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Original Research Article

The spectrum of MEFV gene mutations and genotype-phenotype correlation in Egyptian patients with familial Mediterranean fever

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ABSTRACT

Background: Familial Mediterranean fever (FMF) is an autosomal recessive disease mainly affecting subjects of the Mediterranean origin. It is an auto-inflammatory periodic disorder that is caused by mutations in the Mediterranean fever gene (MEFV) located on chromosome 16.
Methods: The current study was designed to assess the prevalence and frequency of different MEFV gene mutations among 104 FMF clinically diagnosed Egyptian patients and to evaluate the change extent in the values of some biochemical markers (ESR, CRP, Fibrinogen-C, SAA and IL1) in different participants with different FMF severity scores.
Results: According to allele status 28 patients (27%) were homozygous mutation carriers, 38 (36.5%) were with compound heterozygous mutations and 38 (36.5%) were identified as heterozygous for one of the studied mutations. Of the studied mutations, M694I, E148Q, V726A, M680I, and M694V accounted for 28.1%, 26.8%, 16.9%, and 11.3% of mutations respectively. The R761H and P369S mutations were rarely encountered mutations (1.4%). The clinical features with M694I were associated with more severe clinical course. There is a drastic elevation in the levels of estimated parameters as their levels were increased as long as the severity of the disease increased.
Conclusions: The diagnosis of FMF cannot be performed on the basis of genetic testing or clinical criteria alone. So, we recommended the combination between clinical and molecular profiling for FMF diagnosis and scoring.

Keywords: Allele frequency, ASO-PCR, Egyptian population, FMF, MEFV gene

INTRODUCTION

Familial Mediterranean fever (FMF) is the most widespread and best-characterized monogenic Auto-inflammatory disease, affecting mainly ethnic groups originating in or around the Mediterranean basin. This disease is characterized by irregular, self-limited febrile episodes of inflammation of serous membranes and marked elevation of acute-phase proteins. Amyloidosis, the most significant complication of FMF, is the major cause of serious long-term morbidity and mortality.[1]

Its first definition as a disease was based on a case report, published under the title "benign paroxysmal peritonitis" by the allergy specialist Siegel from New York, as a compilation of Jewish patients with similar complaints.

In 1992, it was reported that the abnormality associated with FMF is found on chromosome 16, and the gene responsible for the disease was identified in 1997. The disease is accompanied by a marked decrease in quality of life due to the effects of attacks and subclinical inflammation in the period between attacks.[2]

In the past, various criteria were suggested for diagnosis. One of the most commonly used criteria includes the Tel-Hashomer criteria and diagnosis sets recommended by Livneh et al.[3,4] The clinical symptoms of FMF are non-specific and difficult to distinguish from similar symptoms arising from completely different diseases, i.e. FMF is easily mistaken for appendicitis.[5-7]

The goals of therapy are to reduce morbidity and to prevent complications of the disease. Treatment of FMF at this point consists of taking colchicine, a neutrophil-suppressive agent.[8] Colchicine has been the mainstay of FMF treatment for over 40 years, completely preventing attacks in 60-65% of patients and inducing partial remission in a further 30-35%.[9]

The FMF disease is caused by mutations in the Mediterranean fever (MEFV) gene located on the short arm of chromosome16p13.3. The gene consists of 10 exons and encodes a pyrin protein (also called marenostrin) consisting of 781 amino acids. Although the exact mechanism of pyrin action has not yet been determined, it is considered to be a negative inflammation regulator.[10]

Most of the mutations identified occur in exon 10 (e.g. M680I, M694V, M694I and V726A). Apart from this, mutations in exon 2 (E148Q) and other exons have also been identified. Most of the mutations are point mutations, known as missense mutations, and are characterized by single-nucleotide changes.

