Clinical and Molecular Diagnosis of Familial Mediterranean Fever in Egyptian Children

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Abstract

Background. Familial Mediterranean Fever (FMF) is an autosomal inherited disorder affecting certain races including Arabs. Diagnosis depends mainly on clinical basis, but mild forms may remain undiagnosed. **Objectives.** This study aims at an accurate diagnosis of FMF in Egyptian children by detection of genetic mutations in addition to clinical assessment. **Subjects and methods.** Subjects included 66 Egyptian cases (37 males and 29 females) with a mean age of onset of 6.9 years. They had been referred from health centers and hospitals of the Delta region, Egypt. Analysis of the clinical manifestations was performed using Tel-Hashomer criteria in addition to 10 items clinical score system. For all these cases, DNA analysis was made for three common mutations M680I, M694V, and V726A using amplification refractory mutation system (ARMS-PCR) technique. **Results.** Most of the cases had attacks ranging from 3-5 days duration with the mean of 3.6 days. Their rate of recurrence was variable but 47 % of them had suffered attacks 10-30 times/ year. Abdominal pain was the most common symptom (87.9%) followed by fever (82%), arthritis or arthralgia (56.1%), chest pain (45%) and myalgia (6%). Laparotomy had been done during attacks for exploration or appendectomy in 27.7% of cases. Positive mutations were detected among 42 cases (63.6%), of them 14 (21.2%) were compound heterozygotes, 7 (10.6%) were had homozygotes while 21 (31.8%) were simple heterozygotes. Allele M694V was the most frequent one (18.8%) followed by V726A (17.4%) and M680I (12.1%). Taking positive mutation as a guide for diagnosis, a cutoff clinical score level was determined with =15 for unlikely, =20 for definite and 15-20 for probable diagnosis. **Conclusion.** Diagnosis of FMF among Egyptian children cases although based mainly on clinical suspicion requires to be confirmed through detection of the corresponding mutation which can be easily made using the simple ARMS-PCR technique.

Key words

Familial Mediterranean Fever - MEFV gene mutations - diagnosis - clinical aspects

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Introduction

Familial Mediterranean Fever (FMF), or recurrent polyserositis, is a recessively inherited disorder that especially affects Sephardic Jews, Turks, Armenians and Arabs. In these populations, the carrier frequency was estimated to be as high as 1 in 5 persons (1,2).

The disorder is characterized by recurrent episodes of unprovoked inflammation involving the joints; the pleural and peritoneal cavities; and less frequently, the skin. FMF peritonitis, the most common manifestation of this disease, may resemble acute abdomen, leading to laparotomy and appendectomy that reveal only an inflamed peritoneum and neutrophilic exudates. If a surgical procedure is avoided, the attack resolves itself spontaneously (3).

Patients are treated with colchicine, a neutrophil-suppressive agent that has been shown to decrease the frequency and severity of attacks when administered on a long-term basis. Some patients develop amyloidosis that can also be prevented by prophylactic colchicine administration (4).

Until recently, diagnosis of FMF was based on clinical manifestations, ethnicity, family history and response to colchicine. In cases where these components are atypical or unhelpful, FMF was difficult to diagnose. After identification and isolation of the gene responsible for FMF (*MEFV*) on short arm of chromosome 16, diagnosis of FMF became reliable (5).

The three common *MEFV* gene mutations: M680I, M694V, and V726A can be rapidly and accurately characterized using the amplification refractory mutation system based on the polymerase chain reaction (ARMS-PCR) technique (6).

This study was planned as an attempt to obtain accurate diagnosis of FMF among Egyptian children cases using molecular genetic technique (PCR-ARMS). This includes the assessment of the three common mutations in the Mediterranean area in addition to adequate analysis of presenting clinical manifestations.

Subjects and methods

This study comprised 66 childhood cases with a suspected diagnosis of FMF. Their manifestations at referral time ranged from full blown textbook picture of the disease e.g recurrent high fever with abdominal pain, joint affection, myalgia, chest pain, etc to clinical situations with hesitant diagnosis. These cases were referred from various hospitals and health centers of the Nile Delta region of Egypt to Genetics Department, Mansoura University Children Hospital for confirmation of diagnosis through molecular analysis. They included 37 males and 29 females. Their age mean ± SD was 10.48+ 3.85 years. The age of onset, however, was before the age of 10 years in most of the cases (51 cases, 92.4%) with a mean ± SD of 6.9 ± 2.8 years. Informed consent was obtained from all subjects in addition to an approval from the local University authority to establish a DNA test for routine diagnosis of FMF cases.

