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RESEARCH ARTICLE

Serum Paraoxonase I and its Gene Polymorphism (Q/R192) in Egyptian Children with Familial Mediterranean Fever (FMF)

Marwa A. Hamed*[1], Samia S. Mahmoud[1], Huda Marzouk[1], Mervat Mamdouh Khorshied[2] and Yomna M. Farag[1],

[1]Depatment of Pediatrics, Faculty of Medicine, Cairo University, Egypt
[2]Depatment of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Egypt

*Corresponding Author
Marwa A. Hamed
(mirosalem1981@gmail.com)

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Abstract: ***Background***: Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent, irregular, and self-limited attacks of chest and abdominal pain associated with fever. Human paraoxonase1 (PON1) is an antioxidant enzyme located on high density lipoprotein. ***Objective***: To evaluate the anti-oxidant enzyme, paraoxonase-1, during attack-free period of FMF and to compare the frequency of the PON1 Q/R192 polymorphism in Egyptian children with FMF and control. ***Methods***: This prospective cross-sectional study was conducted on "90" Egyptian children (50 with FMF and, 40 control). Fifty children diagnosed as having FMF according to the new FMF criteria. Determination of disease severity was done using F-SS-2 score. The efficacy of treatment was evaluated using the FMF50 score. Paraoxonase-1 (PON1 Q/R192) genetic polymorphism was detected by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay. Estimation of PON1 serum level was done by enzyme linked immunosorbent assay (ELISA) technique. ***Results***: PON-1 level showed significant increase in controls 273.1 rather than patients with statistically highly significant value. ROC curve defined the best cutoff values of PON-1 level in both groups and showed PON-1 level was reliable to detect oxidative activity (P<0.0001) with sensitivity 68% and specifically 92.5%. Heterozygous mutation was the most frequent and was present in 41 patients (82%). The most frequent mutations in heterozygous type were M694I, E148Q, V726A detected in 12 patients of 50 (24%). In correlation between serum PON-1 and presence of one or more mutated MEFV gene, there was significant relation between serum PON-1 enzyme & FMF gene mutation. ***Conclusion***: Serum PON-1 level was found to be significantly lower in FMF patients reflecting oxidative stress in these patients & PON-1 phenotype didn't show increase risk of disease occurrence in Egyptian children with FMF.

Keywords: Serum Paraoxonase I, Gene Polymorphism, Egyptian, Familial Mediterranean Fever.

INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent, irregular, and self-limited attacks of chest and abdominal pain associated with fever **[1]**. Prevalence of FMF varies throughout the world. The highest prevalence of FMF was reported in Mediterranean and Middle Eastern countries. Although the disease affects mainly Turkish, Armenian, Jewish, and Arabic people, it can be seen all over the world. Beyond the periodic fever attacks and serositis, the most important complication of the disease is amyloidosis. Colchicine, the main therapeutic agent of FMF, prevents amyloidosis highly effectively if it is used properly **[2]**.

The pathogenesis of the disease is not completely understood, even though the FMF gene has been identified **[3]**. Gain of the function mutations of the pyrin, leads to upregulation of the inflammatory cytokines especially interleukin-1B. Over 100 mutations related to FMF have been identified so far. Mutations located in exon 10 such as M694V, M694I, and M680I are related to more severe disease phenotype **[4]**.

Human paraoxonase1 (PON1) is an antioxidant enzyme located on high density lipoprotein. It has been associated with the detoxification of organophosphates and possibly in the prevention of low-density lipoprotein oxidation **[5]**.

Two major genetic polymorphisms of PON1 have been described due to glutamine or arginine at position 192 (Q/R192) and methionine or leucine at position 55 (L/M)**[6]**. PON1 activity and polymorphisms have been found to be associated with several diseases as SLE, Behcet disease, rheumatoid arthritis and Henoch-Schönlein purpura **[5]**. This study was done to evaluate the anti-oxidant enzyme, paraoxonase-1, during attack-free period of FMF and to compare the frequency of the PON1 Q/R192 polymorphism in Egyptian children with FMF and control.

Patients and methods

This prospective cross-sectional study was conducted on "90" Egyptian children (50 with FMF and, 40 control) in Specialized Pediatric hospital Faculty of Medicine, Cairo University (Abo Elresh Hospital). Fifty children diagnosed as having FMF according to the new FMF criteria **[7]** and in attack-free period (At least 2 weeks

from the end of last FMF attack period according to the physical examination and clinical symptoms), together with forty healthy children, age and sex matched, coming for regular follow-up at the outpatient clinic. Inclusion criteria included patients with age of disease onset before 18 years and were in attack-free period. Exclusion criteria included patients with acute FMF attack, patients with associated autoimmune disorders or with abnormal lipid profile.

