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Research Article

Profile of Gene Positive Familial Mediterranean Fever in Kurdish Children in Sulaymaniyah City, Iraq

Hayder Fakhir Mohammad*

Department of Pediatrics, College of Medicine, University of Sulaimani, Region of Kurdistan, Iraq

ABSTRACT

Background: Familial Mediterranean fever (FMF) is a hereditary systemic auto- inflammatory disease affecting people of certain ethnic origins. In Iraq, few studies addressed FMF but none tackled patients' genotypes. This study was carried out in Sulaymaniyah, Iraq to identify the demographic, clinical, laboratory and genetic characteristics of FMF in Kurdish children.

Methodology: Sixty-four gene-positive FMF children were prospectively studied over 9-years starting at Jan 2011. Parameters analysed were age, sex, symptoms' onset-diagnosis interval (SO-DI), symptoms, family history and parents' consanguinity. Mediterranean fever (MEFV) gene mutations were analysed *via* real time PCR.

Results: There were 41 (64.1%) males. Age ranged between 23 months to16 years with a mean of 7.8 year. Parents were consanguineous in 32.8% and family history was positive in 46.9%. The average SO-DI was 14.6 months. Common presentations were fever (100%), abdominal pain (80%), diarrhoea and/or constipation (21.9%) and arthritis (26.6%) mainly of the knee (n=11). Neither erysipelas-like erythema nor amyloidosis were observed. The genotype was (46.8%) heterozygous, (17.2%) homozygous, (31.3%) compound heterozygous and (4.7%) complex heterozygous. Simple heterozygotes were diagnosed relatively later than other genotypes. The most frequent MEFV gene mutation alleles were E148Q (n=22), M680I (n=20), V726A (n=17) and M694V (n=13). Parents' consanguinity was influential in homozygotes only while positive family history was significant in all genotypes except the compound heterozygote.

Conclusions: To the best of my knowledge this is the first study of FMF genotypes in children from Iraq and Kurdistan Region which including this number of patients. Although FMF diagnosis is mainly clinical, genetics contribute to diagnosis, prognosis and family counselling.

Keywords: Pediatrics; Clinical pediatrics; Familial Mediterranean Fever; MEFV gene mutation; Autosomal recessive autoinflammatory disease; Kurd; Children; Sulaymaniyah; Iraq

INTRODUCTION

Familial Mediterranean Fever (FMF), first known as periodic disease or recurrent polyserositis is an autosomal recessive autoinflammatory disease characterized by recurrent 1-3 days self-limited episodes of fever, serositis, arthritis, and erysipelas rash complicated sometimes with AA amyloidosis [1]. FMF was first described by Janeway and Mosenthal in 1908, received its current name by Heller in 1955 and was genetically diagnosed in 1997 [2]. The disease is caused by > 50 mutations in the Mediterranean fever (MEFV) gene which are very common in people of eastern Mediterranean origin [3]. A 10-exon gene located on the short arm of chromosome 16 encodes a 781 amino acid protein called pyrin (from the Greek for fever). Pyrin is expressed in granulocytes, monocytes, and dendritic cells, and in peritoneal, synovial, and dermal fibroblasts [1-3]. Attacks may be triggered by stress, infection and trauma [1,3-5].

According to Tel-Hashomer, the major diagnostic criteria are recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis), amyloidosis of AA type without a predisposing disease and favorable response to regular colchicine treatment while recurrent febrile episodes, erysipelas-like erythema and FMF in a first degree relative are the minor criteria. Two or more major or one major plus two minor findings is sufficient for FMF diagnosis [6]. Response to colchicine as stated earlier is a major diagnostic

***Corresponding to**: Hayder Fakhir Mohammad, Department of Pediatrics, College of Medicine, University of Sulaimani, Region of Kurdistan, Iraq, Email: hayderfmoh@yahoo.com

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criterion [6]. Alternatively, metaraminol infusion can provoke typical FMF attack and has a sensitivity index of 90% (Metaraminol challenge) [7]. Treatment of FMF is centered on prevention of painful attacks and the development of amyloidosis. Non-steroidal anti-inflammatory medications or narcotics may be used but colchicine remains the gold standard [1-3,7].

