MEFV Genotype and Clinical Features of Familial Mediterranean Fever (FMF) in Cyprus

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Background

- Familial Mediterranean Fever (FMF) is an auto-inflammatory disease which is highly common in Cyprus.
- It is characterized by its prevalence in specific populations such as Armenians, Arabs, Turks, Jewish, Greeks and other people with Mediterranean ancestry. [1]
- FMF patients suffer from various symptoms, ranging from periodic fever and abdominal pain, to myalgia and polyserositis. In addition, orchitis, skin lesions and exertional leg pain are possible features. [2]
- FMF has a very diverse genotype and it occurs due to a defect in the MEFV gene which has an autosomal recessive pattern of inheritance.
- The diagnosis of FMF is often based on **Tel-Hashomer criteria**. [3]

  Major criteria: 1- Recurrent febrile episodes with peritonitis, pleuritis or synovitis,
  2-Amyloidosis of AA-type without predisposing disease
  3-Favorable response to daily colchicine

  Minor criteria: 1-Recurrent febrile episodes
  2-Erysipleas like erythema
  3- Positive history of FMF in a first degree relative

  Definite diagnosis → 2 major or 1 major + 2 minor criteria
  Probable diagnosis → 1 major + 1 minor criteria
- FMF attacks vary in duration and severity. An attack can last from 1 to 3 days and sometimes even longer. [3]

Methods

Medical records of suspected FMF patients were studied in a dedicated private FMF clinic. All patients included in the study either fulfilled the Tel-Hashomer criteria or had MEFV mutation detected. 111 patients met the inclusion criteria.

Results

- Among 111 patients, 62 (56%) were female and 49 (44%) were male.
- Two patients were found to carry homozygous MEFV genes and 15 patients had no MEFV mutations detected despite manifesting FMF clinical features.
- 71 patients (64%) were found to experience the attacks for 72hours, 26 (23.4%) for 96 hours, 14 (12.6%) for 48 hours and 1 for 36 hours.

Figure 1: Number of patients presenting with the clinical features

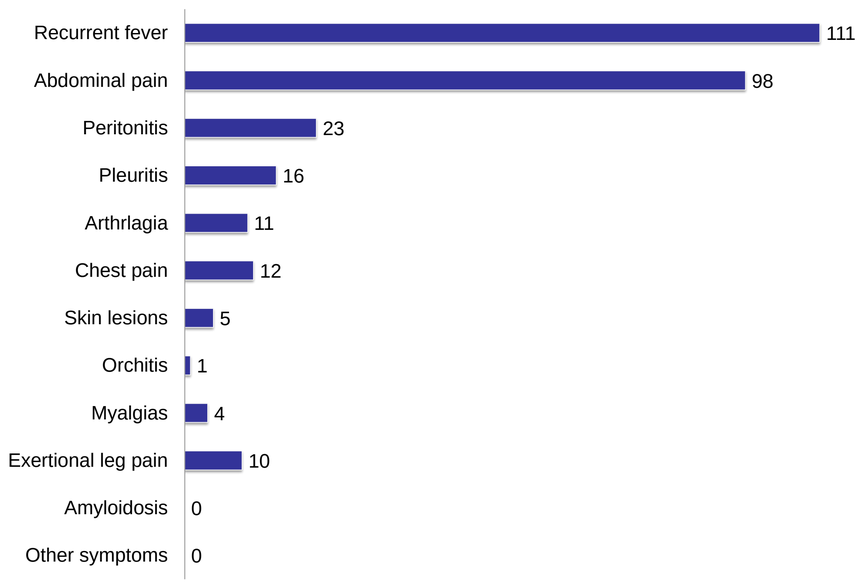
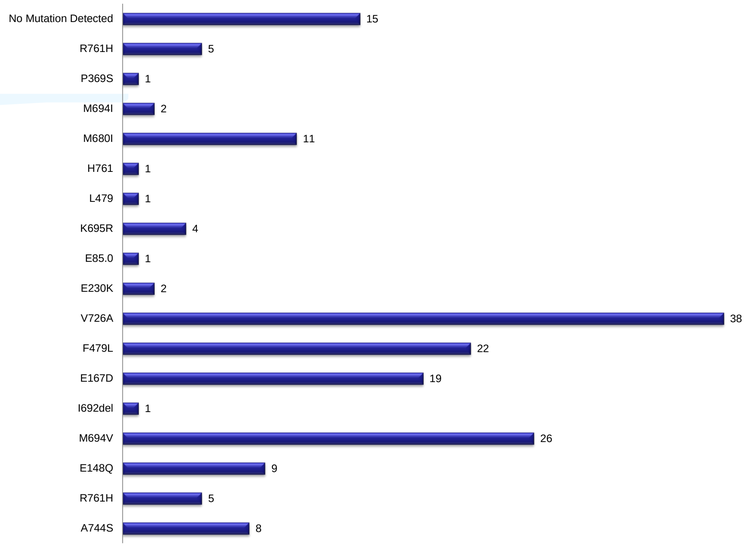