I. Analysis of clinical manifestations

The clinical manifestations of these cases were analyzed according to Tel-Hashomer clinical criteria for confirmation of diagnosis (7,8). In addition, these manifestations were also analyzed according to a score system of 10 items developed by us comprising family history, consanguinity, attack duration and frequency, fever, abdominal pain, chest pain, joint affection, myalgia and history of operations. Distribution of cases according to this score system is shown in Table I. This score has a maximum value for diagnosis of 27 and a minimum of 10. In this 10 items score, we excluded colchicine response (adopted by Tel-Hashomer) due to the drug non-compliance in the form of "irregular use", "use only during attacks" or "not using at all".

II. DNA extraction and purification

Venous blood samples (3 ml) were collected on EDTA (ethylenediamine tetraacetate) containing tubes, DNA was extracted promptly using DNA extraction and purification kit (Gentra Systems, USA) according to manufacturer's instructions and then stored at -20 C till use.

III. Mutation analysis

For the 66 cases the three common mutations were analyzed using ARMS-PCR method as described previously (6). This assay comprised two complementary reactions, each was conducted with the same substrate DNA. One reaction included an ARMS primers specific for the normal DNA sequence while the second included a mutant-specific primers. The complementary reaction with the normal primer set served as an internal control for PCR amplification and

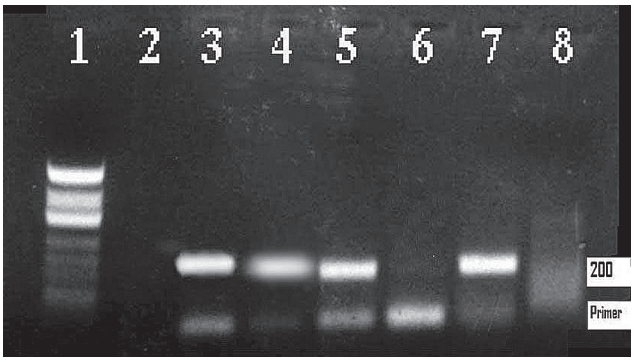

Fig.1 DNA electrophoresis of amplified segments of FMF gene (~200bp) using normal and mutant primers corresponding to mutations: M694V (lanes 3,4 showing positive bands for the mutant and normal primers), V726A (lanes 5,6 showing only positive band for the normal primer) and M680I (lanes 7,8 showing only positive band for the normal primer) indicating that this case is genotyped as M694/undefined. Lane 1 shows DNA size marker, and lane 2 corresponds to negative control (no DNA sample).

Fig.2 DNA electrophoresis of amplified segments of FMF gene (~200bp) using normal and mutant primers corresponding to mutations: M694V (lanes 3,4 showing positive bands for the mutant and normal primers), V726A (lanes 5,6 showing positive band for the normal and mutant primers) and M680I (lanes 7,8 showing positive band for the normal primer only) indicating that this case is genotyped as M694/V726A. Lane 1 shows DNA size marker, and lane 2 corresponds to negative control (no DNA sample).

allowed discrimination of homozygotes from heterozygotes. In addition, master mixes were used to check for integrity of individual of materials Confirmation of negative reactions by a second set of experiments was done as well.

Each DNA sample was tested for the three mutations. The PCR amplification was performed in a final volume of 25 µL containing 100 ng of purified genomic DNA, 0.5 U of Taq polymerase and its 1X PCR buffer (contains 15 mmol/L of MgCl2), 0.2 mmol/L of deoxynucleoside 5'-triphosphate mix, and 10 pmol of each primer. The reaction was heated to 94°C for 9 minutes for denaturation, followed by 35 cycles with denaturation at 94°C for 10 seconds, annealing at 60°C for 10 seconds, and extension at 72°C for 30 seconds. Final extension was done for 10 minutes at 72°C. The amplified products were separated by electrophoresis on a 2% agarose gel. Ethidium bromide staining of the agarose gel was used to detect the amplified fragments.

