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FAMILIAL MEDITERRANEAN FEVER: A STUDY OF 32 CASES

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ABSTRACT

From April 1983 to September 1990, 32 patients with familial mediterranean fever (FMF) were studied. FMF is characterized by short, self-limited, febrile episodes that occur with inflammation of serosal surfaces. Major symptoms include fever and abdominal pain, presenting as acute surgical abdomen. These attacks are associated with considerable morbidity and in some patients lead to unnecessary surgery. Diagnosis of this disease depends on the absence of any objective markers and the recognition of the symptoms in a susceptible individual. Duration of disease on admission was 1.5-19 years. Except in two pairs of siblings, no familial association was noted. This is the first review of the cases of FMF from Iran.
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INTRODUCTION

Familial mediterranean fever is an uncommon disease which was not recognized as a separate disease until 1945.[1] It is a genetic disorder restricted to certain ethnic groups and characterized by idiopathic, recurring, self-limited attacks of febrile serosal inflammation involving the peritoneum, synovium, or pleura. This disease exhibits a preference for people of Mediterranean ancestry, particularly Jews and Armenians, and generally has an onset below 20 years of age.[9] Some individuals develop amyloid nephropathy which is usually fatal.

While analgesics have been useful during the acute phase of attacks, there has been no effective method of preventing the recurrence of the attacks. Since Goldfinger's suggestion in 1972,[2] colchicine has been shown in a number of double-blind studies to be effective in preventing or ameliorating the attacks.[3-6] Preliminary data have been presented suggesting that this drug may also improve the prognosis of the amyloid nephropathy of FMF.[7,8]

METHODS AND MATERIAL

From April 1983 to September 1990, 32 cases of familial mediterranean fever were studied. 21 were male and 11 were female. Pertinent features of patients are shown in Table I.

The most common presenting symptoms were fever and self-limited attacks of inflammation at multiple foci. In most cases the following studies were performed: CBC, ESR, urinalysis, blood and urine cultures, BUN, ASO, Latex, CRP, PPD skin test, febrile agglutinations, ultrasonography of abdomen, roentgenograms of chest, gallbladder, upper gastrointestinal tract, small bowel and colon, IVP, liver function tests.

Diagnostic criteria based in this survey were: (1) periodic attacks of some regularity with decreasing interval between attacks in most of the cases; (2) lack of other diseases whether infectious of noninfectious; (3) dramatic response to colchicine almost in all patients; (4) recurrence of symptoms upon colchicine withdrawal.

RESULTS

As mentioned before, 32 cases of FMF were diagnosed. Familial incidence occurred in only two pairs. 81.25% of the patients had an onset below 20 years of age. The common presenting features were fever and abdominal pain. Abdominal attacks, similar to those

TABLE I. Main features of FMF patients

Case No	Age (yr) and sex	Form of Attacks	Previous Surgery	Age at onset (yr)	Duration of disease	family history
1	28, F	Fever, abdominal	—	20	8	–
2	40, M	Abdominal, articular	—	25	15	–
3	23, M	Fever, Abdominal	Appendectomy	4	19	–
4	23, M	Fever, Abdominal	—	16	7	–
5	18, M	Fever, Abdominal, articular	—	10	8	–
6	24, M	Fever, Abdominal	Appendectomy	7	17	–
7	18, M	Fever, Abdominal, articular	—	12	6	–
8	19, M	Fever, Abdominal	—	15	4	–
9	9, F	Abdominal, urinary retention	—	2	7	–
10	20, F	Abdominal, articular	—	16	4	–
11	32, M	Fever, Abdominal, articular	—	19	13	–
12	17, M	Fever, Abdominal	—	14	3	–
13	5, M	Fever, Abdominal	—	3.5	1.5	–
14	32, F	Fever, Abdominal, constipation	—	24	8	–
15	43, F	Fever, Abdominal	Appendectomy	35	8	–
16	28, M	Fever, Abdominal	—	18	10	+
17	35, F	Fever, Abdominal	—	18	17	+
18	21, F	Fever, Abdominal, articular	—	18	3	–
19	22, F	Fever, Abdominal	—	19	3	–
20	5, M	Fever, Abdominal	—	2	3	–
21	42, M	Articular	—	20	22	–
22	18, M	Fever, Abdominal	—	13	5	–
23	32, M	Articular	—	22	10	–
24	4, F	Fever, Abdominal	—	1.5	2.5	–
25	26, F	Fever, Abdominal	—	20	6	–
26	36, M	Fever, Abdominal, Chest, Erysipilas-like rash	—	33	3	–
27	24, F	Fever, Abdominal	—	19	5	–
28	35, M	Fever, Abdominal, constipation, Vomiting	—	30	5	–
29	23, M	Fever, Abdominal, articular	—	14	9	–
30	8, M	Fever, Abdominal, Vomiting	—	5	3	+
31	28, M	Fever, Abdominal, Chest	—	21	7	+
32	27, M	Fever, Abdominal, Vomiting	—	21	6	–

