Adult-Onset Familial Mediterranean Fever in Northwestern Iran; Clinical Feature and Treatment Outcome

H Nobakht[1], F Zamani[2], H Ajdarkosh[3], Z Mohamadzadeh[4], SM Fereshtehnejad[5], M Nassaji[6*]

1. Assistant Professor of Gastroenterology and Hepatology, Fatemieh hospital, Semnan University of Medical Sciences, Semnan, Iran
2. Associate Professor of Gastroenterology and Hepatology, Firoozgar Hospital, Gastrointestinal and Liver Disease Research Center (GILDRC), Tehran University of Medical Sciences, Tehran, Iran
3. Assistant Professor of Gastroenterology and Hepatology, Firoozgar Hospital, Gastrointestinal and Liver Disease Research Center (GILDRC), Tehran University of Medical Sciences, Tehran, Iran
4. Research Fellow, Imam-Khomeini General Hospital, Ardabil University of Medical Sciences, Ardabil, Iran
5. Research Fellow, Firoozgar Hospital, Gastrointestinal and Liver Disease Research Center (GILDRC), Tehran University of Medical Sciences, Tehran, Iran
6. Assistant Professor of Infectious Diseases, Fatemieh hospital, Semnan University of Medical Sciences, Semnan, Iran

*Corresponding Author:
Mohammad Nasaji, MD
Department of Infectious Diseases, Fatemieh Hospital, 17 Shahrivar Blvd, Semnan University of Medical Sciences, Semnan, Iran. P.C 35187-944331
Tel: +98 231 3328017
Fax: +98 231 3328302
E-mail: hnassaji@yahoo.com
Received: 28 Dec. 2010
Accepted: 05 Feb. 2011

ABSTRACT

BACKGROUND

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by sporadic, paroxysmal attacks of fever and serosal inflammation. Although the disease usually begins before the age of 20 years, we aimed to evaluate the demography, clinical features and treatment outcome of familial Mediterranean fever in Iranian adult patients above 20 years old.

METHODS

In this cross-sectional study, adult patients (first attack at the age of >20 years) with a diagnosis of FMF who referred to the gastroenterology and rheumatology Clinics of Ardebil University of Medical Science (situated in north west of Iran) over the period of 2004-2009 were enrolled. FMF diagnosis was based on clinical criteria.

RESULTS

Forty four FMF patients (30 male and 14 female) with the mean [± Standard Deviation (SD)] age of first attack of 29 ± 7.8 years were enrolled. Abdominal pain (95.5%) and fever (91%) were the most common clinical findings. All of the patients had satisfactorily responded to therapy. Response was complete in 76.7% and partial in 23.3% of the patients. There was no clinical or laboratory evidence of amyloidosis at the time of diagnosis or during follow-up.

CONCLUSION

Our findings demonstrated that adult-onset FMF in Iran has different characteristics (more common in males, lesser prevalence of arthritis and erysipelas-like erythema, less delay in diagnosis) and treatment outcome (favorable response even to low-dose colchicine) in comparison with the previous data on early onset patients.

KEYWORDS

Familial Mediterranean fever; Adult onset, Clinical features; Treatment

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary autoinflammatory disease, which primarily affects several ethnic groups

originating in the Mediterranean basin including Jews (mainly non-Ashkenazi), Armenians, Turks, Arabs, and less commonly Greeks and Italians. However, in recent years, more and more cases have been reported in countries out of this area, such as the USA and Japan.[1]

Caused by mutations in MEFV gene,[1] FMF is a disorder characterized by lifelong recurrent and self-limited episodes of paroxysmal attacks of fever and serosal inflammation, resulting in pain in the abdomen, chest, joints and muscles.[2]

Most patients with FMF experience their first attack in early childhood. In 65 percent of cases, the initial attack occurs before the age of 10, and in 90 percent before the age of 20; while it rarely occurs beyond the age of 40 years. In each case, the disease may present differently or may change its course over the patient's lifetime. Similarly, different manifestations of FMF have been observed among populations of various ethnic origins. However, attacks generally tend to decrease with aging in most FMF patients.[3] Each attack lasts 1-4 days on average and resolves spontaneously.[4]