METHODS

Fifty FMF patients who were being followed-up in the Pediatric Rheumatology clinic of the Specialized Pediatric hospital, Cairo University from the period of October 2014 to May 2015 were interpreted with respect to demographic data (age, sex, family history of FMF), and full clinical examination including weight, height, age at onset of illness, age at initiation of colchicine, number of attacks /month, duration of attack/hour, dose of colchicine at time of study and clinical pattern of the disease as fever, abdominal pain, arthritis.

Determination of disease severity was done using F-SS-2 score. The Degree of Severity in Familial Mediterranean Fever (FMF), as defined by **Mor et al., [8]** is determined using six clinical criteria. These include; having more than one site of inflammation during a single attack, more than two affected sites over the course of the disease, demanding more than 2 mg of colchicine per day to attain remission, suffering more than two pleuritic attacks during the disease course, having more than two episodes of erysipelas-like erythema, and having disease onset before the age of 10 years. Based on the number of criteria met, disease severity is classified as severe if more than three criteria are present, intermediate if two criteria are met, and mild if fewer than one criterion is fulfilled.

The efficacy of treatment was evaluated using the FMF50 score **[9]**, which includes 7 criteria assessing treatment response: changes in attack frequency and duration, patients'/parents' and physicians' global assessments of disease severity (each on a 10 cm visual analogue scale), changes in arthritis attacks, exertional arthralgia/myalgia/leg pain, and acute phase reactants (measured at least two weeks after the last attack). A positive treatment response was defined as improvement in at least five of six criteria without worsening in any, demonstrating high sensitivity and specificity.

Complete blood picture (CBC), ESR, C-reactive protein, triglyceride, total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol measurements were made in the hospital's laboratory at time of study. Paraoxonase-1 (PON1 Q/R192) genetic polymorphism was detected by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay. Estimation of PON1 serum level was done by enzyme linked immunosorbent assay (ELISA) technique.

Regarding estimation of Paraoxonase-1 (PON1) level in serum, venous blood samples of the participants (patients and controls) were obtained by sterile venipuncture. Samples were centrifuged and serum was separated in a sterile plain tube. Samples were stored at –80°C degrees until they were analyzed. Serum PON-1 level was determined using Human Paroaxanose-1 (PON) ELISA kit (Cat. No.201-12-2158, Sigma Aldrich Co, UK).

The sensitivity of this assay was defined as the lowest protein concentration that could be differentiated from zero. It was determined by subtracting two standard deviations to the mean optical density value of twenty zero standard replicates and calculating the corresponding concentration.) Assay range was 2ng/ml to 600ng/ml. This assay has high sensitivity and excellent specificity for detection of PON1.

Serum PON1 level was measured with spectrophotometric method at which dietyl-pnitropheyilphosphate is used as substrate. Molar absorptivity coefficients (17100 M-1 cm-1 and 1310 M-1 cm-1, respectively) were used for calculation of activities of PON1. One unit for PON1 activity was defined as 1 nmol 4 nitrofenol/ mL serum/min.

Regarding determination of PON1Q/R192 genetic polymorphism, venous blood samples were obtained from all the participants (patients and controls) by sterile venipuncture in EDTA vacutainers. Blood samples were kept at -20oC until being processed. Genomic DNA extraction from peripheral blood leucocytes was done using Gene JET Whole Blood Genomic DNA purification Mini kit (Fermentas Life Sciences, Canada) according to manufacturer's instructions. The concentration and purity of the recovered DNA were assessed by spectrophotometry, and the samples were stored in elution buffer at −20°C until use. Detection of PON1Q/R192 single nucleotide polymorphism (SNP) was performed by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique **[10]**. Amplification was performed in a thermocycler (Perkin Elmer 9700; Perkin Elmer, Foster City, CA, USA) using the following program: initial denaturation (heating) at 94°C for 4 minutes followed by 32 cycles of 40s at 94°C, 50s at 58°C, and 40s at 72°C, with a final extension step of 10 min at 72°C. Digestion of the PCR production with 3U of ***BspPI*** (Fermentas, Lithuania) resulted in three fragments of 99 bp, 66 bp and 33 bp. All digested products were analyzed on 3% agarose gel stained with ethidium bromide and examined under ultraviolet transillumination.

Statistical Analysis

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 15.8 (MedCalc© Software bvba, Ostend, Belgium). Normality of numerical data distribution was tested using the Shapiro-Wilk test. Skewed numerical variables were presented as median

and interquartile range (IQR) and between-group differences were compared using the Mann-Whitney U test. Fisher's exact test was used to compare independent categorical variables. Ordinal data were compared using the chi-squared test for trend. Correlations were tested using the Spearman rank correlation. Receiver-operating characteristic (ROC) curve analysis was used to examine the value of PON-1 for discrimination between cases and controls and for discrimination between subgroups of patients. P-values <0.05 were considered statistically significant.