Genetic testing can be used as adjunctive evidence in ambiguous cases. Although FMF is often regarded as recessively inherited disorder, with the attendant expectation that patient will have 2 mutations in trans, it should be noted that in some series as many as 30-50% of patients with typical FMF have only a single demonstrable mutation, and small percentage have no identifiable MEFV mutation [1,2]. The most frequently observed mutations in the MEFV gene in Turks are M694V, M680I, V726A and E148Q; in Armenians are M694V, M680I, V726A and E148Q; in North African Jews are M694V and E148Q; in Iraqi Jews are V726A, M694V, E148Q and M680I; in Ashkenazi Jews are E148Q and V726A while in Arabs, the most frequent mutations are V726A, M680I, M694V, M694I and E148Q [6]. M694V homozygotes tend to have a severe disease [1,3-5].

In Iraq, few studies [8-11] addressed FMF but none tackled the genetic features of the disease. The current study (the first on FMF in children from Iraq and the first on FMF in Kurdish population) aims to analyze patients' genotypes as well as the demographic, clinical and laboratory characteristics of the disease.

PATIENTS AND METHODS

This prospective study was conducted in Sulaymaniyah city, Region of Kurdistan, Iraq over 9 years (Jan 1, 2011 to Jan 1, 2020). During this period 3,357 children of different ethnic origins presented with recurrent abdominal pain, fever and joint pain suspected to have FMF and all were seen by the author in his private clinic or as outpatients or inpatients in Sulaymaniyah Pediatric Teaching Hospital (SPTH). Genetic studies for FMF were positive in 64 Kurdish children. All were 16 years old or below and all children (or their parents) agreed to participate in the study. The study protocol was approved by the University of Sulaimani Medical College Ethical Committee.

History was obtained from children and/or parents (of children below 6) and physical exam was performed. Thereafter, patients were subjected to a comprehensive workup including complete blood count (CBC), blood film, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood culture, general stool exam, general urine exam, urine for culture, serum iron, serum ferritin, total iron binding capacity, serum calcium, vitamin D level, H. pylori serological tests, renal function tests, liver function tests, random and fasting blood sugar, abdominal ultrasound, chest X ray, Echocardiogram and electrocardiography (ECG). Clinical diagnosis of FMF was considered if patients had two major or one major plus two minor Tel-Hashomer diagnostic criteria [6]. Clinical diagnosis was then supported by genetic study. Children with comorbid diseases or tested negative for MEFV gene mutations were excluded to provide homogeneity. Arab and Turkmen kids with gene-positive FMF were also excluded.

Prior to 2016, genetic studies were done abroad as they weren't available in Sulaymaniyah but thereafter, 2 private labs began to perform these studies. Each patient was genetically rechecked by the same lab during the follow up period and was excluded from the study if a different genetic profile was obtained. Peripheral blood samples in vacationers containing EDTA as anticoagulant were used for genomic DNA extraction by using Real prep DNA extraction kit from promega-USA. The MEFV gene variants were genotyped by multiplex Real Time PCR method detecting 18 common pathogenic variants (Centogene–Turkey). The variants were M694V, M694I, M680I, V726A, E148Q, P369S, A744S, E84K, G304R, E148V, F479L, E167D, T267I, L110P, P283L, K695R, R761H and E230K/Q.

In this study Kurdish children were either pure Kurd (with no relatives from other nationalities such as Turkmens or Arabs) or Kurds with up to 3rd degree relative from another nationality. Family history of FMF was considered positive if the child had an up to 3rd degree relative affected by the disease. Parents were regarded consanguineous if they were up to 4th degree relatives. FMF patients carrying one mutated allele of MEFV gene were considered simple heterozygotes while FMF patients with 2 identical mutated MEFV alleles were considered homozygotes. However, if the patient has 2 different alleles, he/she was considered a compound heterozygote. If 3 or more different alleles were present, such a patient was designated as a complex heterozygote.

All children received colchicine therapy; 0.5 mg/day for children below 5 and 1-2 mg/day for older children. Complete response to colchicine was defined as complete control of the clinical manifestations and normalization of acute phase reactants (APRs); incomplete response was defined as persistence of some clinical manifestations and/or some elevated APRs, and no response when there was no improvement in attack frequency and/or severity of the disease despite colchicine treatment.

