up (years), mean $\pm$ SD	1.46 $\pm$ 1.21	2.59 $\pm$ 3.15	0.36

FMF= Familial Mediterranean Fever

\*p value less than 0.05 are considered statistically significant

Genotype distribution of the study groups are demonstrated in Table 2. Out of 40 FMF patients 4 (10%) were homozygotes 32 (80%) were heterozygotes and 4 (10%) were gene negative.

**Table 2:** Genotype distribution of study populations.

MEFV Mutation	Group 1 (n=13)			Group 2 (n=27)		
	Homozygous	Heterozygous	Negative	Homozygous	Heterozygous	Negative gene
M680I						
N	0	3	0	0	5	0
%		23			18.5	
M694V						
N	1	0	0	2	3	0
%	7.6			7.4	11.1	
E148Q						
N	1	1	0	0	8	0
%	7.6	7.6			29.6	
V726A						
N	0	5	0	0	4	0
%		38.4			14.8	
M694I						
N	1	0	0	0	0	0
%	7.6					
M762V/M694V						
N	0	0	0	0	1	0
%					3.7	
M680I/V726A						
N	0	0	0	0	1	0

%	3.7					
Normal						
N	0	0	2	0	0	2
%	15.3			7.4		

**Table 3:** Clinical features of study groups.

Item	Group 1 (N=13)		Group 2 (N=27)		p value
	N	%	N	%	
Fever	13	100	27	100	~
Abdominal pain	12	92	26	96.3	0.55
Arthritis	12	92	22	81.5	0.35
Chest pain	3	23	4	14.8	0.4
Erysipelas-like erythema	3	23	7	25.9	0.58
Proteinuria	0	0	0	0	~
Amyloidosis	0	0	0	0	~

\*p value less than 0.05 is considered statistically significant

The most common clinical feature was fever and was noted in all 40 patients (100%), followed by abdominal pain in 38 patients (95%), arthritis in 34 patients (85%), erysipelas-like erythema (ELE) in 10 patients (25%) and chest pain in 7 patients (17.5%) (Table 3).

Disease severity score were mild in 1 patients (2.5%), moderate in 24 patients (60%) and severe in 15 patients (37.5%). All the 40 patients received colchicines in a dose ranging from 0.5 to 2 mg/day, out of them, 11 patients (27.5%) showed complete response to colchicine and 29 patients (72.5%) showed incomplete response and none of the patients showed any response.

The mean number of attacks per year before treatment was 49.2 ± 22.7, while the mean No. of attacks per year after treatment was 16.05 ± 11.1 (Table 4).

**Table 4:** Comparison between disease severity score, response to colchicine therapy, and number of attacks per year in study groups.

Item	Group 1 (n=13)	Group 2 (n=27)	p value	
Disease severity score, n (%)	Mild	0(0)	1(3.7)	
	Moderate	7(53.8)	17 (63.0)	0.35
	Severe	6(46.2)	6 (33.3)	
Response to colchicine, n (%)	Complete	3 (23.1)	8 (29.6)	
	Incomplete	10 (76.9)	19 (70.4)	0.48
	No response	0 (0)	0 (0.0)	
Colchicine dose to control attacks, mean ± SD	1.54 ± 0.42	1.52 ± 0.58	0.82	
Number of attacks per year, mean ± SD	Before treatment	41.54 ± 12.60	52.8 ± 25.62	0.41
	After treatment	13.38 ± 6.99	17.33 ± 12.60	0.52

\*P-value less than 0.05 is considered statistically significant

Out of 40 patients, 11 (27.5%) underwent surgery (tonsillectomy in 8 patients and appendectomy in 3 patients). Group 1: patients underwent surgery were 8 patients (61.5%), 5 of them had tonsillectomy and 3 had appendectomy.

Group 2: patients underwent surgery were 3 patients (11.11%) who had tonsillectomy. Diseases may be associated with FMF

were determined in 2 patients; associated systemic lupus erythematosus (SLE) in one patient (3.7%), and juvenile idiopathic arthritis (JIA) in one patient (3.7%).