described in the literature,[10-13] occurred in all except two patients, and lasted from two to four days. Articular attacks alone occurred in two patients. One interesting finding was urinary retention during the attacks which was noted in one patient (case 9). There was remission of symptoms during pregnancy in three cases. The response to colchicine in nearly all patients was excellent. In a male patient who had been on colchicine prophylactic regimen for five years, there was no attack 30 months after colchicine was withdrawn (case 2, preparation of the article). In this study we did not notice any case of amyloidosis.

DISCUSSION

FMF is a genetic disorder restricted to certain ethnic groups. In a series of 1327 cases, ninety-five percent affected were Jews (mainly Sephradic Jews), Armenians, Arabs and Turks[9-14] (Table II, III). Therefore the diagnosis of FMF is made much easier when the patient is a member of the said groups. Familial history had been recorded positive from 6.5-80% of affected individuals.[15,16] In our study, from 32 patients, one was Armenian, another was a Kurd, and one was Azari Turk. In two pairs of siblings (12.5%) familial association was noted. The diagnostic methods in our study was based on positive clinical manifestation and several criteria which have been mentioned before (see material and methods). Laboratory findings during the acute attacks in most patients included increase of ESR from 40-90 mm/hr and WBC counts from 8500-20,000 mm^3. No biochemical and hematological markers have been found to distinguish normal individuals from FMF patients. Highest ESRs were observed mainly in the patients with prolonged duration of attacks. Many explanations including infectious, allergic, hormonal or psychosomatic origins have been proposed for the acute inflammatory episodes of FMF. However, the etiology of this disease remains unclear.

Recently, it has been suggested that FMF might be caused by a genetically determined defect in the normal regulation of acute inflammatory responses. Abnormalities of suppressor T lymphocytes, altered metabol-

TABLE II. Ethnic origin of FMF patients

	Number of patients	Percent
Sephradic Jews	664	50%
Armenians	289	22%
Arabs	151	11%
Turks	87	7%
Ashkenazi Jews	71	5%
Other	58	4%
Other Jews	7	—
	1327	100%

TABLE III. Source of report

	Number of patients	Percent
Israel	647	49%
U. S.	308	23%
Lebanon	196	15%
Turkey	83	6%
Other	93	7%
Totals:	1327	100%

ism of lipoxygenase products of arachidonic acid and absence of normal inhibitor of the complement-derived anaphylatoxin C5a have been described in FMF.

Abdominal pain was noted in 93.75%, joint involvement without any other manifestation was seen in two cases, polyarthralgia in one patient (case 21), and ankle arthritis in all attacks was observed in another patient (case 23). Cold weather plays a role as a predisposing factor in attacks of these patients. Pleural involvement was seen in two cases.

retention of urine which was noted in one patient and, persisted for the first 24-36 hrs of attacks (case 9). This finding has not been reported by other authors. Dermatologic manifestations such as erysipelas-like erythema is a common finding in FMF. Nearly one half of Sohar's patients have had skin changes.[15] Except in one patient (case 26) we did not observe such lesions in our patients. In 20 cases of FMF reported from Turkey, no skin manifestations have been recorded.[24]

Pregnancy often has a definite effect on the attack pattern. Classically there has been remission during pregnancy,[15,18,19]

lactation.[21] Nixon and Priest reported a patient with remissions during pregnancy and during internment in a World War II prison camp.[20] However, this pattern is not universal. Schwabe and Peters reported four patients with remission, five with exacerbation, and one patient who experienced both patterns, during pregnancy.[18] In a case report by Shwayri and Tutunji, the family history included two sisters with an increase in attacks during four pregnancies.[22]

In our pregnant patients attacks resolved during pregnancy and were continued for four months after delivery, and repeated the next pregnancies in two cases (case 14, 25) and even up to three years in another (case 15).

Amyloidosis is a most important manifestation or complication of FMF. In a large series, there has been reports of amyloidosis from 0 to 60%.

The highest frequency of amyloidosis in FMF may occur in Turks.[24]

frequency, ranging from 12-42%.[26,27]

fically concerning amyloidosis in Ashkenazi Jews has appeared in English literature.

with even proteinuria among 38 Ashkenazi Jews reported by Siegal.[25]

In this study, we did not notice any cases of amyloidosis. Three patients underwent laparotomy (appendectomy) with diagnosis of acute surgical abdomen and in one patient, three surgical operations was done.