No laboratory tests specific to FMF are available at present. Acute phase markers such as the erythrocyte sedimentation rate (ESR), C-reactive protein, fibrinogen and serum amyloid A (SAA) are frequently increased during episodes.[11]

Although the knowledge of FMF is expanding rapidly and the prevalence of FMF mutations in some Arab populations have already been reported, but data on Egyptian population remains very limited. Therefore, this study was aimed to identify the prevalence and frequency of different MEFV gene mutations in Egyptian patients suffering from FMF and to elucidate the probable genotype phenotype correlation between the participants. Furthermore, the present study was performed to evaluate the effectiveness of some biochemical markers in reporting the degree of severity among the mutation carriers.

METHODS

Patients' enrollment

A nationwide survey of familial Mediterranean fever from December 2014 to July 2015 was conducted in accordance with guidelines approved by local research ethics committee that confirms to the ethical guidelines of the 1975 Declaration of Helsinki.

All patients were unrelated of Egyptian origin attending different rheumatology clinics, military hospitals, Egypt and referred by rheumatologists for molecular diagnosis and genetic counseling. All subjects in this study were matched in regard to sex and age. After obtaining written consent of adult patients, personal and medical data were recorded.

Also, 20 healthy subjects were registered in the study as normal control group in order to compare the levels of estimated biochemical parameters between the studied patients group considering this group as reference congregation.

The diagnosis of FMF was based on previous published Tel-Hashomer criteria. Definite diagnosis requires1 or more major criteria, or 2 or more minor criteria. Major criteria were (1) typical attacks of peritonitis, pleuritis, or pericarditis, (2) fever alone, (3) incomplete abdominal attacks, recurrent febrile episodes accompanied by peritonitis, synovitis, or pleuritis, (4) amyloidosis of the AA type without predisposing disease, and (5) favorable response to continuous colchicines treatment. Minor criteria were (1) recurrent febrile episodes, (2) erysipelas-like erythema, (3) FMF in a first-degree relative, (4) incomplete attacks involving chest, Joint, exertional leg pain, and (5) favorable response to colchicine.

Subjects were excluded on the presence of associated disease that could interfere with clinical assessment; rheumatic disorders, gout, hepatobiliary dysfunction, Behçet's disease, malignant lymphoma, irritable bowel syndrome and cardiovascular disorders. Moreover, patients were excluded due to pregnancy, administration of liver vaccination last three months before enrollment and alcohol or drug abuse.

Disease scoring

The disease severity score adopted by Tel-Hashomer was used for assortment of enrolled patients. The scoring system based on six main elements and included the following features: (i) age at onset [11-20 years (2 points), 6-10 years (3 points)and <6 years (4 points)], (ii) number of attacks per month [<1 (1 point), 1-2 (2 points), [2 (3 points)], (iii) acute or protracted arthritis (2 and 3 points, respectively), (iv) presence of erysipelas-like erythema (2 points), (v) dose of colchicine [less than appropriate dose (0 point), appropriate dose (1 point) and more than appropriate dose (2 points)], and (vi) development of amyloidosis (3 points). The severity score is the sum of each parameter. A score of 3-5 is accepted as mild, 6-9 moderate and >9 is severe disease.

Disease treatment

The newly diagnosed naïve adult patients received dose of at least 1 mg daily and increase dose to 1.5-2 mg for patients with ongoing episodes on the previous dose. It is

also recommended to give colchicine in divided doses in case of side effects.

Samples collection

10ml of venous blood samples were withdrawn from different participants in different vacutainer tubes. 4ml were collected on EDTA coated tube for DNA extraction used for mutation screening and determination of ESR value. Two ml of citrated blood was used for detection of fibrinogen C. In the meantime, the rest of blood sample was kept in clean glass tube without additives for the determination of the rest of acute phase reactants including CRP, interleukin 1 and serum amyloid A.

Mutation analysis

Genomic DNA was extracted from peripheral blood samples using the DNA isolation kit according to the manufacturer's instructions (Qiagen, Germany). Patients were screened for eight MEFV gene mutations present in the hotspot regions (exons 2,3 and 10) including E148Q, P369S, M680I, M694V, M696I, V726S, A744S and R761H by ASO-PCR. The sequence of forward and reverse primers for both wild and mutant types used for ASO-PCR was adopted from previous reports and the amplified products were detected by electrophoresis on 2% ethedium bromide stained agrose gel.