RESULTS

Table **(1)** shows that case group included 27 males & 23 females with mean age 8 years and control group included 26 males & 14 females with mean age 8 years. Regarding PON-1 level in FMF case & control group, PON-1 level showed significant increase in controls 273.1 (221.5 – 342.8) rather than patients (165.7±149.2) with statistically highly significant P value (< 0.001). Figure (1) showed the ROC curve defined the best cutoff values of PON-1 level in both groups. It showed that PON-1 level was reliable to detect oxidative activity (P<0.0001) with sensitivity 68% and specifically 92.5%.

Table **(2)** shows numerical characteristic data of cases group, that showed the minimum period between age of presentation till age of diagnosis was 6 months & maximum period was 2 year. Labs were done during attack free period, ESR was elevated in some patients of the study group with mean value 26 and median 21.CRP was elevated in some patients of the study group with mean value 7.7 and median 6. Figure (2) shows that according to FMF severity score**,** 38 patients (76%) had moderate disease severity, and 10 patients (20%) had mild disease severity and only 2 patients (4%) had a severe disease course

Table 1. Demographic characteristics, PON-1 level of FMF cases and controls.

Variable	FMF Cases (n=50)	Controls (n=40)	p-value
Age (years)	8.0 (6.0 – 10.5)	8.0 (5.0 – 10.0)	.466¶
Gender (M/F)	27/23	26/14	.389§
PON-1 level (U/l)	97.5 (48.5 – 264.5)	273.1 (221.5 – 342.8)	**<.001**

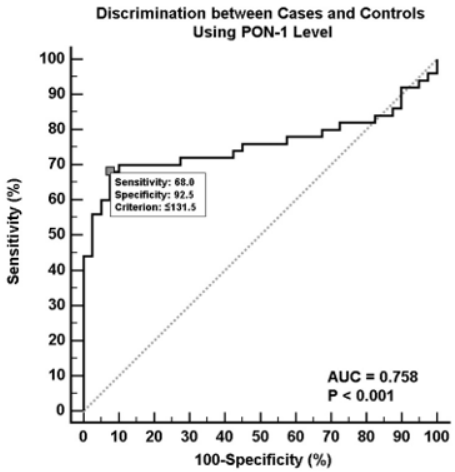

Figure (1**):** Receiver-operating characteristic (ROC) curve for discrimination between cases and controls using PON-1 level with sensitivity 68% and specificity 92.5%.

Table 2. Characteristics and laboratory investigations of FMF cases

Variable	Minimum	Maximum	Mean	SD	Percentiles			Media
					25th p.	50th p.	75th p.	
Current age (years)	1.4	15.0	8.3	3.5	6.0	8.0	10.5	
Age at presentation (years)	.0	12.0	4.6	3.2	2.5	4.0	6.0	
Age at diagnosis (years)	.6	14.0	6.6	3.2	4.0	6.3	8.0	
Duration of disease (years)	1.0	11.0	3.6	1.9	2.0	3.0	4.5	
Frequency of attackes per month	.04	4.28	2.42	4.58	.50	1.00	2.00	
Duration of colchicine therapy (years)	.08	7.00	1.63	1.30	1.00	1.00	2.00	

TLC (k/mm^3)	3.5	16.4	7.1	2.8	5.0	6.4	8.0	6.4
Hemoglobin (g/dl)	9.8	15.6	12.1	1.0	11.5	11.9	12.7	11.9
Platelets (k/mm^3)	137	481	291	80	226	277	328	277
CRP (mg/l)	6.0	48.0	7.7	7.0	6.0	6.0	6.0	6.0
ESR (mm/h)	8	70	26	15	16	21	32	21
HDL (mg/dl)	16	69	34	15	20	30	49	30
LDL (mg/dl)	90	151	118	14	106	118	127	118
TAG (mg/dl)	60	135	87	20	69	80	107	80
Total clolesterol (mg/dl)	98	190	144	25	124	143	167	143

TLC: total leucocytic count (n: 4000-11000 k/mm^3), CRP: C-reactive protein (n: < 6), ESR: erythrocyte sedimentation rate (n: 20 mm/hr), HDL: high density lipoprotein (n: > 35 mg/dL), LDL: low density lipoprotein (n: 65-160 mg/dL), TAG: triglyceride (n: up to 150 mg/dL)

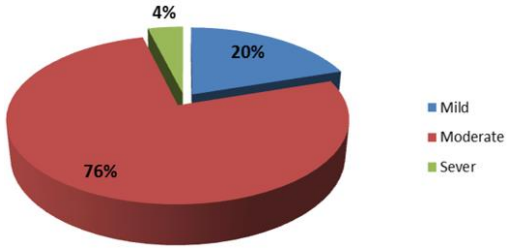

Figure (1): Severity score

Table **(3)** shows that heterozygous mutation was the most frequent and was present in 41 patients (82%) followed by compound heterozygous present in 7 patients (14%) and then homozygous mutation present in 2 (4%). The most frequent mutations in heterozygous type were M694I, E148Q, V726A detected in 12 patients of 50 (24%), while the most frequent mutation in compound heterozygous type wasM694V-M694I detected in 3 patients (6%) thenE148Q-V726A was found in 2 patients (4%)**.**