Statistical analysis was performed by SPSS (Statistical Package for Social Sciences) program, version 23 (IBM SPSS). The data presented in tabular forms showing the frequency and relative frequency distribution of different variables. Z Score calculator for 2 populations proportion was used to compare the different patients' groups. P-values of 0.05 were used as a cut off point for statistical significance.

RESULTS

Besides the 64 gene-positive FMF Kurdish children, there were 11 Arabic and 4 Turkmen children with gene-positive FMF but were not enrolled in the study. The frequency of gene-positive FMF cases in this cohort of single pediatrician practice was, therefore, 79 out of 3,357 (2.4%) while the annual rate was 8.8 case per year (Table 1-7).

DISCUSSION

Epidemiology

While all ethnic groups are susceptible to FMF, it usually occurs in people of Mediterranean origin including Sephardic Jews, Mizrahi Jews, Ashkenazi Jews, Armenians, Azerbaijanis, Arabs, Kurds, Greeks, Turks, and Italians [12]. Estimates of the incidence of FMF in specific eastern Mediterranean populations range from 1 in 2,000 to 1 in 100, depending on the population studied [11]. Turkey is probably the country with the highest number of FMF in the world, since the prevalence of FMF is approximately 1: 400 to 1: 1,000. In Israel, the prevalence is slightly more than 1: 1,000 while in Armenia, the prevalence is about 1: 500. Other countries in the Middle East such as Jordan, Syria, and Lebanon have many FMF patients, but their exact number is not known [13]. Despite being called (Mediterranean), FMF seems to be unrestricted to people

Table 1: Demographic Characteristics of children with FMF in this study.

Demographic Characters		Number (Percent)
Gender	Male	41 (64.1)
	Female	23 (35.9)
Age	<2 years	1 (1.6)
	2-5 years	20 (31.3)
	6-10 years	24 (37.5)
	11-14 years	14 (21.9)
	15-16 years	5 (7.8)
Residence	Center of city	55 (85.9)
	Peripheral	9 (14.1)
Consanguinity with other nationalities	Kurds with up to 3rd degree relative from another nationality.	34
	Pure Kurds.	30 (46.9)
Religion	Muslim	64 (100)
Family History of FMF	Yes	30 (46.9)
	No	34 (53.1)
Consanguinity of the Parents	Yes	21(32.8)
	No	43 (67.2)

Note: Age ranged between 23 months to 16 years with a mean of 7.8 ± 4.1 year.

Table 2: Clinical Presentations and Laboratory Investigations.

Parameter	Number, %	Mean ± SD
Fever (37.8C° to 40.5 C°)	(64, 100)	39 C° ± 0.7 C°
Abdominal pain	(51, 79.7)	
Arthritis	(17, 26.6)	
Diarrhea	(8, 12.5)	
Constipation	(6, 9.4)	
Chest pain	(1, 1.6)	
Scrotal swelling	(1, 1.6)	
Myalgia	(1, 1.6)	
Henoch–Schönlein purpura	(1, 1.6)	
Splenomegaly	(1, 1.6)	
WBCs Count >11.000 x10^9 cell/L	(n=56, 87.5%)	13,193 ± 3,523 cell/L
Increased Neutrophil count	(n=46, 72%)	--
ESR (mm/hour); normal value <15	Range (42-95)	64.48 ± 12.73
CRP (mg/L); normal=0-10	Range (48-96)	73.75 ± 17.45

Note: No patient had erysipelas-like erythema, amyloidosis or history of unnecessary surgeries. It is worthy to mention that in between the attacks some patients had mildly raised ESR and CRP despite control of the symptoms

Table 3: Time interval between onset of symptoms and time of diagnosis.

Duration	(Number, %)
<3 months	(5, 7.8)
4-9 months	(17, 26.6)
10-16 months	(15, 23.4)
17-23 months	(10, 15.6)
24-30 months	(16, 25.0)
> 30 months	(1, 1.6)
Total	(64, 100)

Note: The symptoms onset-diagnosis time interval ranged between 2 months to 3 years with a mean of 14.6 ± 9.22 months

Table 4: Pattern of Arthritis.