Biochemical analyses

ESR was determined according to method described by Westergren, that depends on formation of rouleaux by RBCs that sink at constant rate.[12] CRP was quantified with immunoturbidimetric methods as per the manufacturer's instructions of C-Reactive protein latex kits (COBAS INTEGRA/Cobas System) in Roche Hitachi Cobas C 501 analyzer. Assessment of fibrinogen C was performed on an automated coagulation analyzer (ACP TOP, Beckman coulter and Fullerton, CA). In the meantime, the levels of serum interleukin 1 and amyloid A were determined in accordance with the ELISA manufacturer's instructions (Assaypro, Saint Charles, Missouri, USA).

Statistical analyses

The collected data were analyzed using the statistical package for the social sciences (SPSS software) version 21. Determined variables were expressed as mean ± standard deviation and compared using one way analysis of variance (ANOVA). Computing the correlation matrix of different measured biochemical parameters was also calculated. The genotype frequency was performed using the genetic analysis in Excel 6.5 software and the predictors association with degree of FMF severity was identified. For all statistical tests, a p value of less than 0.05 was considered statistically significant.

RESULTS

The study group consists of 260 clinically diagnosed FMF patients with mean age 23±4 years. Of these referred patients, 156 subjects were excluded from the study due to lack of the clinical information or any conditions makes the subjects unsuitable for inclusion such as enrolment in another study, intake of an investigational drug and failure or refusal to cooperate with given instructions.

The enrolled patients were classified according to mutation and allele status into three groups; homozygous, heterozygous and compound heterozygous mutation carriers. Homozygous mutations were positive in 28 patients (27%) of whom 26 were male and 2 were female. While, 38 heterozygous mutations carriers were included with male: female ratio (0.9:1). Also, compound heterozygous mutations were detected in 22 male and 16 female subjects.

Table 1: Demographic presentation and clinical findings of all studied FMF groups.

Item	Homozygous	Heterozygous	Compound heterozygous	P<
Age (Years)	25.83±2.32	23.75±2.12	25.92±2.26	N.S
Age of onset (Years)	22.21±2.58	20.31±2.51	22.63±2.74	N.S
Age at diagnosis (Years)	24.52±2.75	22.53±2.79	24.46±3.6	N.S
Male: Female	26: 2	18 : 20	22:16	N.S
Family history of FMF (n %)	21 (75.0%)	11 (28.9%)	18 (47.3%)	N.S
Fever	26 (92.8%)	34 (89.5%)	34 (89.5%)	N.S
Abdominal pain	25 (89.2%)	35 (73.6%)	32 (57.8%)	N.S
Arthritis	16 (57.1%)	23 (60.5%)	18 (47.4%)	N.S
Chest attack	14 (50%)	18 (47.4%)	13 (34.2%)	N.S
Amyloidosis	4 (14.2%)	1 (2.6%)	1 (2.6%)	N.S
Splenomegaly	2 (7.1%)	3 (7.9%)	1 (2.6%)	N.S

Among homozygous FMF mutation carriers; the mean age, the mean age of onset and the mean age at diagnosis were 25.83±2.32, 22.21±2.58 and 24.52±2.75 years respectively. Also, these parameters were recorded as 23.75±2.12, 20.31±2.51 and 22.53±2.79 years for heterozygous carrier group. In the meantime, these items were 25.92±2.26, 22.63±2.74 and 24.46±3.6 years in compound heterozygous mutation carriers.

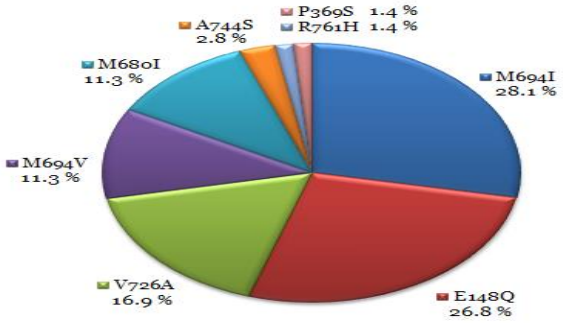

Figure 1: Allele frequency of different screened mutations among FMF participants.