Our study groups were compared as regarding platelets count, mean platelet volume (MPV), CRP and ESR (Table 5), MPV was significantly higher in group 1 patients with splenomegaly. Out

of 40 FMF patients, MPV was normal in 26 (65%) patients, low in 10 patients (25%) and high in 4 patients (10%) and distributed as follows in the two groups: i) Group 1: 10/13 (76.9%) patients had normal MPV, 1/13 (7.7%) patient had low

MPV and 2/13 (15.4%) patients had high MPV, and ii) Group 2: 16/27 (59.3%) patients had normal MPV, 9 (33.3%) patients had low MPV and 2(7.4%) patients had high MPV.

Table 5: Laboratory finding of the study groups.

Variables	Group 1 (patients with splenomegaly) (n=13)	Group 2 (patients with no splenomegaly) (n=27)	p value
Platelets counts ( $\times 10^3/\text{mm}^3$ ) mean $\pm$ SD	338.2 $\pm$ 78.25	334.3 $\pm$ 64.32	0.74
Mean platelet volume (fl)* mean $\pm$ SD	8.9 $\pm$ 0.9	8.3 $\pm$ 0.5	0.03*
CRP mg/dl mean $\pm$ SD	10.8 $\pm$ 27.6	6.8 $\pm$ 9.7	0.29
ESR Mm/h mean $\pm$ SD	27.2 $\pm$ 23.3	25.7 $\pm$ 22.8	0.62

\*Pvalue less than 0.05 is considered statistically significant

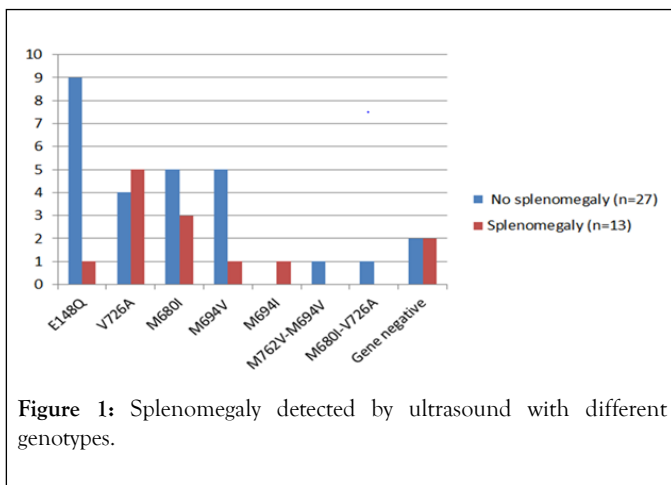


Figure 1: Splenomegaly detected by ultrasound with different genotypes.

E148Q mutation was the most frequent genotype among patients with no splenomegaly (9/40 patients, 22.50%), on the other hand V726A mutation was most frequent genotype among patients with splenomegaly (5/40 patients, 12.50%) (Figure 1).

V726A mutation had also relatively lower mean platelet count, higher MPV, and higher median ESR (298.89  $\pm$  48.41  $\times 10^3/\text{mm}^3$ , and 9.11  $\pm$  1.78 fl, 25 mm/h, respectively) than other genotypes (Table 6).

Table 6: Platelet count, Mean platelet volume, C-reactive protein, and Erythrocyte sedimentation rate in some patients of the most frequent genotypes.

Variables	Mutations				
	E148Q (n=10)	V726A (n=9)	M680I (n=8)	M694V(n=6)	M694I (n=1)
Platelets counts ( $\times 10^3/\text{mm}^3$ ) mean $\pm$ SD	363.5 $\pm$ 91.55	298.89 $\pm$ 48.41	341.5 $\pm$ 95.87	332 $\pm$ 63.41	213
Mean platelet volume (fl) mean $\pm$ SD	8.65 $\pm$ 1.44	9.11 $\pm$ 1.78	8.8 $\pm$ 1.51	7.75 $\pm$ 1.30	8.5
CRP (mg/dl), median (range)	0 (0-96)	0 (0-24)	0 (0-18)	3 (0-96)	0
ESR (mm/h), median (range)	18 3-40	25 7-45	17.5 8-26	12.5 5-80	20

## DISCUSSION

FMF is an auto-inflammatory disease of an autosomal recessive inheritance, caused by mutation of MEFV gene that is located on the short arm of chromosome 16 [12]. FMF is characterized by intermittent attacks of fever, abdominal pain, and arthritis [13]. It frequently occurs among Turkish, Armenians, Jews (Arabs, Ashkenazi) and Mediterranean region ethnics [14].