Table (3**):** Mutation type in the FMF cases

Gene	**Homo (2) N. (%)**	**Hetero (41) N. (%)**	**Compound hetero (7) N. (%)**
V726A	0 (0.0%)	12 (24.0%)	0 (0.0%)
E148Q	0 (0.0%)	12 (24.0%)	0 (0.0%)
M694I	1 (2%)	12 (24.0%)	0 (0.0%)
M680I	0 (0.0%)	5 (10.0%)	0 (0.0%)
M694V-M694I	0 (0.0%)	0 (0.0%)	3 (6%)
E148Q-V726A	0 (0.0%)	0 (0.0%)	2 (4%)
M694V	1 (2%)	0(0.0%)	0 (0.0%)
M680 (GIC)V726A	0 (0.0%)	0 (0.0%)	1 (2%)
V726A-E148Q	0 (0.0%)	0 (0.0%)	1 (2%)
Total	2 (4%)	41 (82%)	7 (14%)

Patients were divided into two groups according to PON-1 level, group 1 had normal PON-1 level (PON-1 >148 U/l) (n=16) and group 2 had low PON-1 level (PON-1 ≤148 U/l) (n=34). Table **(4)** shows that there was significant relation between serum PON-1 enzyme & frequency of attacks per month, as with low PON-1, there were increased frequency of attacks per month. In correlation between PON-1 and lab. parameters, there was highly significant relation (P<0.001) between PON-1 level & HDL, as normal levels of PON-1 enzyme with high HDL levels & low PON-1 levels with low HDL levels, also there was significant correlation between PON-1 level& ESR (P<0.022). In correlation between PON-1 level and clinical features, PON-1 showed no statistically significant difference with clinical features. In correlation between PON-1 and FMF50 score, PON-1 showed no statistically significant relation with FMF50 score. In correlation between serum PON-1 and presence of one or more mutated MEFV gene, there was significant relation between serum PON-1 enzyme & FMF gene mutation.

Table (4): Relation between PON-1 level and patients' characters, laboratory parameters, clinical features, FMF50 score, and FMF Gene mutation

Variable	**Normal PON-1 level (n=16)**		**Low* PON-1 level (n=34)**		**p-value¶**
	Median	**IQR**	**Median**	**IQR**	

Current age (years)	8.8	6.0 – 11.0	8.0	5.5 – 10.5	.404
Age at presentation (years)	5.0	2.8 – 7.5	3.0	2.0 – 6.0	.135
Age at diagnosis (years)	7.0	5.3 – 9.0	5.8	3.5 – 8.0	.189
Duration of disease (years)	3.0	3.0 – 4.0	3.3	2.0 – 5.0	.942
Frequency of attacks per month	.50	.50 – 1.0	1.00	.50 – 4.0	**.044**
Duration of colchicine therapy (years)	1.0	1.0 – 2.0	1.00	1.0 – 3.0	.930
laboratory Parameters					
TLC (k/mm3)	6.1	4.7 – 7.1	6.5	5.2 – 8.5	.183
Hemoglobin (g/dl)	12.3	11.8 – 13.0	11.8	11.4 – 12.7	.086
Platelets (k/mm3)	277	215 – 312	277	234 – 331	.467
CRP (mg/l)	6.0	6.0 – 6.0	6.0	6.0 – 6.0	.110
ESR (mm/h)	26	20 – 35	20	14 – 31	**.022**
HDL (mg/dl)	51	37 – 60	25	20 – 32	**<.001**
LDL (mg/dl)	119	107 – 127	117	105 – 124	.610
TAG (mg/dl)	84	69 – 105	80	70 – 107	.876
Total cholesterol (mg/dl)	133	116 – 170	147	128 – 167	.365
Clinical Features					
Fever	16 (100%)		34 (100%)		NA
Abdominal pain	16 (100%)		34 (100%)		NA
Chest pain	9 (56.3%)		15 (44.1%)		1.000¶
Myalgia	12 (75%)		21 (61.8%)		.773¶
Arthralgia	14 (87.5%)		24 (70.6%)		.324¶
Oral ulcers	3 (18.8%)		6 (17.6%)		.266¶
Arthritis	1 (6.3%)		5 (14.7%)		.385¶
Convulsions	0 (0%)		1 (2.9%)		.440¶
Testicular affection	0 (0%)		0 (0%)		NA
Erysipelas-like rash	0 (0%)		1 (2.9%)		.440¶
Vasculitis	0 (0%)		0 (0%)		NA
FMF50 Score					
Good response to colchicine therapy	16 (100%)		21 (61.8%)		0.058
Poor response to colchicine therapy	0 (0.0%)		13 (38.2%)		
FMF Gene mutation					
Heterozygous	14 (87.5%)		27 (79.4%)		**.010**
Compound heterozygous	2 (12.5%)		5 (14.7%)		
Homozygous	0 (0.0%)		2 (5.9%)		