Pattern	Joint involved	(Number, %)
Monoarticular	Knee	(7, 41.1)
	Ankle	(2, 11.8)
	Elbow	(1, 5.9)
	Wrist	(1, 5.9)
Symmetrical 2 joints	Both knees	(4, 23.5)
Polyarticular Symmetric	Juvenile rheumatoid arthritis –like	(2, 11.8)
Total		(17, 100)

Note: All patients (except one non-compliant child) responded very well to colchicine and became attack-free

Table 5: Distribution of MEFV Gene Mutations.

Mutation	Genotype	Number, %	Total (n, %)
Simple	M694V	8, 12.5	
Heterozygote	E148Q	7, 10.9	(30, 46.87)
	V726A	7, 10.9	
	M680I	4, 6.3	
	P396S	4, 6.3	
Homozygote	M680I-M680I	4, 6.3	(11, 17.18)
	E148Q-E148Q	3, 4.7	
	M694V-M694V	1, 1.6	
	V726A-V726A	1, 1.6	
	P396S-P396S	1, 1.6	
	M694I-M694I	1, 1.6	
Compound heterozygote	E148Q-M680I	5, 7.8	(20, 31.25)
	M680I-V726A	4, 6.3	
	F4726A-E148Q	3, 4.7	
	V726A-R761H	3, 4.7	
	E148Q-G304R	2, 3.1	
	M680I- T267I	1, 1.6	
	M694V-K695R	1, 1.6	
	R761H-M694V	1, 1.6	
Complex Heterozygote	M694V-M680I-M694I-E148Q	1, 1.6	(3, 4.68)
	E148Q-P369S-M694V-V726A-M680I	1, 1.6	
	M694V-M691V-M694I-V726A	1, 1.6	
	Total		(64, 100)

Note: The most frequent mutations were E148Q (n=22), M680I (n=20), V726A (n=17) and M694V (n=13) while the least frequent was T267 (n=1)

Table 6: Correlation between some demographic characteristics and the genotypes of patients.

Demographic Character		Genotypes (n, %)				Total	P-Value
		Heterozygote	Homozygote	Compound Heterozygote	Complex Heterozygote	n (%)	
Gender	M	(18, 28.12)	(8, 12.5)	(13, 20.3)	(2, 3.12)	(41, 64.1)	0.899
	F	(12, 18.75)	(3, 4.7)	(7, 10.9)	(1, 1.6)	(23, 35.9)	
Consanguinity of parents	Yes	(7, 10.9)	(10, 15.6)	(4, 6.25)	(0,0)	(21, 32.8)	0.025
	No	(23, 35.9)	(1, 1.6)	(16, 25)	(3, 3.12)	(43, 67.2)	
Family History	Yes	(7, 10.9)	(9, 14.1)	(11, 17.18)	(3, 4.7)	(30, 46.9)	0.001
	No	(23, 35.9)	(2, 3.12)	(9, 14.1)	(0, 0)	(34, 53.12)	
Consanguinity with other nationalities	Yes	(14, 21.9)	(9, 14.1)	(10, 15.62)	(1, 1.6)	(34, 53.12)	0.196
	No	(16, 25)	(2, 3.12)	(10, 15.62)	(2, 3.12)	(30, 46.9)	

Note: In all genotype's males were more frequently affected than females. Only one third of the whole study group had consanguineous parents (not significant). When the influence of parents, consanguinity on different genotypes was considered, it was significant in the homozygous subgroup only. Family history was positive in (n=30, 46.9%) of the whole study group ($p<0.05$; not significant). When influence of family history on different genotypes was considered, it was significant in all except the compound heterozygous. Consanguinity with other nationalities did not influence the rate of FMF except in the homozygotes (n=9, 81.8%)

Table 7: Correlation between symptoms onset-diagnosis time interval with the genotypes.

Genotype	Symptoms onset-diagnosis time interval						Total
	<3 m (N, %)	3-9 m (N, %)	10-16 m (N, %)	17-23 m (N, %)	24-30 m (N, %)	> 30 m (N, %)	(N, %)
Heterozygote	(0, 0)	(1, 1.6)	(4, 6.25)	(8, 12.5)	(16, 25)	(1, 1.6)	(30, 46.9)
Homozygote	(3, 3.12)	(6, 9.4)	(2, 3.12)	(0, 0)	(0, 0)	(0, 0)	(11, 17.2)
Compound heterozygote	(2, 3.12)	(10, 15.6)	(6, 9.4)	(2, 3.12)	(0, 0)	(0, 0)	(20, 31.25)
Complex heterozygote	(0, 0)	(0, 0)	(3, 3.12)	(0, 0)	(0, 0)	(0, 0)	(3, 4.68)
Total	(5, 7.8)	(17, 26.6)	(15, 23.4)	(10, 15.6)	(16, 25)	(1, 1.6)	(64, 100)