Figure 2: Frequency of MEFV genes in FMF patients



Discussion

- In the population studied females were slightly more affected than males with a ratio of 5:4
- Recurrent fevers and abdominal pain were found to be the most common presentations and it is consistent with the typical presentation of FMF [4].
- V726A mutation was the commonest genotype detected in 38 patients followed by M694V (26 patients) and E167D (19 patients). These findings are not totally consistent with the prevalence of the genotypes in other countries. For instance, in a study of Jewish population M694V was found to me the most prevalent genotype. [5]
- 15 patients who were diagnosed to have FMF using the Tel-Hashomer criteria were found to be MEFV mutation negative. Nevertheless, according to literature these patients could have mutations upstream or downstream to the MEFV related metabolic pathway. [6]
- An important limitation to our study was the small number of sample population. Perhaps, with a larger sample size the findings would've been different.

Conclusion

The findings of the study suggest a list of common clinical features seen in Cypriot FMF patients. These features can be used to direct the clinical diagnosis towards or away from FMF in order to avoid misdiagnosis or delay the diagnosis. Moreover, the list of the prevalent MEFV mutations can be used to further review the panel test for FMF genetic screening. Finally, further epidemiological and molecular studies should be carried out with bigger sample sizes in order to further understand the status of this disease in the Cypriot population.

References

[1] Grateau, G., 2004. Clinical and genetic aspects of the hereditary periodic fever syndromes. *Rheumatology*, *43*(4), pp.410-415.

[2] Eshed, I., Rosman, Y., Livneh, A., Kedem, R., Langevitz, P., Ben-Zvi, I. and Lidar, M., 2014. Exertional leg pain in familial Mediterranean fever: a manifestation of an underlying enthesopathy and a marker of more severe disease. *Arthritis & Rheumatology*, *66*(11), pp.3221-3226.

[3] Livneh, A., Langevitz, P., Zemer, D., Zaks, N., Kees, S., Lidar, T., Migdal, A., Padeh, S. and Pras, M., 1997. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis & Rheumatology*, *40*(10), pp.1879-1885.

[4] Samuels, J. and Ozen, S., 2006. Familial Mediterranean fever and the other autoinflammatory syndromes: evaluation of the patient with recurrent fever. *Current opinion in rheumatology*, *18*(1), pp.108-117.

[5] Zaks, N., Shinar, Y., Padeh, S., Lidar, M., Mor, A., Tokov, I., Pras, M., Langevitz, P., Pras, E. and Livneh, A., 2003. Analysis of the three most common MEFV mutations in 412 patients with familial Mediterranean fever. *Genetics*, *5*, pp.585-588.

[6] Ben-Zvi, I., Herskovizh, C., Kukuy, O., Kassel, Y., Grossman, C. and Livneh, A., 2015. Familial Mediterranean fever without MEFV mutations: a case–control study. *Orphanet journal of rare diseases*, *10*(1), p.34.