As regards the clinical features of the study groups; fever and abdominal pain were the most predominant presenting features in all groups. While, arthritis and chest attack were detected at constant relative rate in homozygous and compound heterozygous groups. Amyloidosis and splenomegaly were the least documented features that detected in the different study groups. Table 1 lists the main demographic and clinical characteristics of all study groups.

The results of clinical diagnosis of the enrolled subjects showed 30 patients with mild FMF symptoms and 34 subjects suffering from moderate FMF episodes. In addition, 40 patients with severe attacks were monitored.

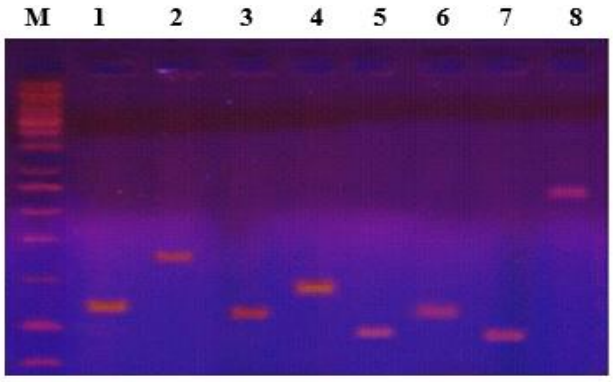

Figure 2: ASO-PRO products on ethidium bromide stained agarose gel for representative patient's samples: M: DNA marker (100-1500 bp), lane 1-8: DNA of patient amplified by primer for; E148Q mutation (227 bp), P369S mutation (352 bp), M680I mutation (219 bp), M694V mutation (275 bp), M694I mutation (192 bp), V726A mutation (230 bp), A744S mutation (183 bp) and R761H mutation (671 bp) respectively.

Altogether the distribution of genotypes in the 104 included patients presented in Figure 1 demonstrated that, the most common genotype was M694I (28.1 %) followed by E148Q (26.8 %) and V726A (16.9 %). Of the FMF mutations analyzed in this study, R761H and P369S mutations were relatively rare among patients of this ethnic group (1.4%). Figure 2 showed representative samples of ASO-PCR products for the different diagnosed FMF mutations on ethidium bromide stained gel.

Table 2: Comparison between disease severity score in the three study groups.

	Homozygous (n %)	Heterozygous (n %)	Compound (n %)
Mild	6/28 (21.4%)	20/38 (52.7%)	4/38 (10.5%)
Moderate	8/28 (28.6%)	10/38 (26.3%)	16/38 (42.1%)
Severe	14/28 (50%)	8/38 (21%)	18/38 (47.4%)

In details, the frequency of the detected homozygous mutations were monitored with the following decreasing order M694I (17.35%), M680I (3.8%), V726A (3.8%) and M694V (1.95%). In the heterozygous group, the most common mutation was E148Q with percentage of (26.8%) followed by M680I with percentage 5.8%. In contrast, the rare mutations detected in this group of mutation carriers were M694I, V726A and A744S with percentage less than 2%. Itemizing 38 compound heterozygous group, the point mutations observed in the following order; M694I/V726A, E148Q/M694I, E148Q/V726A, M694I/M694V, M694V/V726A and M680I/M694I.

The disease severity score was mild in 28.8% of patients which noted in significant proportion in heterozygous population than other populations. Out of 34 moderate FMF patients, 10 subjects were carriers for heterozygous mutations. While homozygous mutations were documented in 8 patients and the rest of moderate cases were with compound heterozygous mutations. In the 40 severely affected FMF participants, 14 subjects were homozygous, 8 were heterozygous and the remaining

were compound heterozygous mutation carriers (Table 2).

The results of examination of genotype-phenotype correlation corroborated that, the clinical features with M694I in different forms were associated with more severe clinical course compared to those seen with other mutations. While the distribution and frequency of M694I and E148Q were higher in moderate cases. Also, M694I were implicated in mild FMF episodes with high frequencies. From this stand point; M694I was considered as bad genotype that affects the degree of FMF severity.