Out of our 40 patients 26 were girls and 14 were boys with a female to male ratio (F:M) 1.85:1. Group 1 included 13 patients out of them 6 were females (46.2%) and 7 were males (53.8%), F:M=1.1:1, while group 2 included 27 patients of whom 20 were females (74%) and 7 were male (26%), F:M=2.8:1. Our results come in agreement to the retrospective study done by Duşunsel et al., in [15] that reviewed the medical records of 102 Turkish patients and documented a female: male ratio of 1.3:1 (a slight female preponderance). This was not in agreement with El-Garf et al. [16] and Dursun et al. [7] who reported F:M ratios of 1:1.9 and 1:1.5 respectively. Although a Male predominance of FMF had been reported among Arabs, Armenian, and Jewish, most studies had reported that FMF affects both genders in a similar ratio [17].

Mean age of onset, mean age at diagnosis, and mean time interval between disease onset and diagnosis of all study population were  $4.12 \pm 2.12$  and  $6.47 \pm 2.81$  and  $3.01 \pm 3.27$  years respectively. Duşunsel et al. [15] reported higher mean age of onset and mean age at diagnosis of  $6.8 \pm 3.7$  and  $9.7 \pm 3.7$  respectively, than that observed in our patients. Our study populations had age of onset earlier and much lower than reported by Ebru et al. [18] as well who reported mean age of onset of  $6.8 \pm 3.7$  years. That might be attributed to the early detection of FMF patients in our rheumatology pediatric unit by clinical suspicious before the confirmation by genetic analysis.

The inherited recessive pattern of FMF was supported on the basis of consanguinity and family history. In our study 37.5% of patients had consanguineous parents. A positive family history of FMF was recorded in 10 patients (25%). El-Garf et al. [16] reported family history and consanguinity in 33.1% and 23.5% of their patients respectively. Some reported a higher percent of parental consanguinity that could be attributed to familial predisposition of FMF in certain population [19].

According to MEFV gene mutations analysis, the five most frequent mutations, (M694V, M694I, V26A, E148Q, and M680I) are responsible for the majority of FMF patients in the Middle East [20]. In our study, the most commonly detected mutations were E148Q, V726A, M680I, M694V, and M694I mutations and were detected in 25%, 22.5%, 20%, 15%, and 2.5% of patients, respectively. Reports regarding MEFV mutations are not similar, one report stated that E148Q was the most common mutations, followed by V726A and M694V [21], while the other reported V726A as the most frequent mutation followed by M694V, M680I, E148Q and M694I [16]. Reports from Egypt are different, that observation could indicate mutational heterogeneity of FMF in the Egyptian population.

In our study, 10% of patients were homozygotes (M694V/M694V) was most frequent homozygous mutation in 7.5% of patients), 75% were heterozygotes, 5% were compound

heterozygotes and 10% were gene negative. Comparable to our results, Dundar et al., [22] reported that 26.41% of their patients were heterozygotes, 15.29% were compound heterozygotes, and 8.60% were homozygotes; however, 49.6% of patients had no MEFV mutations.

Fever was the most common presenting feature in our patients and was documented in 40 out of 40 patients (100% of cases), followed by abdominal pain in 38 patients (95%), and arthritis in 34 patients (85%), ELE in 10 patients (25%) and chest pain in 7 patients (17.5%). Almost all patients with FMF have periodic febrile episodes that last from several hours up to 5 days; typical episode includes fever and one or more symptoms of abdominal pain (90%), arthritis or arthralgia (85%), and chest pain (20%) [22]. Similar results were nearly reported by other studies [15,16,23]. On the other hand, Sayarlioglu et al., reported that abdominal pain was the most common symptom, followed by fever, arthritis, pleuritis and ELE [17].