Regarding PON-1 Q192 Rallele frequency in FMF cases, the Q allele was observed in (72%), while the R allele was found in (28%). While, within the control group, the Q allele frequency was (54%), and the R allele frequency was (26%). Table **(5)** shows that there was no statistically significant relation between the PON-1 phenotype and FMF (odds ratio = 1.46, 95% CI = 0.62 – 3.44, p-value = 0.387). However, PON-1 ≤131.5 U/l was associated with significantly higher risk for FMF (odds ratio = 26.21, 95% CI = 7.01 – 97.92, p-value < 0.0001).

Table (5**):** Risk analysis for the relation between FMF and PON-1 phenotype or PON-1 level.

		Case group	**Control group**	**OR (95% CI)**	**p-value***
PON-1 phenotype	QR	28	26	1.46 (0.62 – 3.44)†	0.387
	QQ	22	14		
PON-1 level	PON-1 >131.5 U/l	16	37	26.21 (7.01 – 97.92)‡	**<0.0001**
	PON-1 ≤131.5 U/l	34	3		

OR = odds ratio, 95% CI = 95% confidence interval, †QQ phenotype was referenced to QR phenotype, ‡PON-1 ≤131.5 U/l was referenced to low PON-1 level, PON-1 >131.5 U/l was referenced to normal PON-1 level.

DISCUSSION

Familial Mediterranean fever is the most common monogenic auto-inflammatory disease, presented with recurrent attacks of fever, polyserositis, and arthritis **[11, 12]**. Beyond the periodic fever attacks and serositis, the most important complication of the disease is amyloidosis. Colchicine, the main therapeutic agent of FMF, prevents amyloidosis highly effectively if it is used properly **[2]**.

Mutations in the MEFV gene are associated with increased interleukin-1β (IL-1β), which causes excess inflammation **[13]**. Mutations located in exon 10 such as M694V, M694I, and M680I are related to more severe disease phenotype **[4]**.

In the present study, the mean age was 8.0 (6.0 – 10.5) years (SD± 3.5). Whereas mean age at diagnosis was 6.6 years (SD± 3.2). Regarding the gender, 27/50 (54%) of patients were males, while 23/50 (46%) were females.

There weren't any statistically significant differences between the FMF and control group in terms of age (p = 0.466) and gender (p = 0.389). Similar results were obtained by **Lotfy et al., [14]** the mean age was 9.0±3.7 years. There were (50.7%) males and (49.3%) females (8.5%) of patients had family history of FMF, and (35.2%) of patients had consanguineous parents.

Younger age was reported by **Settin et al., [15]** as the mean age of onset was 6.9 years. There were 56.1% males and 43.9% females. Older age was reported by **[3, 16]**, the mean age for the FMF patients was 10.7 ± 3.1 years. In the FMF group (53.2%) of the patients were female while (46.8%) of them were male.

In our study, the minimum period between age of presentation till age of diagnosis was 6 months & maximum period was 2 years. The disease duration in our study ranged 1 year to 11 years with mean 3.6± 1.9 and median 3.3 years. **Talaat et al., [17]** showed that the meantime interval between disease onset and diagnosis was 2.31 ± 1.57 years ranging from 0.6 – 7 years.

In contrast to us, **Lotfy *et al.*, [14]** reported that the mean age at disease onset was 5.0±2.9 years, and mean age at disease diagnosis was 7.1 ±3.4 years. The mean disease duration was 4±2.8years. This may be due to different number of patients recruited in each study.

In the current study, a male preponderance was noted in all the study population, with an overall M:F ratio of 1.17:1. A male preponderance was noted in different other studies. **Talaat *et al.*, [17]** studied 70 patients with FMF during the period from January, 2011 to July, 2011 also reported a M:F ratio of 1.3:1. **El-Garf et al., [18]** studied 136 Egyptian patients in the period between January, 2005 and July, 2008 recruited from the Rheumatology Clinic, Pediatric Hospital, Cairo University, as well as three referral centers (a general rheumatology, pediatric rheumatology and general pediatric clinics), also reported a M:F ratio of 1.9:1.

In contrast results were reported by **Salah et al., [19]** who studied 45 patients with familial Mediterranean fever (FMF) reported a M:F ratio of 1:1.14. Also, another study by **Salah et al., [20]** reported a M:F ratio of 1:1.07.