In almost all patients the attack is preceded by a prodromal period with symptoms mostly including myalgia, arthralgia, headache, nausea, vomiting, constipation, diarrhea, dyspnea, low back pain, asthenia and anxiety.[5]

The typical manifestations of FMF include fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema. Abdominal attacks are the most common occurring in about 95% of patients. One of the devastating complications of FMF is the development of amyloidosis, which mainly affects the kidneys but may involve other organs as well.[6]

Adult or late-onset disease may have different clinical and demographic features. It is reported that late onset FMF (over 40 years of age) may have a milder clinical presentation.[7,8]

Although accompanied with some side effects, long-term daily colchicine is the mainstay of therapy for the disease. Treatment results in complete remission or marked reduction in the frequency, duration, and severity of attacks in most patients and prevents amyloidosis.[9]

Iran is a large country with different ethnic groups. The 15 to 20 million Azeri Turks living in northwestern of Iran are ethnically closely related to Turkish people living in Turkey. FMF seems to be common in this population.[10,11] There are a few reports of FMF in Iran and based on our knowledge there are no report about the adult-onset type. The purpose of this study was to review clinical presentation, demographic characteristics and treatment outcome of adult patients with FMF in Northwest of Iran.

MATERIALS AND METHODS

In this cross-sectional study, adult patients (first attack at the age of >20 years) with a diagnosis of FMF who referred to gastroenterology and rheumatology clinics of Ardebil University of Medical Science (situated in north west of Iran) over the period of 2004-2009 were enrolled. Patients with a suspicious diagnosis were all excluded from the study.

All patients were of Azeri Turk origin and diagnosis was based on clinical criteria for FMF (Table 1).[12] The study was approved by the Research and Ethical Committee of Ardebil University of Medical Science and an informed consent was obtained from all patients.

Assessment

Main demographic and clinical data including age, sex, age at onset of disease, age at diagnosis, duration of the attacks, frequency of the attacks, attack symptoms and family history of FMF were recorded.

Colchicine (1 mg per day) was started for all patients at the time of diagnosis. All patients were followed during the study for drug adherence, adverse drug reactions and the course of the disease. The patients were followed for a

mean duration of 20.0 ± 14.3 months. Laboratory tests (CBC, BUN, Creatinin and urine analysis) were checked at the beginning and during the follow-up period.

Table 1: Different diagnostic criteria of FMF.

Major Criteria
Typical Attacks
1. Peritonitis (generalized)
2. Pleuritic (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
5. Favorable response to colchicine
Minor Criteria
Incomplete attacks involving one or more of the following sites
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
Supportive Criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age < 20 years at disease onset
4. Features of attacks:
I. Severe, requiring bed rest
II. Spontaneous remission
III. Symptom-free interval
IV. Transient inflammatory response, with one or more abnormal test result(s)
V. White blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
5. Episodic proteinuria/hematuria
6. Unproductive laparotomy or removal of normal appendix
7. Consanguity of parents

Definitions

Response to colchicine was defined as complete (no attack) or partial (>50% decrease in frequency of attacks) and unresponsive according to clinical condition. Good compliance with treatment was defined by adherence to colchicine more than 95% of the time.

Statistical analysis

Data were analyzed by SPSS v.15 software (Chicago, IL, USA). Mean ± SD were calculated for quantitative variables, and frequencies and percentages were reported to describe qualitative variables.

RESULTS

Forty-four patients (30 males and 14 females) with a clinical diagnosis of FMF were included. The male/female ratio was 2.14. Demographic characteristics of patients are shown in Table 2.

Table 2: Characteristic of adult-onset FMF patients.