Results

Analysis of the presenting clinical manifestations of studied cases (Table I), showed that 21.2 % of them had a positive family history for FMF. Parental consanguinity was positive in 63.3 % of these cases. Attack duration was 3-5 days in most of the cases (66.4%) with a mean ± SD of 3.58±2.29 days. Regarding the frequency of attacks per year, 47 % of cases suffered attacks rating between 10 to 30/year, while 36% of them suffered more frequent attacks >30/year. High fever >39° C affected 72% of cases while 16.7% of them did not present with fever. Severe abdominal pain forcing patients to be bed ridden was reported in 66.7% of cases while 21.2% of cases experienced abdominal pain not severe enough to interfere with activity. On the other hand, 8 cases (12.1%) did not have abdominal pain during attacks. Joints were affected during attacks in most of the referred cases, either by arthralgia (40.9%) or by true arthritis (15.2%). Chest pain was a symptom in less than half of cases (45.4%), mostly so severe to interfere with activity (42.4%). Myalgia was reported in 59.1% of cases but was also mild not interfere with activity. Fifteen cases (22.7 %) underwent laparotomy during severe abdominal pain either for exploration or for appendectomy.

Table I Analysis of presenting clinical manifestations of FMF cases related to the 10 items score system

Clinical manifestations	Score 1	2	3
Family history	Negative n=52 (78.8%)	Positive n=14 (21.2%)	-
Consanguinity	Negative n=24 (36.4%)	Positive n=42 (63.3%)	-
Duration of each attack	<3 days n=20 (30.3%)	3-5 days n=43 (65.2%)	>5 days n=3 (4.5%)
Frequency of attacks	<10/year n=11 (16.7%)	10-30/year n=31 (47%)	>30/year 24 (36%)
Fever	Negative n=11 (16.7%)	Up to 39° C n=7 (10%)	> 39° C n=48 (72.7%)
Abdominal pain*	Negative n=8 (12.1%)	Moderate n=14 (21.1%)	Severe n=44 (66.7%)
Joint affection	Negative n=29 (43.9%)	Arthralgia n=27 (40.9%)	Arthritis n=10 (15.2%)
Chest pain*	Negative n=36 (54.5%)	Moderate n=28 (42.4%)	Severe n=2 (3%)
Myalgia*	Negative n=26 (39.4%)	Moderate n=39 (59.1%)	Severe n=1 (1.5%)
Operations	Negative n=51 (77.3%)	Positive n=15 (22.7%)	-

*Moderate means not interfering with the patient activity and severe means that it interferes with the patient activity

Analysis of FMF common mutations (Table II) showed that 42 cases (63.6%) had positive mutations while the rest of the 24 cases (36.36%) were negative for these mutations (Table III). The most common genotype detected was the compound heterozygous genotype M694V/V726A (18.2%) followed by the heterozygous genotype M694V/- (16.7 %), the heterozygous genotype V726A/- (15.2%), while the homozygous genotype M680I/M680I was found in 10.6% of cases. Analysis of allele frequencies in relation to total examined alleles showed that M694V was the most frequent allele (18.8%) followed by V726A (17.42%) and M680I (12.1%) (found in 24, 23 and 9 cases respectively).

Cases were classified according to the Tel-Hashomer criteria, into three categories: a) unlikely: 25 cases; from them, 9 cases had positive mutations, b) probable: 13 cases; of them, 10 had positive mutations and c) definite: 28 cases; and of them, 23 had positive mutations. On the other hand, analysis using the 10 items clinical score revealed that: a) all cases having a score of ≤ 15 (5 cases) had negative mutations, for them a diagnosis was given an assignment of "unlikely" b) all cases having a score of ≥ 20 (10 cases) had positive mutations, for them a diagnosis was given an assignment of "definite" c) cases on the intermediate zone having a score of >15 and <20 (51 cases) including 32 cases having positive mutations and 19 cases with negative mutations, the diagnosis for these cases were given an assignment as "probable" (Table III).