In the present study group, abdominal pain, fever, arthralgia, arthritis, myalgia and chest-pain were the most common clinical features and abdominal pain and fever were the most frequent clinical feature present in almost all patients (100%)

Also, **Özer et al., [21]** showed that in their study, abdominal pain 96.1%, fever 84.7%, arthritis 34%, pleuritis 14.4%, erysipelas 4.6%, and by **Settin *et al.*, [15]** abdominal pain was the most common symptom (87.9%) followed by fever (82%), arthritis or arthralgia (56.1%), chest pain (45%) and myalgia (6%), and **Marzouk et al., [22]** showed that the most frequent symptom was abdominal pain (99%), followed by fever (89.7%), arthralgia (79.4%), chest pain (69.1%), myalgia (39.2%), arthritis (33%), and convulsion (7.2%).

In contrast results were recorded by **El-Garf *et al.*, [18]** the most frequent clinical manifestations were fever (85.3%), abdominal pain (63.2%), arthritis (57.4%) and chest pain (14.7%). **Talaat *et al.*, [17]** reported that fever was the most common presenting feature (95.7%), followed by abdominal pain (94.3%), and arthritis (77.1%).

In the present study heterozygous mutation was the most frequent and was present in (82%) of patients followed by compound heterozygous present in (14%) and then homozygous mutation present in (4%).

In contrast to us, **Özer *et al.*, [21]** reported that 22.2% of patients were homozygous, 28.1% were compound heterozygous, 44.4% were heterozygous, 3.3% were wild type, and 1.9% were not analyzed. The most commonly encountered MEFV gene mutation among the patients was heterozygous.

In our study, the most frequent mutations in heterozygous type were M694I, E148Q and V726A detected equally in 24% of patients, while the most frequent mutation in compound heterozygous type wasM694V-M694I detected in 6% then E148Q-V726A was found in 4%.

Different results were reported by **Öktem *et al.*, [3]** patients were classified into three groups according to mutations; M694V homozygotes 27% of patients, compound heterozygotes 40% and heterozygote mutations 33%.

Also, **Shohat and Halpern [23]** reported the diversity of mutations among Arabs. **Talaat *et al.*, [17]** reported that E148Q, V726A, and M680I mutations were the most common mutations seen in the heterozygous group and were found in 27.5%, 20%, and 15%, respectively.

Salah *et al.*, [19] also reported predominance of four rather than a single gene mutation among Egyptian children. The most frequent gene mutation in the patient group was E148Q heterozygous (35.6%), V726A heterozygous (33.3%), M680I heterozygous (28.9%) and the least common was M694V homozygous, which was

detected only in one case (2.2%). This could be related to the heterogeneous origin of the Egyptian population and the marked effect of different civilizations (such as Romans, Byzantines, and Ottomans beside the original Arab inhabitants) on Egypt since the ancient times; exacerbated by its unique location at the crossroads between Africa, Europe, and Asia.
However, the most frequent mutations among the Arabs of North Africa were M694V and M694I **[24]**. In Syrian patients, M694V and V726A mutations were the most common mutations in 45.8% and 26%, respectively **[25]**.

In our study, according to FMF severity score, 76% of patients had moderate disease severity and 20% had mild disease severity and only 4% had a severe disease course. But Kosan **et al**., (2013), 53.2% of patients had mild disease according to weight scoring, and 46.8% were found to be moderate. No patient with severe disease is detected. This may be due to different scoring system in both studies.

In our study, Laboratory investigations were carried out during attack free period, ESR was elevated in some patients of the study group with mean value 26 and median 21. CRP was elevated in some patients of the study group with mean value 7.7 and median 6. Slightly elevated erythrocyte sedimentation rates and C-reactive protein levels in our patients also showed that continuous subclinical inflammation is present in FMF patients even when free of attack. Similar results were reported by **Öktem *et al.*, [3]**.

Similar results were also recorded by **Özer *et al.*, [21]**. CRP values in symptom-free patients were significantly higher than in the control group ($p<0.001$), despite the role of CRP as an acute-phase reactant. CRP values of FMF patients with proteinuria and without proteinuria were compared. There was no significant difference between these 2 groups. While **Yildirim et al., [26]** showed that ESR and CRP values were similar between the FMF group and healthy control groups ($p>0.05$).

In our study PON-1 levels were decreased in patients of studied group below normal concentrations rather than significant increase in control group, similar results were reported by **Kosan *et al.*, [16]**. Various other reports in the medical literature had indicated alterations in serum PON-1 activities for patients with different rheumatic diseases, such as rheumatic arthritis (RA), psoriasis, SLE, and Behcet's disease **[27-29]**.

Erdem et al., [30] assessed serum PON-1 activities in patients with ankylosing spondiolytis (AS) and reported no significant difference in serum PON-1 activities in patients with AS when compared to those of healthy controls.