Age at the onset of symptoms (mean ± SD) yr	29 ± 7.8
Age at diagnosis (mean ± SD) yr	34.5 ± 9.7
Delayed diagnosis (mean ± SD) yr	5 ± 5.9
Duration of follow-up (mean ± SD) mo	20 ± 14.3
Duration of treatment (mean ± SD) mo	17 ± 13.6
Duration of attacks (mean ± SD) day	2 ± 0.76
Interval between attacks (mean ± SD) mo	2.3 ± 2.2
Positive family history of FMF	11(25%)

SD, standard deviation; yr, year; mo, month

Eleven patients (25%) had positive family history for FMF. Five patients (11.5%) reported their first attack after the age of 40, 10 (23.0%) between 30-40 years of age and 29 (65.5%) cases between 20-29 years of age. One patient discontinued his colchicines because of a hypersensitivity reaction. All 43 patients continuing treatment responded to treatment even though low-dose colchicine (1 mg per day) was administered. Response to treatment was complete in 33 (76.7%) and partial in 10 (23.3%) patients. Moreover, 53.5% of patients had good compliance with treatment, while other 46.5% had irregular usage of the administered drug. All of irregular users developed recurrence of attack after a mean duration of 1.20 ± 0.95 months. The most common symptoms were abdominal pain and fever which occurred in 42 (95.5%), and 40 (91%) of the patients, respectively. Abdominal pain was generalized in 88 % and localized in one or two quadrants in 12% of patients. The clinical presentations are summarized in Table 3.

Table 3: Clinical features of adult-onset FMF patients.

Clinical features	No. (%)
Abdominal pain	42 (95.5)
Fever	40 (91)
Chest pain	12 (27.3)
Arthralgia	6 (13.6)
Arthritis	2 (4.5)
Myalgia	21 (47.7)
Headache	21 (47.7)
Scrotal pain (in male)	8 (26.7)
Pelvic pain (in female)	7 (50)
Nausea and vomiting	13 (29.5)
History of abdominal surgery	6 (13.6)
Skin rash (Erysipelas-like erythema)	1 (2.3)
Diarrhea	6 (13.6)
Constipation	11 (25.6)

Misdiagnosis was made previously in 11 (25%) patients. The most common misdiagnosis was acute appendicitis in 6 (13.6%) patients, all of whom had undergone appendectomy. Other misdiagnoses were diverticulitis, pulmonary embolism, pancreatitis, ischemic heart disease and palindromic rheumatism, each in 1 (2.3%) patient. There was no clinical or laboratory evidence of amyloidosis at the time of diagnosis or during the follow-up period in our patients.

In one patient colchicine was discontinued due to allergic reaction. Other adverse drug reactions occurred in two (4.5%) patients. (hypersensitivity in one and hair loss in another).

DISCUSSION

FMF usually occurs in young age; most patients (90%) begin to suffer from their first attack before 20 years of age. Onset of the disease at an older age may occur but is uncommon after the age 40.[13] The date of onset of FMF is usually determined by history, although misinterpretation and misdiagnosis can occur. Previous studies revealed a subgroup of late or adult-onset patients with different demographic, clinical and probably genetic features.[7,14]

In our patients the mean age of first attack was 29.0 ± 7.8 years and it occurred after the age of 40 in five patients (11.5%). This finding is similar to the study by Sayarlioglu et al.[8] who reported that 5 patients (8.8%) had their first attack after the age of 40. In contrast in the report by Tamir et al.[8] 0.5% of patients had their first attack after the age of 40 years. This difference is probably due to the study population, as we included only adult patients.

The mean age at diagnosis in our study was 34.5±9.7 years that is comparable with other studies reporting a mean age of 34.2 ± 9.5 years.[8] Most studies have reported that FMF affects both sexes equally.[13] Male/Female ratio in our patients was about 2/1. Similarly in a Turkish study,[8] 80% of FMF patients with late onset disease were male. In another report from the northwest of Iran, the disease showed male predominance (1.7/1).[10] However, most patients in their study were under 20 years. By contrast, Ureten et al. declared that the majority of FMF patients were female (female/male: 1.85).[15]

Delay in diagnosis of FMF is common even in endemic areas. The erratic nature of disease and short period of attack make it difficult to make the correct diagnosis early in the course of disease. Awareness of physicians is also an important factor. Mean delay in diagnosis in our patients was 5.0 ± 5.9 years, which was similar to reports by Tamir et al (4.9 ± 5.8 years)[7] and Sayarlioglu et al. (6.0 ± 6.6 years)[8] and different from the study done by Ureten et al. which estimated a mean duration between disease onset and diagnosis of 9.39 ± 8.92 years.[15] The diagnostic delay in patients with adult onset disease seems to be significantly less than those with early onset,[7,8] nonetheless, Tunca et al.[16] showed no significant difference in the diagnostic delay among patients with early (before the age of 18 years) versus late onset disease. We considered that this differnce may be attributed to more attention of adults to new manifestations and more attention to receive a final diagnosis.