Table II Molecular genotyping of three common mutations among studied cases

Genotypes	Freq./Cases	Alleles	Freq./alleles	Freq./Cases
Total	66 (100%)	Total	132 (100%	66(100%)
M680I/M680I	7 (10.6%)	M680I	16 (12.1%)	9 (13.6%)
V726A/M680I	1 (1.5%)	V726A	23 (17.42)	23 (34.8%)
M680I/M694V	1 (1.5%)	M694V	24 (18.18%)	24 (36.4%)
V726A/M694V	12 (18.2%)			
V726A/Undef	10 (15.2%)			
M694V/Undef	11 (16.7%)			
Undef/Undef	24 (36.4%)			

Undef.: undefined allele;Freq.: frequency

Table III Analysis of studied cases regarding our clinical score, Tel-Hashomer score and Mutation analysis

Clinical score		Tel-Hashomer	Mutation analysis	No (%)
< 15	Unlikely	Unlikely	Negative	5 (0.08)
15-20	Probable	Unlikely	Negative	11 (16.7)
15-20	Probable	Unlikely	Positive	9 (13.6)
15-20	Probable	Probable	Negative	3 (0.05)
15-20	Probable	Probable	Positive	9 (13.6)
15-20	Probable	Definite	Positive	14 (21.2)
15-20	Probable	Definite	Negative	5 (0.07)
> 20	Definite	Probable	Positive	1 (0.02)
> 20	Definite	Definite	Positive	9 (13.6)

Discussion

The inherited pattern of FMF which is mostly recessive was supported by the finding of positive consanguinity as well as positive family history among 63.3% and 21.2% of our children cases respectively. Positive family history was also reported by other authors in cases with different ethnic backgrounds varying between 20 and 60% (9-11).

Analysis of age and sex distribution of studied cases showed that 92.4% started to suffer symptoms in the first decade of life with a mean of 6.9 years denoting early presentation of the disease. This is a similar finding to what

was reported in other studies among Egyptians, Turkish, East Mediterranean Arabs, and Jewish cases (9,11-13). Male frequency was higher than female, a finding presumed by other authors to be due to partial penetrance in females (11,14,15). However, a higher frequency of female sex was also reported in studies done on Italians and Arabs (10,16).

As regards the clinical manifestations, most of the cases had attack duration of 3-5 days with a frequency of 10-30 per year. A shorter duration of attacks (2-3 days) was reported among Jewish cases (12) and an attack frequency of 12 per year among Italian cases (16). In our cases, abdominal pain was the most common feature (87.9%) followed by fever (82%), myalgia (60.6%), joint affection by arthritis or arthralgia (56.1%) and chest pain (45.4%). Interestingly, 22.7% of cases had undergone surgery to rule out appendicitis, intestinal obstruction or peritonitis. In another study among Egyptians, the clinical features were: fever (100%), abdominal pain (95%), arthritis (55%), pleurisy (40%) with no skin rash or pericarditis. Also they have reported that 25% of the cases had a past history of appendectomy or laparotomy (13). In a group of Arab patients, the most common manifestations were peritonitis (93.7 per cent), arthritis (33.7 per cent) and pleurisy (32 per cent). The authors reported lack of manifestations of amyloidosis, skin lesions, organomegaly and lymphadenopathy (14). On the other hand, in another study on Arabs, Rawashdeh and Majeed stated that 82% had recurrent abdominal pain, 43% had pleurisy, 37% had arthritis, 15% had cutaneous manifestations, 12% had splenomegaly and 4% had hepatomegaly (9). Tunca *et al* studied a large series of Turkish cases and noted that their clinical features included peritonitis (93.7%), fever (92.5%), arthritis (47.4%), pleuritis (31.2%), myalgia (39.6%), and erysipelas-like erythema (20.9%) (11). In a mixed populations of Sephardic Jews, Armenians, Arabs, Turks, French and others, the main clinical characteristics of the patients were: fever (83.3%), abdominal signs (74.0%), thoracic signs (24%), joint signs (50.3%), erysipela-like erythema (8.2%), splenomegaly (8.5%) and amyloidosis (4%) (10).