In our study, similar to the study of **Isik *et al.*, [27] and Kul et al., [31]** PON levels were found to be significantly lower in patients with Behcet's disease (BD)when compared to the healthy control group. Besides, also similar to the study of **Isik *et al.*, [27]** PON levels in the patients of the active group were found to be lower, although not statistically significant, compared to the patients of the inactive group.

In the present study, there was significant difference in serum HDL levels within the patients with FMF. Genotype distribution for the PON1 192 polymorphism of the control group in the present study was like the data obtained for the control groups of previously reported studies **[32, 33]**.

In our study, all patients were further classified according to their PON1 Q/R192 gene polymorphism, namely QQ, QR and RR genotypes, there were 22 (44%) of patients were wild (QQ), 28 (56%) of patients were heterozygous (QR) and no homozygous polymorphism (RR) were reported. Our results were different with a study done by Turkish study of **Öktem *et al.*, [3]**, they classified all patients according to their PON1 Q/R192 gene polymorphism, namely QQ, QR and RR genotypes, PON1 Q/R192 genotype distribution (QQ: 52%; QR: 46 %; RR: 2 %).

In the present study, by using odd's ratio, there is no statistically significant relation between the PON-1 phenotype and FMF (odds ratio = 1.46, 95% CI = 0.62 – 3.44, p-value = 0.387). However, PON-1 level≤131.5 U/l was associated with significantly higher risk for FMF (odds ratio = 26.21, 95% CI = 7.01 – 97.92, p-value < 0.0001). Similar results were obtained by **Öktem *et al.*, [3]**, who showed that there was no statistically significant relation between the PON-1 phenotype and FMF.

CONCLUSION

According to the present study, we can conclude that PON-1 ≤131.5 U/l is considered as a risk factor for having FMF. In conclusion, serum PON-1 levels are useful in predicting risk factor for development of FMF and are important in evaluating inflammation during remission period of FMF.

Ethical Considerations

The study was conducted in agreement with the Declaration of Helsinki, following approval by IRB of the Faculty of Medicine, Cairo University (Approval Code:). An informed and written consent was taken from each patient. All patients in this study were informed about the clinical research and were informed about how the operation is carried out. All data was collected by the researcher himself.

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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REFERENCES