A significant proportion of patients with FMF have positive family history.[15-17] In our study, only 25% of patients had positive family history of FMF which is mostly similar to the prevalence rate of 23% reported in one Turkish study.[18] This may be due to occurrence of new mutations in some populations which needs to be further evaluated.

The hallmark of FMF is recurrent acute febrile attack and involvement of abdomen, chest, joints, muscles, scrotum and skin. Abdominal pain is present in about 95% of patients, and the clinical picture is that of acute peritonitis. Likewise, in our patients abdominal pain (95.5%) and fever (91%) were the most common clinical findings which are in

accordance with most other studies.[16,19] However, Tsuchiya-Suzuki et al.[20] reported that only 55% of patients suffered from abdominal symptoms. Our study depicted that 26.7% of male FMF cases had scrotal pain 50% of females had pelvic pain which is not previously mentioned by other studies.

Arthritis and erysipelas-like erythema were seen in 4.5% and 2.3% of our patients respectively, which is less frequent than reports in younger patients.[15,18,21] In agreement with our findings, Tunca et al.[16] concluded that arthritis, arthralgia, myalgia, and erysipelas-like erythema were significantly less frequent among the adult-onset patients.

Amyloidosis is the most significant complication of FMF, usually affecting the kidneys and resulting in renal insufficiency. On the other hand, there are unexplained ethnic differences in the prevalence of amyloidosis. In untreated North-African Jews, Armenians, and Turks, its prevalence reaches as high as 60% or more, whereas in Ashkenazi and Iraqi Jews, American- Armenians, and Arabs, it is less common.[4] None of our patients had clinical or laboratory evidence of amyloidosis during follow-up period, similar to a study in Japan that amyloidosis was seen in only 1 of 80 patients.[20] This implies that late onset FMF may have a less aggressive behavior probably due to different mutation as compared to early onset disease. Earlier diagnosis and therapy with higher compliance to treatment in this group are the other probable contributing factors.

Misdiagnosis is common in FMF patients because the disease involves different organs and may have different clinical presentations. The differential diagnosis is broad and may be different in adults.

Consequently, diseases mistaken for FMF may be different in adults than in children, probably due to the lower prevalence or even lack of a number of diseases such as diverticulitis, pulmonary embolism and pancreatitis during childhood. Misdiagnosis was seen in 11 (25%) of our patients. Six patients (13.6%) had abdominal operation with impression of acute appendicitis. In the study done by Ureten et al. 20% of patients underwent appendectomy; most of the patients were operated before the diagnosis of FMF was made.[15] Other misdiagnoses in our patients were diverticulitis, pulmonary embolism, pancreatitis, ischemic heart disease and palindromic rheumatism.

All of our patients who could continue colchicine, had satisfactory response to therapy. Response was complete in 76.7% and partial in 23.3% of patients. This is similar to other studies[7,8] and indicates that response to colchicine in adult onset FMF is excellent and lower doses of colchicine may be adequate (1 mg per day).This is the first study to describe the characteristics of Iranian FMF patients whose disease started after the age of 20 years. There are some limitations to our study. The most important one is the absence of genetic analysis as well as mutation studies. Lack of a reliable and complete family history to form genealogy trees of the patients is one limitation which inhibits the precise genetic analysis.