Four separate investigations have confirmed that colchicine is effective in FMF.

regimens used 0.6 mg of colchicine twice a day, everyday. Some patients have required higher doses for maximal effect.[2,16,28]

in pediatric patients. The regimen was 0.6 mg tablet every hour for four hours then one every two hours for four hours, and then one every 12 hours for two days. Patients who began the protocol at the first premonition of an attack were able to abort or ameliorate a significant number of attacks. In some individuals these regimens have induced a complete remission. Preliminary data suggest that colchicine may also reduce the degree of nephropathy associated with amyloidosis.[17,18] Response to colchicine therapy in our study was excellent. Prophylactic dose of colchicine was 0.6 mg every other day except in two patients, who used higher doses of drug (Cases 5 and 25). Unlike other reports, our pediatric patients needed smaller doses.

REFERENCES

1- Sohar E, Gafni J, Blum A, Pras M, Heller H: Primaryperireticular (typical) amyloidosis in Israel. Its relation to FMF. QJ Med 32: 211. 1963.

2- Goldfinger SE: Colchicine for familial Mediterranean fever. N Engl J Med 283: 1302, 1972.

3- Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW: Colchicine therapy for familial Mediterranean fever. A double-blind trial. N Engl J Med 291: 934. 1974.

4- Goldstein RC, Schwabe AD: Prophylactic colchicine therapy in familial Mediterranean Fever. A controlled double-blind study. Ann Intern Med 81: 792, 1974.

5- Reimann HA: Colchicine for periodic peritonitis. JAMA231: 64, 1975.

6- Zemer D, Revach M, Modan B, Schor S, Sohar E, Gafni J:A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. N Engl J Med 291: 932, 1974.

7- Ravid M, Rabson M, Kedar (Keizman) I: Prolonged colchicine treatment in four patients with amyloidosis. Ann Intern Med 87:

668. 1977.
8- Zemer D, Pras M, Sohar E, Gafni J: Colchicine in familial Mediterranean fever. N Engl J Med 294: 170. 1976.
9- Meyerhoff J MD: Familial Mediterraneanfever. Report of a large family. Medicine: 59:1:1980.
10- Sohar E, Gafni J, Pras M, Heller H: Familial Mediterranean fever, a survey of 470 cases and review of the literature. Amer J Med 43: 227, 1967.
11- Siegal S: Benign paroxysmal peritonitis. Ann Intern Med 23: 1, 1945.
12- Siegal S: Familial paroxysmal polyserositis analysis of fifty cases. Amer J Med 39: 893, 1964.
13- Mamou H: La Maladie periodique. Expansion Scientifique Franc, Paris, 1956.
14- Reich CB, Franklin EC: Familial Mediterranean fever in an Italian family. Arch Intern Med 125: 337. 1970.
15- Sohar F, Gafni J, Pras M, Heller H: FMF, A survey of 470 cases and review of the literature. Am J Med 43: 227. 1967.
16- Sohar E, Pras M, Gafni J:FMF and its articular manifestations. Clin Rheum Dis 1: 195, 1975.
17- Wright Daniel G: FMF, In: Wyngaarden JB, Smith LH (eds). Cecil's Textbook of Medicine, Philadelphia, W.B. Saunders' Company, 1196-1198, 1988.
18- Schwabe AD, Peters RS: Familial Mediterranean fever in Armenians. Analysis of 100 cases. Medicine. 53: 453, 1974.
19- Reimann HA, Moadie J, Semerdjian S, Sahyoun PF: Periodic peritonitis heredity and pathology. Report of seventy-two cases. JAMA 154: 1254, 1954.
20- Nixon RK, Priest RJ: Familial, recurring, polyserositis simulating acute surgical condition of the abdomen. N Engl J Med 263: 18. 1960.
21- Ehrenfeld E N, Polishuk WZ: Gynecological aspects of recurrent polyserositis (familial Mediterranean fever, periodic disease). Isr J Med Sci 6: 9. 1970.
22- Ozedemir AI, Sokmen C: FMF among the Turkish people. Am J Gastroenterol 51. 311. 1969.
23- Ozer FI, Kaplaman E, Zileli S: FMF in Turkey. A report of 20 cases. Am J Med 50: 336, 1971.
24- Nimoityn P, Lasker N, Soriano RZ: Detection of urinary amyloid in FMF. Br Med J2. 284, 1976.
25- Eliakim M: Incidence of amyloidosis in recurrent polyserositis (familial Mediterranean fever). Isr J Med Sci 6: 2,1970.
26- Gafni J, Ravid M, Sohar E: The role of amyloidosis in FMF. A population study. Is J Med Sci 4: 995, 1986.
27- Schwabe AD, Terasaki PI, Barnett EV, Territo MC, Klinenbery JR, Peters RS: FMF recent advances in pathogenesis and management. West J Med 127: 15, 1977.