

Familial Mediterranean Fever: A Continuously Challenging Disease

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Familial Mediterranean fever is perhaps the most common Jewish national monogenic disease. It is frequently encountered in Israel, with an estimated prevalence of 1:400 and a carrier rate of gene mutations ranging from 1:3 (Iraqi Jews) to 1:20 (Iranian Jews) [1]. Despite being a potentially lethal disorder that adversely impacts the affected subjects' social, familial and work life [2], it is not recognized by the governmental health authorities as a "national disease." FMF receives only a fraction of the attention it deserves. As part of the promotional activity to improve the status of the disease and inspire research on FMF, we launched a series of FMF meetings. The first was held at Sheba Medical Center in March 2010; at that meeting twenty presentations of original studies of FMF were delivered, four of which appear in this issue of *IMAJ*.

The paper by Naimushin et al. [3] deals generally with the subject of genotype-phenotype correlation. Ever since the cloning of the *MEFV* (MEditerranean FeVer) gene and detection of its major mutations in 1997 [4], it was hoped that the wide spectrum of phenotypic diversity of the disease would be partly explained by the large number of *MEFV* mutations that have been detected. Eventually, it appeared that only limited linkage could be delineated; carriage of the M694V, M694I and M680I mutations usually predicts a severe clinical course, while a series of other mutations, including E148Q, entails a mild course, sometimes completely asymptomatic. Further research focused on E148Q, even challenging its role as a disease-causing mutation. However, opinion remains divided [5-7]. Naimushin and team adopted a genuine molecular approach, showing that the substitution of glutamine (Q) for glutamic acid (E), caused by the E148Q sequence change, does affect the structure of the *MEFV* product, the pyrin molecule, although very mildly. This study pushes again the E148Q mutation pendulum toward the category of a

"true" disease-associated mutation, leading to a meaningful molecular change.

Kilim et al. [8], in their paper, illuminate the role of genetic testing in the diagnosis of FMF. To date, due to the lack of a specific biochemical test, the diagnosis of FMF is based on the typical clinical presentation [9]. Although in most cases the diagnosis of FMF is straightforward, some patients manifest an atypical picture. In these patients genetic diagnosis is likely to be helpful [10]. Genetic testing of FMF in Israel is generally performed by direct detection of the most common *MEFV* mutations, using restriction enzyme analysis [11]. This approach covers about 90% of mutation-bearing cases. Kilim et al. demonstrate that changing from direct detection to sequence analysis increases the yield of *MEFV* mutation detection by an additional 6.7% due to identification of certain rare mutations. Regrettably, there are still some physicians who deny a diagnosis of FMF and delay colchicine treatment if *MEFV* mutations are not found on routine testing. Applying the sequence method may lead to detection of rare mutations and thereby dispel doubts regarding the accurate diagnosis of FMF in patients with painful febrile attacks, but with negative genetic testing by the direct detection method.

In recent years it was found that FMF patients have increased risk of acquiring additional inflammatory diseases, particularly polyarteritis nodosa, Behcet's disease, various glomerulopathies and most importantly Henoch Schonlein purpura. The latter is a leukocytoclastic vasculitis, typically occurring in childhood and presenting with palpable purpura and hematuria or diffuse abdominal pain, or a combination of these [12]. However, the disease may manifest in an atypical manner. In this issue, Eshach-Adiv et al. [13] report two FMF patients presenting with intestinal intussusception as the first manifestation of their HSP. In one of these patients the intussusception was also the first manifestation of his FMF. Intussusception is a rare but known complication of HSP. FMF with its known risk for the development of peritoneal adhesions, leading occasionally to small bowel obstruction [14], may create a suitable setting to precipitate intussusception. Therefore, the authors appropriately advocate considering FMF in HSP patients who develop intussusception.

Finally, the study by Kivity et al. [15] deals with the most dreadful complication of FMF, amyloidosis. Most affected patients will proceed to develop end-stage renal disease, requiring kidney replacement. In those patients, undergoing kidney transplantation, chronic rejection and infections related to impaired immunity may increase the level of inflammation markers, which in turn may interfere with the evaluation of the FMF disease activity. Subclinical inflammation in this stage is a significant risk factor associated with numerous adverse clinical outcomes, mostly continuous amyloid deposition, including amyloid deposition in the transplanted kidney [16]. Serum amyloid A is the best tool to gain insight into the inflammation status of the patient, particularly with respect to prevention of amyloidosis progression [16–18]. Kivity et al. found that in FMF patients with a kidney transplant the "normal" serum amyloid A levels are slightly higher than those in healthy subjects (20 mg/L versus 10 mg/L). Any serum level above this might be linked to a subclinical inflammation of FMF and should be down-regulated rigorously, using cautious colchicine dose increments.

It is hoped that the last national FMF conference, as well as those in the years to come will increase awareness of this common Israeli genetic disease, and augment interest in the disease among the decision-making agencies, particularly those working in the fields of patient care, social support, and research, and thereby direct more attention and financial resources to FMF.

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