● Correlation significant P- value at level 0.01

Note: All homozygote patients (n=11), 90% (n=18) of compound heterozygote and all complex heterozygote patients (n=3) were diagnosed within 16 months or less from start of symptoms while 75% (n=25) simple heterozygote patients were diagnosed after 16 months from symptoms onset

living in the Mediterranean region. In recent years, approximately 170 cases have been reported in Japan [6]. On the other hand, there are countries where FMF has not been found or reported. These include sub-Saharan African countries, Ethiopia, Yemen, and Scandinavian states, as well as South Asian and Far Eastern countries such as India and Thailand [13].

FMF in Iraq

We traced the medical literature searching for FMF in Iraqi patients and found that Pras et al (1998) commented that North African Jews and Iraqi Jews were the 2 largest population groups suffering from FMF in Israel [11]. Yuval et al referred to a family of Georgian Iraqi origin living in Israel in which FMF occurred in 2 consecutive generations [14]. Fayadh et al. (2005) reported on 30 Iraqi adults with FMF; 8 of them (27%) lived in the north of Iraq and possibly were Kurds [8]. Al-Sultany (2007) published a 2-year series of 23 FMF cases in Iraqi Arabic adults [9]. In the present study, which enrolled Kurdish children with genetically-proven FMF, the incidence based on a single pediatrician practice was 7.1 cases per year. This figure is close to that reported by Majeed and Barakat (1989) from Saudi Arabia (8 cases per year) [11]. The real prevalence of FMF among Kurds in Iraq could be higher if adult patients were added and if all hospitals participated in the study. Hence, the impression among many physicians that FMF is unknown or rare among Kurds is incorrect.

Age and Sex

In this study, there were 41 (64.1%) males with a male to female ratio of 1.8: 1. Male predominance was similarly reported by Fayadh et al (1.5: 1) [8], Al-Sultany (2.8: 1) [9], Tunca (1.2: 1) [15], and Montazeri & Pahlavanazdeh (1.9: 1) [16]. The peak age incidence was among children aged 6-10 years (n=24, 37.5%). Rawashdeh and Majeed (1996) reported on 192 children with FMF in northern Jordan aged 4 months to 16 years [17] while the study of Al-Wahadneh A et al. from Jordan involved 56 patients aged 1 to 14 years [18]. Brik R et al. from Israel studied children aged 2 to 17 years with a mean of 11.7 ± 5.8 year [19]. Al-Sultany study involved adult patients whose age ranged between 14 and 59 years [9] while Fayadh et al didn't mention the age of their adult patients [8]. Dajani et al. described four Egyptian FMF patients aged 26-50 years [11]. In Salehzadeh study from Iran, the youngest patient was 1.5 years while the oldest was 76 years old with a mean of 21.03 years [20]. The results of these studies clearly indicate that FMF can affect people at any age from infancy to adulthood.

Religion, Ethnicity, Parents' Consanguinity and Family History

Although FMF is highly prevalent in Jews [12], Muslims and people from other religions are not immune. Kurds are among the people living in the basin of Mediterranean Sea and hence are prone to FMF. Consanguinity with other nationalities did not influence the rate of FMF in this study except in the homozygotes (n=9, 81.8%). Only one third of the whole study group had consanguineous parents. When the influence of parents, consanguinity on different genotypes was considered, it was significant in the homozygote subgroup only. Family history was positive in (n=30, 46.9%) of the whole study group ($p<0.05$; not significant). Despite being (Familial), FMF does occur in people with negative family history of the disease. This fact is shown by many authors who reported different rates of positive family history among their patients such as Hentgen et al. (36.4%) [21], Fayadh et al. (66%) [8], Al-Sultany (39.1%) [9], Rawashdeh and Majeed (62%) [17], Al-Wahadneh and Dahabreh (50%) [18] and Salehzadeh (15.1%) [20].

