Clinical Characteristics of Familial Mediterranean Fever (FMF) in Cyprus

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Aims

- To determine the epidemiological and clinical characteristics of patients with Familial Mediterranean Fever in Cyprus
- To determine the most common genetic mutations prevalent in the Cypriot population with FMF
- To determine the presence of potentially fatal disease complications, primarily AA amyloidosis and end-stage renal disease, in the Cypriot population with FMF

Introduction

- Familial Mediterranean Fever (FMF) is an autosomal recessive genetic disorder that is extremely prevalent in Cyprus. Worldwide, it is found primarily in Mediterranean populations, including Armenians, Turks, North Africans, Arabs, Greeks, Italians and those of Jewish ancestry [1].
- In 1908, it was first defined to be "unusual recurrent peritonitis" when the first patient, a 16-year-old girl of Jewish descent, presented with recurrent fever, abdominal pain and leukocyotosis [2].
- FMF is an autoinflammatory disease [2] characterized by recurrent febrile polyserositis, as well as nonspecific manifestations, such as abdominal pain that may resemble common disorders such as acute appendicitis or cholecystitis, and thus, often delay the diagnosis of FMF [1].
- The Tel Hashomer Hospital established the first criteria for the diagnosis of FMF, which included: [3]
  - Three major criteria: Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis, amyloidosis of the AA type without predisposing disease, and response to colchicine treatment.
  - Three minor criteria: Recurrent febrile episodes, Erysipelas-like erythema, and FMF in a first degree relative.
- For a definitive diagnosis, 2 major or 1 major and 2 minor criteria must be present. If only 1 major and 1 minor criteria is observed, a probable diagnosis is established [3]. In 1997, The Livneh criteria was established, which added monoarthritis, chest pain and exertional leg pain to the Tel Hashomer criteria and removed amyloidosis as a criteria for diagnosis as it was found to be a late manifestation in most cases [4].
- FMF is a clinical diagnosis, which can be supported by genetic testing. The absence of detected genetic mutations does not exclude the possibility of an FMF diagnosis [2]. MEFV is a gene on chromosome 16 that has been found to be responsible for FMF. It contains 10 exons and 3505 nucleotides, and codes for pyrin/marenostrin which has an auto-regulatory effect on leukocytes and thus, has a part in regulating the inflammatory response [2].
- FMF is treated with colchicine, which aims to prevent painful attacks by shortening the length of episodes and prolonging the period between attacks, and prevent the risk of the development of complications such as amyloidosis and end-stage renal disease [1] (proteinuria, nephrotic syndrome, uremia and death), diagnosable by biopsy [5]. These manifestations are the most severe, and contribute to the worst prognosis [6]. During attacks, non-steroidal anti-inflammatory drugs can be used for pain and fever management [1].
- There are a lack of studies about FMF in Cyprus, and comparatively many more in other Mediterranean populations. This study will seek to assess the characteristics of FMF in Cyprus, as it is important to evaluate its current status and increase awareness to promote early detection and prevent misdiagnoses.

Methods

Study Population: 73 Patients with Familial Mediterranean Fever were identified from a patient database

Data Collection: Patient charts were obtained and information was gathered on:

- Patient characteristics (sex, age, ethnicity)
- Clinical characteristics and symptoms
- Genetic testing results

Data Analysis: Data analyzed with Microsoft Office Excel

Results

Participant Information: There were 73 patients who were included in this study, 54.8% of whom are female, and 45.2% of whom are male. The sample consists of patients of all ages who have been referred to an FMF specialist by doctors from all regions of Cyprus.