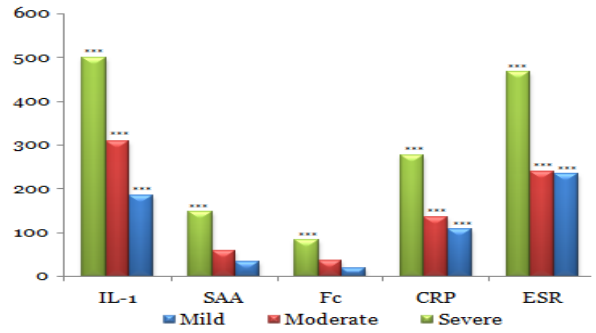

Figure 3: Percentage change of ESR, CRP, fibrinogen-C, SAA and IL-1 in all groups versus control group.

The results of biochemical investigations presented in Figure 3 revealed that, a drastic highly significant elevation in interleukin 1, ESR and CRP values were observed on admission in all FMF patient groups when compared with their levels in normal control group. Also, the mean levels of SAA and fibrinogen C were highly significant increase in sever group by 248.52% and 83.25% respectively in comparison with their levels in reference group. In contrast, non-significant differences in mild and moderate cases were observed.

DISCUSSION

Awareness of the incidence, prevalence of disease, and health threats are essential for more effective prevention and treatment of diseases and for elucidating environmental, behavioral, and biological factors associated with health conditions.

Although there is plenty of literature on FMF, there are only a few studies about the outcome measurements of this disorder. Moreover, the tools to assess the outcome have been developed for FMF patients. Since the identification of MEFV as the gene mutated in FMF, genetic analysis has become useful for confirming the diagnosis made traditionally by clinical findings.

As a Mediterranean population, Egyptians are particularly prone to develop FMF. To some extent, little information is available on the molecular spectrum of FMF in Egyptian patients.

From this stand point, this study aimed to identify the distribution and frequency of MEFV mutations in patients who had been diagnosed as having FMF and to elucidate the precise genotype-phenotype correlation in a cohort of Egyptian FMF patients. In the same time, the present study was performed to evaluate the effectiveness of some biochemical markers in reporting the degree of disease severity among the participants.

In this study, male preponderance was noted in the most of the study population, with overall male: female ratio of 1.7: 1. This demographic finding was mostly similar to previous studies as Elgarf et al, accounted a relatively closed ratio (1.9: 1).[13] Settin et al who studied Egyptian FMF patients for confirmation of the diagnosis through molecular analysis also reported male superiority.[14] In contrast, Dusunsel et al documented female plurality with male: female ratio of 1: 1.3.[15] From these findings we suggested that, FMF may have incomplete penetrance in male or female subjects.

The mean age of disease onset and age of FMF diagnosis in our patients were comparable to some extent with the results obtained in the previous retrospective clinical and molecular studies that were carried out by Ebru and Tunca et al.[16,17] It has been suggested that the late onset and longer delay in the diagnosis might be results from mild and moderate phenotypic manifestation due to environmental factors and extremely low incidence of the disease.

The rate of parental consanguinity has been reported in the previous study as 20-25%.[18] Parental consanguinity of our patients was higher (48%) compared to mentioned percentage of the studied population. More frequent parental consanguinity may be responsible for the higher ratio of parent-to-offspring transmission.

The clinical features of FMF in the studied group differ somewhat from those of other populations of the Mediterranean basin. The most common symptom is fever (90.3%) and the other frequent symptoms reported were abdominal pain and arthritis. These results are closer to frequencies of FMF manifestations in previous studies from Arab countries, Italy, Armenia, Turkey and Israel that reported the clinical findings as follows: fever 92-100%, abdominal pain 91-96% and arthritis 33-70%.[19]

Although the clinical symptoms and the other course of the illness are still the cornerstone of the diagnosing FMF, molecular confirmation can help and make the diagnosis earlier in suspected cases.[20] Identification of the causative gene, MEFV, with genetic analysis is useful for establishing or confirming the diagnosis of FMF, especially in the following situations: atypical clinical signs, late onset beginning, and absence of family history or ethnic background.[4,21,22]

The reported FMF mutations in heterozygote form and compound heterozygote were the most frequent variants observed among the studied population (36.5 % for each) compared to the frequency of homozygote form (27%). This observation was Contradictory with the results of Oztuzcu et al who reported that; the mutations were heterozygous in 62.6%, compound heterozygous in 15%, homozygous in 22.4%.[23] The discrepancy in the results is possible to different sample size, different origin of the participants or genetic heterogeneity.