Genetics

Many different mutations of the MEFV gene can cause FMF. Having one mutation is unlikely to cause the condition. Having two mutations either a copy from both parents (homozygote), and two different mutations (compound heterozygote), one from each parent is the threshold for a genetic diagnosis of FMF [12]. FMF is an autosomal recessive disorder [11]. Yuval et al. (1995) found 77 families with 240 FMF patients, in which the disorder affected more than one generation. In 75 of these families, the occurrence of FMF in more than one generation was found to be consistent with a recessive mode of inheritance due to a high gene frequency and consanguinity of the parents. In 2 families, however, one of Ashkenazi and the other of Georgian Iraqi origin, FMF occurred in 4 consecutive generations; hence, the transmission could be explained only by autosomal dominance inheritance [14]. In a series of 72 FMF Armenian patients from Lebanon, Reimann et al. (1954) described 20 affected persons occurring in 5 generations, with 3 instances of skips in the pedigree suggesting that the high gene frequency and small breeding group could account for the findings as representing pseudo-dominant inheritance [11].

In this series, homozygote gene mutations were observed in (n=11, 17.18%) of patients while most patients (n=53, 82.8%) had heterozygote gene mutations mainly in the form of simple heterozygotes (n=30, 46.87%). These findings mimic studies from Iran [20] and Turkey [22] in which heterozygotes exceeded homozygotes. It is of interest to note that FMF occurred in 21.3% of Iranian patients despite having no identifiable mutation [20]. The most frequent mutations in the current series were E148Q (n=22, 34.4%), M680I (n=20, 31.3%), V726A (n=17, 26.6%) and M694V (n=13, 20.3%) while the least frequent was T267 (n=1, 1.6%). In Jordan, the order of MEFV gene mutations was different as M694V was on the top (64%) followed by heterozygous M694V-

V726A (23%) and E148Q (8%) [18]. Similarly, M694V mutation was on the top in studies from Iran [20], Turkey [22] and Japan [23].

Clinical Features

All patients in this study had fever. According to one view, patients who do not define high fever do not measure their body temperature and therefore report high fever as negative [6]. No patient underwent unnecessary operation and none had amyloidosis. The clinical features of patients in the present study simulated the previous studies from in Iraq [8,9] in which patients presented with fever followed by abdominal pain and then arthritis but differed in the rate of unnecessary abdominal surgery; (n=5, 17%) in the study of Fayadh et al. [8] and chest pain (70%) in Al-Sultany series [9]. Likewise, pleuritic chest pain was reported in 23% of FMF children from northern Jordan [11,17] and in 33% of Kuwaiti and Saudi FMF children [11]. FMF patients from Japan [24], on the other hand, had a lower rate of abdominal pain (40%) but higher rates of chest pain (26.6%), arthritis (56.3%), Erysipelas-like erythema (17.7%), and amyloidosis (3.6%) as compared to the present study.

Seventeen patients in this series (26.6%) presented with arthritis. The rate of arthritis in this study equaled that of Jordanian FMF children (26%) [11,17] and was close to that of Kuwaitis (34%) [11] but was half that of Saudis (50%) [11] and Japanese (56.3%) [24]. Similar to this study, Japanese FMF patients had mostly single joint involvement (70%) with knees and ankles being the most frequently affected joints but at higher rates than this study (65.4% and 30% respectively) [24].

There are similarities and differences between different ethnic groups in regard to severity of the disease, response to colchicine and occurrence of complications particularly amyloidosis. For instance, when north African and Iraqi Jews were compared, the formers were found to have a more severe disease manifested by an early age of onset, an increase in frequency and severity of joint involvement, a higher incidence of erysipelas-like erythema, and a higher dose of colchicine necessary to control the symptoms. The clinical variation in disease severity among different population groups may be attributed to involvement of additional genes, environmental factors and different mutations in MEFV gene [10].

The symptoms onset-diagnosis time interval ranged between 2 months to 3 years with a mean of 14.6 ± 9.22 months. This (delayed diagnosis period) was shorter than Rawashdeh and Majeed [11,17] who reported 3.7 years as the mean interval. All homozygote patients (n=11), 90% (n=18) of compound heterozygote and all complex heterozygote patients (n=3) were diagnosed within 16 months or less from start of symptoms while 75% (n=25) simple heterozygote patients were diagnosed after 16 months from symptoms onset. Besides the influence of genotype, we think that mild symptoms and unawareness of the physicians may partially account for the late diagnosis of FMF.

