Familial Mediterranean Fever in Ashkenazi Jews: The Mild End of the Clinical Spectrum

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ABSTRACT. ***Objective.*** To characterize familial Mediterranean fever (FMF) in Ashkenazi patients, a Jewish subgroup in which FMF has rarely been described before.

Methods. A retrospective analysis, comparing demographic, clinical, and genetic measures of the cohort of Ashkenazi Jewish patients with FMF (n = 57), followed at the National Center for FMF in Israel, to age and sex matched patients of Iraqi Jewish (n = 62) and North African Jewish (NAJ; n = 61) origin.

Results. Age at disease onset and diagnosis was earlier in NAJ than among Ashkenazi and Iraqi patients. Family history of FMF was described by only 30% of Ashkenazi patients as opposed to the majority of Iraqi and NAJ patients (p = 0.001). The frequency of abdominal and febrile attacks was similar among the 3 groups, while chest and joint attacks were far less common in Ashkenazi and Iraqi compared to NAJ patients. A good response to colchicine was noted in a similar proportion of Ashkenazi and Iraqi patients (82-84%) as opposed to only 56% of NAJ patients (p = 0.0001). Proteinuria, renal failure, and amyloidosis were most frequent among the NAJ patients (18, 6.6, and 9.8% compared to 5.3, 0, and 3.5% and 1.6, 0, and 0% in Ashkenazi and Iraqi patients, respectively).

Conclusion. Ashkenazi patients with FMF stand at the mildest end of the clinical spectrum of FMF. This is notwithstanding the tendency for amyloidosis, the frequency of which is not trivial and which deserves particular awareness. (J Rheumatol First Release Dec 15 2009; doi: 10.3899/jrheum.090401)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER ETHNIC GROUPS

Familial Mediterranean fever (FMF) is a recessively inherited genetic disorder, characterized by recurrent, self-limited attacks of fever and serositis[1]. Originally reported predominantly in people of the Mediterranean basin, FMF has been increasingly recognized in ethnic groups all over the world. Most of the disease knowledge in Jews has been acquired from observations of 2 main patient populations, the Iraqi and the North African Jews (NAJ). The latter tends to experience a more severe disease course, coupled with a relatively higher risk of developing amyloidosis[2]. The cloning of the FMF gene (the MEditerranean FeVer gene, or MEFV) has shown that this rather austere North African clinical phenotype is frequently associated with homozygosity to the M694V mutation, while the milder manifestations observed in Iraqi patients correlate with genotypes bearing the V726A mutation[3].

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Accepted for publication September 9, 2009.

In contrast to the high frequency of FMF in these Sephardic Jewish extractions, the disease was deemed rare in the Jews of Ashkenaz[4], and mostly ruled out at the outset in this patient population on the premise of atypical origin. However, since the advent of the FMF gene, much higher carrier frequencies than expected, based on estimates from disease prevalence alone, have been reported in Ashkenazi Jews (AJ)[6-11], challenging the conventional views on FMF occurrence in this population and suggesting that FMF is underdiagnosed in AJ, perhaps because of lower awareness or a milder clinical phenotype[12]. These conflicting data have led us to reevaluate the size, phenotype, and genotype of the AJ cohort in our FMF patient population.

MATERIALS AND METHODS

AJ patient retrieval. A computerized search of the registry of the National Center for FMF yielded 57 cases of patients of AJ descent with FMF, which were compared to the same magnitude of NAJ and Iraqi patients. All patients fulfilled the Tel-Hashomer criteria for the diagnosis of FMF.[5]

Statistical analysis. Differences between categorical variables among AJ, Iraqi, and NAJ patients were analyzed using the chi-square test or Fisher's exact test, according to the size of the cells examined. The student's t test was used for comparison of continuous variables between the 2 study groups. All tests of significance were 2-tailed; p values < 0.05 were considered statistically significant.