1. Chawla, N., et al. "Strategies for Medical Management of Pediatric Eosinophilic Esophagitis." *Journal of Pediatric Gastroenterology and Nutrition*, vol. 63, no. 6, 2016, pp. e152–57.
2. Yildiz, M., et al. "Evaluation of Co-Existing Diseases in Children with Familial Mediterranean Fever." *Rheumatology International*, vol. 40, no. 1, 2020, pp. 57–64.
3. Öktem, F., et al. "Genetic Polymorphisms of Paraoxonase1 192 and Glutathione Peroxidase1 197 Enzymes in Familial Mediterranean Fever." *Genetics and Molecular Research*, vol. 13, no. 2, 2014, pp. 3292–300.
4. Gangemi, S., et al. "Lack of Clear and Univocal Genotype–Phenotype Correlation in Familial Mediterranean Fever Patients: A Systematic Review." *Clinical Genetics*, vol. 94, no. 1, 2018, pp. 81–94.
5. Hashemi, M., et al. "The L55M Polymorphism of Paraoxonase-1 Is a Risk Factor for Rheumatoid Arthritis." *Genetics and Molecular Research*, vol. 9, no. 3, 2010, pp. 1735–41.
6. Uyar, O., et al. "Investigating Paraoxonase-1 Gene Q192R and L55M Polymorphism in Patients with Renal Cell Cancer." *Genetics and Molecular Research*, vol. 10, no. 1, 2011, pp. 133–39.
7. Yalçınkaya, F., et al. "A New Set of Criteria for the Diagnosis of Familial Mediterranean Fever in Childhood." *Rheumatology*, vol. 48, no. 4, 2009, pp. 395–98.
8. Mor, A., et al. "Evaluation of Disease Severity in Familial Mediterranean Fever." *Seminars in Arthritis and Rheumatism*, vol. 35, no. 1, 2005, pp. 57–64.
9. Ozen, S., et al. "FMF50: A Score for Assessing Outcome in Familial Mediterranean Fever." *Annals of the Rheumatic Diseases*, vol. 73, no. 5, 2014, pp. 897–901.
10. Mackness, B., et al. "Serum Paraoxonase (PON1) 55 and 192 Polymorphism and Paraoxonase Activity and Concentration in Non-Insulin-Dependent Diabetes Mellitus." *Atherosclerosis*, vol. 139, no. 2, 1998, pp. 341–49.
11. Özen, S., Batu, E. D., and S. Demir. "Familial Mediterranean Fever: Recent Developments in Pathogenesis and New Recommendations for Management." *Frontiers in Immunology*, vol. 8, 2017, p. 253.
12. Barut, K., et al. "Familial Mediterranean Fever in Childhood: A Single-Center Experience." *Rheumatology International*, vol. 38, no. 1, 2018, pp. 67–74.
13. Chae, J. J., I. Aksentijevich, and D. L. Kastner. "Advances in the Understanding of Familial Mediterranean Fever and Possibilities for Targeted Therapy." *British Journal of Haematology*, vol. 146, no. 5, 2009, pp. 467–78.
14. Lotfy, H., et al. "Serum Amyloid A Level in Egyptian Children with Familial Mediterranean Fever." *International Journal of Rheumatology*, 2016, pp. 1–6.
15. Settin, A., et al. "Clinical and Molecular Diagnosis of Familial Mediterranean Fever in Egyptian Children." *Journal of Gastrointestinal and Liver Diseases*, vol. 16, no. 2, 2007, pp. 141–45.
16. Kosan, C., et al. "Paraoxonase 1 and Arylesterase Levels in Children with Familial Mediterranean Fever." *European Review for Medical and Pharmacological Sciences*, vol. 17, no. 3, 2013.
17. Talaat, H. S. E.-D., et al. "The Expanded Clinical Profile and the Efficacy of Colchicine Therapy in Egyptian Children Suffering from Familial Mediterranean Fever: A Descriptive Study." *Italian Journal of Pediatrics*, vol. 38, no. 1, 2012, p. 66.
18. El-Garf, A., et al. "MEFV Mutations in Egyptian Patients Suffering from Familial Mediterranean Fever: Analysis of 12 Gene Mutations." *Rheumatology International*, vol. 30, no. 10, 2010, pp. 1293–98.
19. Salah, S., et al. "Bone Mineral Density in Egyptian Children with Familial Mediterranean Fever." *Iranian Journal of Medical Sciences*, vol. 41, no. 1, 2016, pp. 2–?.
20. Salah, S., et al. "MEFV Gene Mutations in Egyptian Children with Henoch-Schönlein Purpura." *Pediatric Rheumatology*, vol. 12, no. 1, 2014, p. 41.
21. Özer, S., et al. "Simple Markers for Subclinical Inflammation in Patients with Familial Mediterranean Fever." *Medical Science Monitor*, vol. 21, 2015, p. 298.
22. Marzouk, H., et al. "Mean Platelet Volume and Splenomegaly as Useful Markers of Subclinical Activity in Egyptian Children with Familial Mediterranean Fever: A Cross-Sectional Study." *International Journal of Chronic Diseases*, 2015, Article ID 152616.
23. Shohat, M., and G. J. Halpern. "Familial Mediterranean Fever — A Review." *Genetics in Medicine*, vol. 13, no. 6, 2011, pp. 487–98.
24. Soriano, A., and R. Manna. "Familial Mediterranean Fever: New Phenotypes." *Autoimmunity Reviews*, vol. 12, no. 1, 2012, pp. 31–37.
25. Mattit, H., et al. "Familial Mediterranean Fever in the Syrian Population: Gene Mutation

Frequencies, Carrier Rates and Phenotype–Genotype Correlation." *European Journal of Medical Genetics*, vol. 49, no. 6, 2006, pp. 481–86.

26. Yildirim, K., et al. "Trace Element Levels in Patients with Familial Mediterranean Fever." *The Eurasian Journal of Medicine*, vol. 43, no. 2, 2011, pp. 79–?.
27. Isik, A., et al. "Paraoxonase and Arylesterase Levels in Rheumatoid Arthritis." *Clinical Rheumatology*, vol. 26, no. 3, 2007, pp. 342–48.
28. Bodolay, E., et al. "Evaluation of Paraoxonase Activity in Patients with Mixed Connective Tissue Disease." *The Journal of Rheumatology*, vol. 35, no. 2, 2008, pp. 237–43.
29. Toker, A., et al. "Serum Lipid Profile, Paraoxonase and Arylesterase Activities in Psoriasis." *Cell Biochemistry and Function*, vol. 27, no. 3, 2009, pp. 176–80.
30. Erdem, F. H., et al. "Evaluation of Serum Paraoxonase and Arylesterase Activities in Ankylosing Spondylitis Patients." *Clinics*, vol. 65, no. 2, 2010, pp. 175–79.
31. Kul, A., et al. "Paraoxonase and Arylesterase Levels in Behçet's Disease and Their Relations with Disease Activity." *Biochemical Genetics*, vol. 55, no. 4, 2017, pp. 335–44.
32. Kafadar, A. M., et al. "Paraoxonase 192 Gene Polymorphism and Serum Paraoxonase Activity in High-Grade Gliomas and Meningiomas." *Cell Biochemistry and Function*, vol. 24, no. 5, 2006, pp. 455–60.
33. van Himbergen, T. M., et al. "Paraoxonase (PON1) Is Associated with Familial Combined Hyperlipidemia." *Atherosclerosis*, vol. 199, no. 1, 2008, pp. 87–94.