Figure 1: Clinical Symptoms Exhibited by Cypriot Patients with FMF

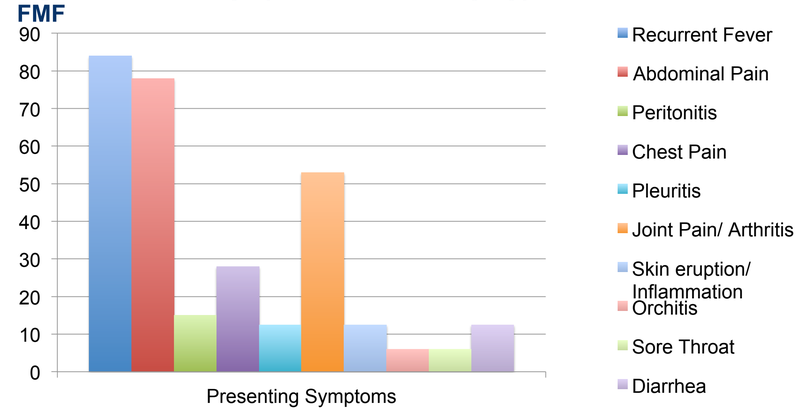

Figure 1: This figure illustrates the most common presentations seen in Cypriot patients symptomatic of FMF. Recurrent bouts of high fever were seen in 84.4% of patients, and 78.1% of patients presented with abdominal pain. Joint pain was another relatively common manifestation of FMF, seen in 53.1% of patients.

Figure 2: Genetic Mutations of the MEFV Gene in Cypriot Patients with FMF

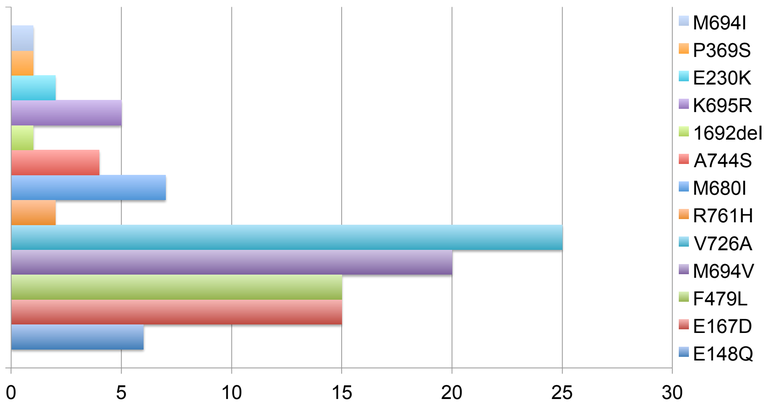

Figure 2: This figure demonstrates a comparison of the prevalence of the different mutations found to contribute FMF in the population sampled. The most prevalent mutation in the sample was discovered to be V726A, which was expressed by 25 patients, which is 34.2 % of our sample. M694V, F479L and E167D were the next most prevalent mutations, seen in 27.3%, 20.5% and 20.5% of the sample, respectively. While some patients tested negative for MEFV mutations, others were seen to have multiple co-existing mutations.

Significant laboratory findings: 9.38% of symptomatic patients had an elevated ESR. An elevated CRP was seen in 12.5% of patients. Less than 6% of patients presented with elevated white blood cell counts and liver enzymes (AST, ALT, GGT).

Presence of amyloidosis or signs of renal dysfunction: Only one patient was found to have an abnormal creatinine measurement, however upon rectal biopsy, the patient was not found to have amyloidosis. Further investigation showed no significant renal impairment.

Discussion

- The most common presentations of recurrent fever and abdominal pain are in line with those in other Mediterranean populations [6]
- The scarcity of amyloidosis and renal dysfunction in the Cypriot population with FMF greatly improves the prognosis of this disease as the remainder of the symptoms are not fatal, and easily controlled with medication. In comparison with other studies, this clinical picture seems to be most like that of Turkey [6] and least like that of Israel, where amyloidosis has been seen in 26.5% of patients [5].
- The second most prevalent mutation found in our study, M694V, has been associated with significantly increased disease severity and risk of amyloidosis elsewhere [1]. It is interesting that our patients with this mutation have not been known to develop severe FMF; This prompts the further exploration of the Cypriot variant of FMF to determine environmental etiologies or other factors that come into play.
- There are a few limitations to this study, such as a small sample size that is more representative of Nicosia than the whole of Cyprus. Additionally, given the relapsing and intermittent nature of this condition, records show that many patients have not attended the clinic regularly, or at all since their first visit or genetic test. This could limit the accuracy of all symptoms experienced, including the detection of renal complications.

Conclusions

The results of this study indicate that Familial Mediterranean Fever in Cyprus manifests in a variety of ways in terms of symptomatology and genetic mutations. Due to its high prevalence in Cyprus and the lack of expertise on the subject among the Cypriot community as a whole, it is necessary for there to be further research on the topic, as well as measures put into place to increase screening and early detection to optimize diagnosis and treatment.

References

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