The cloning of MEFV considerably improved our understanding of FMF population genetics. Four missense mutations (M680I, M694V, M694I, and V726A), clustered within 46 amino acids of a predicted 781–amino acid protein, were responsible for a large percentage of mutations in the two initial study panels of families (17,18). In an analysis of American periodic fever referrals four previously undescribed MEFV mutations were reported including E148Q, K695R, A744S, and R761H (19). A French group presented another four mutations including E167D, T267I, F479L, and I692del (20). Two additional mutations (T681I and M694del) were recently reported by an English group (21,22).

Analyzing three common mutations of FMF, we found that 63.6% of cases had positive mutations varying between simple heterozygous (31.8%), compound heterozygous (21.2%) and homozygous (10.6%). Among the studies alleles, M694V was the most common allelic mutation found followed by V726A then M680I (18.8 %, 17.42% 12.1% respectively). In general, M694V was found in 36.4% of our studied cases followed by V726A (34.8%) and M680I (13.6%). In another study in Egypt, Zekri *et al* reported that the M694V mutation was detected in 100% and V726A mutation in 85% of their cases (13). Al-Alami *et al* studied a mixed Arabic population samples from Egypt, Syria, Iraq and Saudi Arabia found only 53.4% mutation positive with mutational types M694V and V726A the most common (23).

In a study of Arab cases from Jordan and have found that 59% had 1 or 2 mutations; of them, 22.6% were homozygous, 13% were compound heterozygous, and 22.4% patients simple heterozygous. Of the studied mutations , M694V, V726A, M680I, accounted for 38%, 26%, 10% respectively (24). Among a sample of Israeli-Arab cases, 78.5% had one or 2 mutation-bearing chromosomes. The most prevalent mutation was V726A, followed by M680I, and M694V (25).

In cases from Syria, 89% were positive either for one, two or three mutations including homozygous (30.1%), compound heterozygous (36.1%) and simple heterozygous (19.2%). The allelic frequency of M694V, V726A, M680I mutations was in the form of 45.8%, 26%, 4.8% respectively (26).

Among Maghreb cases, the most frequent mutations were M694V and M694I. These mutations account for different proportions of the MEFV mutations in Algeria (5%, 80%), Morocco (49%, 37%), and Tunisia (50%, 25%) patients. They pointed out that M694I mutation is specific to the Arab population from Maghreb (27).

In a mixed population of Jewish and Arab children with FMF, the M694V mutation was found in 92% of Jewish patients and in only 30% of the Arab patients. All other mutations were identified among 94% of the Arab patients, but with no particular prevalence for any one of them (28). The M694V mutation was elevated among cases of Sephardi Jews (10.9%), and Oriental Jews (9.2%) while it was very low among Ashkenazis (0.8%) (29). The most common mutation in the Italian sample was M694V (16 %) (16).

In Turkish cases, the mutation type M694V was the most frequent; found in 51.4% of cases, especially in Non Ashkenazi Jewish followed by M680I mutation (14.4%) detected among the Armenian ancestry persons followed by mutation V726A (8.6%) found in Armenians, Ashkenazi Jews and Iraqi Jews (11). In a previous study of Turkish cases, the frequency of the mutations was: M694V - 51.55%, M680I - 9.22% and V726A -2.88% (30).

Analyzing the clinical data of these cases versus the molecular results, we observed that among cases labeled "unlikely" according to Tel-Hashomer clinical criteria, 9 cases (36%) had positive mutations. These cases were labeled "probable" according to the 10 items clinical score (having a score >15 and <20). This shows that Tel-Hashomer criteria are more sensitive than specific and can give false negative results. The same observation was also reported by Grateau *et al*., who found that among the patients unlikely to have clinical diagnosis of FMF according to Tel-Hashomer criteria,

16% positive for two FMF mutations (10). Also Samli *et al* reported that 45.9% of cases diagnosed as unlikely according to Tel-Hashomer criteria had positive FMF mutation (8).

We therefore have reached the conclusion that diagnosis of FMF among Egyptian cases, although based mainly on clinical suspicion, needs to be confirmed through detection of the corresponding mutation, that can be easily done using the simple ARMS-PCR technique.

Conflicts of interest

None to declare.

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