RESULTS

Included in the study were 180 patients with FMF: 57 AJ, 62 Iraqi, and 61 NAJ. The majority of AJ patients were of

Polish extraction (32%), 21% were Romanian, 21% were Russian, 12% were German, 5% were from the former Czechoslovakia, 4% were Hungarian, and an additional 5% hailed from various other countries.

Age at disease onset was a decade earlier among NAJ compared to AJ and Iraqi patients ($p < 0.001$); the delay in reaching a diagnosis of FMF was most profound in AJ patients ($p = 0.016$), and a family history of FMF was reported by only a minority of Ashkenazim ($p < 0.001$; Table 1).

Abdominal and febrile attacks were comparable among the 3 patient groups, while chest and joint attacks as well as erysipeloid erythema were significantly less prevalent among AJ and Iraqi patients compared to NAJ patients (Table 2). Colchicine dose needed to control attacks was lower in patients of AJ and Iraqi origin compared to NAJ ($p < 0.001$) and the proportion of patients with "mild" disease prior to initiation of colchicine was highest among AJ patients ($p < 0.0001$).

Proteinuria, renal failure, and amyloidosis were more prevalent among NAJ patients ($p < 0.05$ for each variable). Nonetheless, 3.5% of AJ patients did develop amyloidosis. The percentage of mutated alleles was comparable among the 3 patient groups (about 80% in each; Table 3). The most common genotype among AJ patients was V726A/V726A (48.6%, $p < 0.0001$). Conversely, there were no M694V homozygous patients among the AJ patients, and the frequency of M694V heterozygous patients, as well as M694V/V726A and M694V/E148Q compound heterozygous patients, was also significantly reduced in this group. One case of amyloidosis developed in an AJ patient carrying the V726A/E148Q complex allele in conjunction with V726A on the second allele. All 4 of 6 NAJ with amyloidosis and MEFV gene analysis carried the M694V/M694V genotype.

DISCUSSION

In this first comprehensive report of the clinical and genetic characteristics of AJ patients with FMF, we show that the

Table 1. Demographic characteristics.

Characteristic	Ashkenazi, n = 57	Iraqi, n = 62	North African, n = 61	p*
Male (%)	57.9	59.7	49.2	NS
Family history of FMF (%)	29.8	82.3	77	< 0.001
Age at FMF onset (yrs ± SD)	21.6 ± 13.6	25.4 ± 14.9	9.6 ± 9.1	< 0.001
Age at FMF diagnosis (yrs ± SD)	34.3 ± 15.9	34.9 ± 13.3	16.6 ± 12.2	< 0.001
Diagnostic delay (yrs ± SD)	12.8 ± 12.1	9.8 ± 10.9	7.0 ± 8.8	0.016

* North African vs Ashkenazi Jewish extraction. NS: not significant; FMF: familial Mediterranean fever; SD: standard deviation.

Table 2. Disease characteristics by ethnic extraction. Values are expressed as percentages unless otherwise indicated.

Characteristics	Ashkenazi, n = 57	Iraqi, n = 62	North African, n = 61	p*
Abdominal attacks	94.7	93.5	98.4	NS
Chest attacks	36.8	40.3	62.3	0.01
Joint attacks	22.8	32.3	83.6	< 0.0001
Febrile attacks	38.6	21	32.8	NS
Erysipeloid erythema attacks	0	6.5	23	< 0.0001
Pericarditis	0	3.2	0	NS
Number of attack sites involved over course of disease (mean ± SD)	1.9 ± 0.86	1.9 ± 1.1	3.0 ± 1.1	< 0.0001
Proteinuria	5.3	1.6	18	0.002
Renal failure	0	0	6.6	0.02
Amyloidosis	3.5	0	9.8	0.026**
Colchicine dose (mean ± SD)	1.2 ± 0.46	1.3 ± 0.46	1.7 ± 0.57	0.001
Explorative laparotomy	21.1	16.1	27.9	NS
Severity prior to colchicine therapy—mild/moderate/severe	42/53/5	18/71/11	2/62/36	< 0.0001
Response to colchicine—good/partial/poor	84/0/16	82/2/16	56/0/44	< 0.0001

* p values define differences between North African vs Ashkenazi or Iraqi Jews, except for**, which compares North African vs Iraqi Jews ($p = 0.04$ for North African vs Ashkenazi). NS: not significant; SD: standard deviation.