Acute Phase Reactants

During the attacks, all patients in the current series had raised ESR and CRP while WBC count was high in 87.5% and neutrophils were high in 72% of patients. The mean ESR during the attacks in this series exceeded the mean ESR of Yurolmaz A et al. and Basaran O et al. series (31.7 and 40.9 mm/hour) respectively [25,26]. It is worthy to mention that in between the attacks the acute phase reactants returned to normal levels while some patients had mildly raised ESR and CRP despite control of the symptoms. Odabas A et al. from Turkey also observed a significantly elevated CRP in FMF patients in the attack-free period in comparison with the controls ($p < 0.001$) [27]. In a study by Lofty et al. from Egypt, high SAA levels were detected two weeks after last FMF attack in a large percentage of Egyptian FMF children indicating that subclinical inflammation continues during attack-free periods [28].

Clinical Diagnosis

Worthy to note that in the previous studies from Iraq [8,9], the diagnosis was based on clinical grounds and response to colchicine therapy as no genetic tests were available. In many FMF patients' series from different countries, some patients had undergone unnecessary operations such as appendectomy, hemicolectomy, cholecystectomy...etc. reflecting the diagnostic difficulty of FMF. For instance, one third of the Saudi FMF children in one series were subjected to unnecessary operations before making the correct diagnosis [11]. Likewise, a long-time interval between symptoms onset and diagnosis is another indicator of the difficult diagnosis.

Colchicine Therapy

Unfortunately, there is no internationally agreed consensus on the definition of response or unresponsiveness to colchicine [29]. About 20-30% of patients respond only partially to maximal tolerated doses of colchicine and 5% of patients are non-responders [28]. All patients in this series (except one non-compliant child) responded very well to colchicine. All children became attack-free, although some had mildly elevated inflammatory markers in between the attacks. Excellent response to colchicine is similarly reported by other investigators such as Al-Wahadneh and Dahabreh (97%) [18], Fayadh et al. [8], Al-Sultany [9], Majeed and Barakat (93%) [11] and Salehzadeh (97%) [20].

Complications

Amyloidosis is the most severe complication of the disease leading to nephrotic syndrome and end stage renal disease [11]. Worthy to note that occurrence of this serious complication in FMF patients is related to the genotype and regular use of colchicine therapy [13]. Although serum amyloid A protein wasn't checked in the present study as the test wasn't available, but no patient had clinical evidence of renal amyloidosis such as proteinuria or overt nephrotic syndrome [9].

Amyloidosis was also rare in a study from Kuwait and in a study from Saudi Arabia in which just 2 of 88 children developed amyloidosis [11]. In Jordan, 7 of 192 (3.6%) children developed amyloidosis in the study of Rawashdeh and Majeed [17] while it wasn't documented in any of 56 patients after 5 years of follow up in the study of Al-Wahadneh and Dahabreh [18]. In a study of 240 FMF patients from Iran, amyloidosis was diagnosed just once in a patient with resistant nephrotic syndrome and M694I-M694I mutations [20]. In a study from Turkey [30] 7 of 507 (1.4%) patients developed amyloidosis; 5 of them were homozygous for the M694V mutation. Monitoring SAA level in attack-free FMF patients is recommended in order to adjust colchicine dose, and minimize the risk of AA amyloidosis [31].

CONCLUSIONS

To the best of my knowledge, this is the first study of FMF genotypes in children from Iraq and Kurdistan Region that include such number of patients. The prevalence of FMF among the Kurds seems to be comparable to some nearby countries and hence the

impression among many physicians that FMF is unknown or rare among Kurds is incorrect. Although the diagnosis of FMF is mainly clinical, knowing the genotype can support the diagnosis, throw light on prognosis and play a role in family counseling. We hope that the present article will raise the awareness of physicians in the Iraqi Kurdistan Region regarding this disease so that patients can obtain the correct diagnosis and receive the appropriate treatment. Untreated or inadequately treated FMF patients run the risk of amyloidosis, which is an important cause of morbidity and mortality. It is wise to have a national FMF database and a center for FMF patients in our city.

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