In conclusion, our findings demonstrated that adult-onset FMF in Iran is more common in males, arthritis and erysipelas-like erythema are seen less commonly, and there is a shorter delay before diagnosis, and a better treatment outcome (favorable response even to low-dose colchicines). Moreover, a better tolerance of drug with a lower risk of amyloidosis is seen in adult-onset FMF patients. However, the role of genetic or environmental factors should be evaluated and determined in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Eldad Ben-Chetrit E, Touitou I. Familial Mediterranean Fever in the World. *Arthritis Rheum* 2009;**61**:1447–53.

2. Simon A, Van der Meer JW, Drenth JP. Familial Mediterranean fever—a not so unusual cause of abdominal pain. *Best Pract Res Clin Gastroenterol* 2005;**19**:199-213.
3. Onen F. Familial Mediterranean fever. *Rheumatol Int* 2006;**26**:489–96.
4. Fonnesu C, Cerquaglia C, Giovinale M, Curigliano V, Verrecchia E, de Socio G, et al. Familial Mediterranean Fever: a review for clinical Management. *Joint Bone Spine* 2009;**76**:227-33.
5. Lidar M, Yaqubov M, Zaks N, Ben-Horin S, Langevitz P, Livneh A. The prodrome: a prominent yet overlooked pre-attack manifestation of familial Mediterranean fever. *J Rheumatol* 2006;**33**:1089-92.
6. Bakkaloglu A. Familial Mediterranean fever. *Pediatr Nephrol* 2003;**18**:853–9.
7. Tamir N, Langevitz P, Zemer D, Pras E, Shinar Y, Padeh S, et al. Late onset familial Mediterranean fever: a subset with distinct clinical, demographic, and molecular genetic characteristics. *Am Med Genet* 1999;**87**:30–5.
8. Sayarlioglu M, Cefle A, Inanc M, Kamali S, Dalkilic E, Gul A et al. Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases. *Int J clin Pract* 2005;**59**:202-5.
9. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet* 1998;**351**:659–64.
10. Salehzadeh F, Emami D, Zolfegari AA, Yazdanbod A, Habibzadeh S, Bashardost B, et al. Familial Mediterranean fever in northwest of Iran (Ardabil): the first global report from Iran. *Turk J pediatr* 2008;**50**:40-4.
11. Esmaeili M, Bonyadi M, Rafeey M, Sakha K, Somi MH. Common MEFV mutation analysis in Iranian Azeri Turkish patients with familial Mediterranean fever. *Semin Arthritis Rheum* 2008;**37**:334-8.
12. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial mediterranean fever. *Arthritis Rheum* 1997;**40**:1879-85.
13. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967;**43**:227-53.
14. Rozenbaum M, Rosner I. The clinical features of familial Mediterranean fever of elderly onset. *Clin Exp Rheumatol* 1994;**12**:347–8.
15. Üreten K, Gönülalan G, Akbal E, Güneş F, Akyürek O, Ozbek M, et al. Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. *Rheumatol Int* 2010;**30**:911–5.
16. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore)* 2005;**84**:1–11.
17. Kone´-Paut I, Hentgen V, Guillaume-Czitrom S, Compeyrot-Lacassagne S, Tran T, Touitou I.The clinical spectrum of 94 patients carrying a single mutated MEFV allele. *Rheumatology* 2009;**48**:840–2.
18. Inal A, Yilmaz M, Kendirli SG, Altintas DU, Karakoc GB. The clinical and genetical features of 124 children with Familial Mediterranean fever: experience of a single tertiary center. *Rheumatol Int* 2009;**29**:1279–85.
19. Jarjour RA. Familial Mediterranean fever in Syrian patients: MEFV gene mutations and genotype–phenotype correlation. *Mol Biol Rep* 2010;**37**:1–5.
20. Tsuchiya-Suzuki A, Yazaki M, Nakamura A, Yamazaki K, Agematsu K, Matsuda M, et al. Clinical and genetic features of familial Mediterranean fever in Japan. *J Rheumatol* 2009;**36**:1671-6.
21. Özel AM, Demirtürk L, Yazgan Y, Avşar K, Günay A, Gürbüz AK ,et al. Familial Mediterranean fever. A review of the disease and clinical and laboratory findings in 105 patients. *Dig Liver Dis* 2000;**32**:504-9.