Colchicine in a dose of 0.5-2 mg/day was given to all patients; 27.50% showed complete response, 72.50% showed incomplete response and no patients showed any response to therapy. Majeed et al. [24] who prescribed colchicine to their patients in the usual dose the same as reported and stated that generally children aged 5 years or less needed 0.5 mg daily, those between 5-10 years 1 mg daily and 1.5 mg daily in children above 10 years. Very few patients needed 2 mg daily to suppress their symptoms. The response to colchicine was favorable in (96%) of their patients. Al-Wahadneh and Dahabrehin [25] reported a dramatic response to colchicine among FMF patients. The unfavorable response to colchicine therapy in our patients lower than reported might be related to the poor compliance of our patients to therapy.

Subclinical inflammation may continue during attack-free periods in approximately 30% of FMF patient [26]. MPV and splenomegaly correlate with the inflammatory activity of FMF patients at the attack-free period. These may be applicable for clinical chronic inflammatory condition score marker that related to prognosis [7]. In our study, abdominal ultrasonography was done for all FMF patients to detect the presence of splenomegaly that was we detected in 32.5% of our patients that was comparable to study by Dursun et al.[7] who reported splenomegaly in 27.9% among their study population. Aharoni et al. [27] detected splenomegaly in 27.5%, 13.3% of patients with FMF at the attack and at attack free period, respectively.

In our study we found a significant difference in MPV ( $p=0.03$ ) between group1 (splenomegaly) and group 2 (no splenomegaly) with a higher MPV(mean  $\pm$  SD) among group 1 patients with no other significant differences between both groups regarding mean  $\pm$  SD platelet count, CRP and ESR. That was comparable with the study done by Dursun et al. [7] who found that the MPV of FMF patients with splenomegaly ( $8.9 \pm 0.8$  fl) that was significantly higher than that for patients without splenomegaly ( $8.4 \pm 0.5$  fl). Milovanovic et al. [28] have reported that in active disease IL-6 but not thrombopoietin (TPO) is related to platelet count. Thus, IL-6 raises platelet count in reactive thrombocytosis and the neutrophil count.

E148Q mutation was the most frequent genotype among patients with no splenomegaly (22.50%), on the other hand V726A mutation was most frequent genotype among patients with splenomegaly (12.50%). V726A mutation had also relatively lower mean platelet count, higher MPV, and higher median ESR ( $298.89 \pm 48.41 \times 10^3/\text{mm}^3$ , and  $9.11 \pm 1.78 \text{ fl}$ ,  $25 \text{ mm/h}$ , respectively) than other genotypes. Paut et al. [29] noted that homozygosity for the M694V mutation significantly correlated with splenomegaly; however, we could not find this observation in our study similar to Inal et al. [5].

## CONCLUSION

The diagnosis of FMF is based mainly on the clinical criteria and laboratory examinations. Splenomegaly was detected in a considerable number of FMF patients and MPV were significantly higher in patients with splenomegaly. These could help for diagnosis of the FMF and may be applied for clinical chronic inflammatory condition score markers that may be related to prognosis and the development of amyloidosis. Further studies with more number of patients are needed to confirm our results.

## COMPETING INTEREST

No financial or non-financial benefit have been received or will be received from any party related directly or in directly to the subject of this article.

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## ETHICAL APPROVAL

Consents were obtained from parent/caretakers of patients. Data confidentiality was preserved. The Scientific Research Committee of the Department of Pediatrics, Cairo University approved the study protocol.

## AUTHOR CONTRIBUTION

This work was carried out in collaboration among all authors. HS, designed the study protocol, supervised the work and reviewed the manuscript. MS, performed the ultrasound and supervised the work. RH, designed the study protocol, managed the literature searches. MF, designed the study protocol, collected the data, performed the statistical analysis, and wrote the manuscript. All authors read and approved the final manuscript.

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