Table 3. Genotype by ethnic extraction.

Genotype	Ashkenazi n (%)*	Iraqi n (%)*	North African (NAJ) n (%)*	p (NAJ vs Ashkenazi or Iraqi Jewish Origin)
M694V/M694V	0 (0)	6 (10.3)	29 (48.3)	< 0.0001
V726A/V726A	18 (48.6)	4 (6.9)	0 (0)	< 0.0001
M694V/V726A	1 (2.7)	16 (27.6)	2 (3.3)	< 0.0001
M694V/E148Q	1 (2.7)	9 (15.5)	6 (10.0)	0.038***
V726A/E148Q	4 (10.8)	3 (5.2)	0 (0)	0.099
V726A/M680I	1 (2.7)	0 (0)	0 (0)	NS
M694V/?	1 (2.7)	13 (22.4)	22 (36.7)	< 0.0001^
V726A/?	5 (13.5)	1 (1.7)	0 (0)	NS
E148Q/?	3 (8.1)	5 (8.6)	1 (1.7)	NS
?/?	4 (10.8)	1 (1.7)	0 (0)	NS
Not tested**	20 (35.1)	4 (6.4)	1 (1.6)	< 0.0001
Total mutated alleles/ total alleles	61/74 (82.4)****	95/116 (81.9)	97/120 (80.8)	NS

* Percentages are computed for Ashkenazi, Iraqi, and NAJ patients with known genotype (n = 37, n = 58, and n = 60, respectively). Patients were screened for M694V, V726A, and E148Q. ** Percent of total. *** Significant only for Iraqi vs Ashkenazi. **** Two patients had 726/726/148 complex allele. ^ NAJ vs Ashkenazi. NS for NAJ vs Iraqi. ? None of the studied mutations were found. NS: not significant.

clinical phenotype of this group of patients is generally similar to the Iraqi counterpart (including age at disease onset, site and severity of attacks, response to colchicine, etc.) and is significantly milder than the NAJ disease phenotype. Based on our study and our published experience on the spectrum of disease severity, Iranian patients stand at the mildest end[13], followed by AJ and Iraqi Jews, with NAJ at the most severe end of the spectrum.

The mild disease phenotype in Ashkenazim is attributed to carriage of milder disease mutations, mainly V726A and E148Q, and to the complete absence of M694V homozygosity (Table 3). Our findings match the results of Gershoni-Baruch, *et al,* which showed that the V726A allele was the most prevalent among AJ and Iraqi Jews[14]. While Gershoni-Baruch, *et al* did not detect the M694V allele among AJ, we did find 3 heterozygous patients (8.1%) among this cohort.

Our FMF patient registry yielded 57 AJ out of a total of 9700, forming 0.58% of our FMF population. Assuming a "population at risk" of 1.49 million Ashkenazim in Israel, the observed frequency of FMF (q^2) is 1:26,000, and the computed frequency of the allele (q) is therefore 1:161[15]. This is far lower than recent reports of an actual carriage rate among AJ, which ranges from 14 to 21%[7,8,10]. Given the classic disease manifestations described in AJ patients with FMF, it is unlikely that the discrepancy between the observed and expected disease frequency is explained to any large extent by underdiagnosis. A more plausible explanation is that most MEFV mutations in AJ are of low penetrance, leaving asymptomatic the bulk of AJ individuals who conform to the genetic definition of FMF.

Somewhat surprisingly, given the milder disease phenotype, the favorable response to colchicine, and the lack of M694V homozygosity, 3.5% of the AJ cohort developed renal amyloidosis (p = 0.02 vs NAJ). As these patients were indistinguishable, both clinically and genetically, from their ethnic counterparts, strict clinical followup of the AJ patient population as well as their family members, together with screening for proteinuria and serum amyloid A, is strongly suggested[16].

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