Letters to the Editors

Epidemiology and management of familial Mediterranean fever in Armenia: national audit from 1999 to 2018

Sirs,

Considerable research has been carried out on familial Mediterranean fever (FMF) among Armenians (1-6). However, gaps remain regarding management and treatment. Since 1999, molecular-genetic testing has been available at the Center of Medical Genetics and Primary Health Care of Armenia (CMG) where patients with FMF-like symptoms are referred by physicians or are self-referred. Clinical and molecular data for those patients was available for the period of 1999–2018 providing an opportunity to study FMF in Armenia and to assess the early effectiveness of colchicine management for the prevention of periodic attacks.

In the sample of 1031 patients, 62% were males and a median age of disease onset was six years. Half of the population had a family history of FMF. The major clinical symptoms were fever (94%), abdominal (93%), chest (74%) and joint (67%) pains. More than half of patients had compound heterozygote genotypes to develop FMF (Table I) similar to previous research (7, 8). In multivariable analysis only homozygous patients having fever attacks significantly different compared to other genotype groups (OR=6.92, $p<0.001$). Compound heterozygotes and homozygotes with abdominal pain were different compared to those with no mutation, or with one or more than two mutations (OR=4.83, $p<0.001$ and OR=8.46, $p<0.001$, correspondingly).

Interestingly, 4.2% of patients with clinical manifestations of FMF had no mutations identified. Previous research in Armenians showed that rate of FMF patients with no mutations close to zero or those patients were excluded from the studies (7, 8).

Periodic attacks stopped completely among 76% of patients at three months of colchicine treatment. Among the remainder, only 7% showed no response and 2% had a partial response. Among our patients with no mutations, 67% had positive response to colchicine treatment at first three months.

Multiple logistic regression analysis showed that patients with a family history of FMF had a significant difference compared to other adjusted variables regarding efficacy of treatment (OR=2.082, $p=0.006$, $p<0.05$). In previous research, patients with the family history of FMF showed predisposition of developing the disease at an early age (8).

Additionally, patients with abdominal pain were more likely to respond to colchicine treatment compared to those who did not have abdominal pain during periodic attacks (OR=2.47, $p=0.009$, $p<0.05$).

Our study included a large sample size and used standardised clinical and genetic diagnostic procedures to confirm FMF. The conduct and reporting of the study adhered to STROBE Guidelines (*Lancet* 2007; 370: 1453-7).

However, the data was routinely collected and had missing variables or lost of follow-up visits. Colchicine intake and symptom recall during treatment was self-reported and the follow-up was only for three months after starting colchicine. In future, a longer follow up would be valuable.

There are operational implications to the study. It suggests that practitioners refer patients early for accurate genetic diagnosis in order to start treatment promptly to prevent the periodic attacks and complications associated with FMF (amyloidosis, renal failure). In cases of poor response to colchicine therapy (colchicine-resistant or colchicine-intolerance) physicians should try prolonging colchicine or commencing start alternative treatment (such as anti-IL-1 medications) (9). Where patients with no mutations have clinical manifestations of FMF, genetic testing is recommended through sequencing to search for rare FMF mutations or to test for other autoinflammatory disorders (10). This particular group of patients may have a positive response to colchicine therapy and thus it is advised to start the treatment.

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Table I. Demographics, genotype groups and characteristics of periodic attacks of FMF at diagnosis and after first three months of treatment with colchicine of patients diagnosed and followed for FMF by the CMG clinic in Yerevan, Armenia from 1999-2018.

Variables	n=1031 (%)
Gender	
Male	639 (62.0)
Female	390 (37.8)
Age of onset (years), mean (SD)	9.54 (±10.22)
Age groups	
≤10 years	649 (63.0)
11-17 years	164 (15.9)
18>	181 (17.6)
FMF family history	538 (52.2)
Genotype groups	
Homozygotes	256 (24.8)
Heterozygotes	112 (10.9)
Compound heterozygotes	617 (59.8)
More than two mutations	2 (0.2)
No mutation	43 (4.2)
Frequency of attacks at diagnosis	
From one to few times a week	213 (20.7)
More than once a month	8 (0.8)
Once a month	338 (32.8)
Less than once a month	409 (39.7)
Attacks after colchicine	
No attacks	783 (76.0)
Fewer attacks	25 (2.4)
No change	77 (7.5)

For categorical variables Pearson's Chi-Square test was performed if all the cell counts were >5. Otherwise Fisher's exact test was performed. For numerical variables t-test was used. Missing/unknown data: 0.1 to 10%.
FMF: familial Mediterranean fever; CMG: Center of Medical Genetics and Primary Health Care.

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