The five most commonly observed mutations; M694V, M680I, M694I, V726A and E148Q, are responsible for a large percentage (about 65-95%) of observed mutations in different ethnic groups.[19]

M694I mutation frequency was documented as 28.1% in the studied population. The vast majority of this variant was in homozygotic form (17.35%). According to this observation, the frequency of M694I is consistent with previous reports that confirming that, M694I is the most common mutation in Arabian countries including Egypt (42.5%), Algeria (80%), Morocco (37%), and Tunisia (25%).[24,25]

E148Q is one of the five most frequent mutations in all reports and it is the second most common mutation in many studies.[23,26,27] In the present study, E148Q was the second most common mutation with the frequency of 26.8%. However, in other previous reports, the E148Q mutation has been found as the most common mutation in FMF patients.[28] Also, E148Q was identified as the third common mutation in studies conducted by Dundar et al and Ceylan et al with frequencies of 4.42% and 5.15%, respectively.[29,30]

The obtained results clarify that, the third most common mutation was V726A, (16.9%). In previous studies that were performed by Gunesacar et al and Akin et al, the allele frequency of the V726A mutation apprised to be ranged between 1.9% and 13.0%.[26,31] Although V726A was the third most common mutation in several studies, it was the fourth most commonly observed mutation in many studies.[17,23,31,32] Otherwise, V726A is the second most common mutation in Arabs and non-Ashkenazi Jews.[19]

R761H and P369S mutations were monitored as rare mutations of the MEFV gene in our group with 1.4% frequencies. In addition, other reports stated that R761H and P369S were rare mutations as well. In recent studies, the allele frequencies were heightened and ranged from 0.55% to 4.96% for R761H and from 0.99% to 3.77% for P369S.[6,23,32] Therefore, these mutations should be adopted in routine screening profile.

From all mentioned data we can accomplish that, the opposition in our molecular observations is conceivable due to variation in sample size, different radix or genetic puzzle.

Inflammation is the hallmark of rheumatic diseases. Tissue injury response promotes several modifications, which result in elimination of the offending agent, limitation of tissue damage, and restoration of affected structures. The acute-phase inflammatory response includes changes in humoral and cellular components derived from stimuli of cytokines released after tissue injury. The analysis of markers involved in these reactions allows monitoring of the response evolution, and is very useful in the follow-up of patients.[33]

No laboratory tests specific to FMF are available at present. But many reports demonstrated that, acute phase markers such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP), fibrinogen C, serum amyloid A (SAA) and interleukin1 (IL-1) are frequently increased during FMF episodes.[11,34] Also we have got the same observations that are aligned with these reports.

The increase in the levels of acute phase markers largely reflects the inflammatory status in the participants, resulting primarily from the effects of cytokines produced during the inflammatory process by macrophages, monocytes, and a variety of other cells. Interleukin (IL)-6 is the major inducer of most acute phase markers. Some of the other major cytokines relevant to the acute phase response are IL-1 beta, tumor necrosis factor (TNF)-alpha, and interferon gamma. These cytokines also suppress the synthesis of albumin, which is termed a "negative acute phase protein" because its levels decrease with inflammation.[35]

CONCLUSION

In conclusion, there has been some debate about the use of clinical versus genetic criteria, as the diagnosis of FMF cannot be made on the basis of genetic testing alone. In addition, the Tel-Hashomer clinical criteria do not clearly distinguish between different FMF cases. So, we recommend the combined clinical and molecular profiling are useful to discriminate the different phenotypes of FMF. Also, further studies involving a multicentric FMF registration should be established to affirm a correlation between the MEFV genotype and various clinical findings in different ethnic populations.

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