

The Israeli Annual FMF, Amyloidosis and Other Autoinflammatory Diseases Meeting (July 2011): a Bridge Spanning These Entities

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Familial Mediterranean fever is an autosomal recessive disease caused by mutations in the Mediterranean Fever gene (*MEFV*), located on chromosome 16. Being mutated, the *MEFV* gene product, pyrin protein, becomes pro-inflammatory through engagement in the production of the cytokine interleukin-1 beta in an excessive amount. Clinically, FMF is characterized by recurrent short-lived bursts of serous inflammation accompanied by high fever. The most serious manifestation of FMF is AA amyloidosis, caused by a long period of unopposed systemic inflammation (sometimes sub-clinical). The most common presentation of AA amyloidosis is renal, manifested as proteinuria at an early stage, followed by nephrotic syndrome and end-stage renal failure at an advanced stage. Clinical involvement of other organs, such as the heart, thyroid, colon or small bowel may occur, but only at a very late phase of the disease. Colchicine is the drug of choice, but some patients (10%) are resistant to colchicine and continue to suffer from the entire spectrum of FMF manifestations.

Targeted therapy by IL-1 β blockade holds promise as a specific and effective treatment for FMF, especially in patients who do not respond to colchicine. Although there is always some skepticism regarding resistant patients' adherence to colchicine treatment, it was previously shown by Lidar et al. [1] that usually this is not the case since the level of colchicine in the serum of non-responders is comparable to that of responders. Therefore, drugs acting through a mechanism different from that of colchicine are needed. To date, only

case reports and small case series of successful treatment with IL-1 blockade in colchicine-resistant FMF have been published [2]. These observations highlight the need for controlled trials to further evaluate the safety and efficacy of IL-1 antagonists in FMF patients.

Indeed, IL-1 blockade comprised the major part of the second Israeli national meeting on FME, amyloidosis, and other autoinflammatory diseases, held in July 2011 at the Sheba Medical Center. Philip J. Hashkes, from Shaare Zedek in Jerusalem, presented his team's study on riloncept (a fusion protein that binds and neutralizes IL-1) for colchicine-resistant FMF patients. Fourteen FMF patients, unresponsive or intolerant to colchicine, received riloncept or placebo. Riloncept significantly reduced the number of FMF attacks and was shown to have an acceptable safety profile, implying its possible role in the treatment of colchicine-resistant FMF. Ivona Aksentijevich from the National Institutes of Health in the United States devoted her talk to the critical role of IL-1 β in the pathogenesis of autoinflammatory diseases. She also presented data showing that treatment with IL-1 β inhibitors significantly ameliorates clinical and biochemical symptoms of inflammation in patients with autoinflammatory diseases other than FME, such as cryopyrin-associated periodic syndrome (CAPS) and deficiency of IL-1 receptor antagonist (DIRA).

Another key topic in FMF raised at that meeting was AA amyloidosis. Two studies on FMF amyloidosis presented at the conference are published in this issue of *IMAJ*. The first study, by Nussinovitch et al. [3], assessed the effect of FMF and amyloidosis on the cardiovascular system. The second work, by Ben-Zvi and colleagues [4], evaluated risk factors for the development of amyloidosis in a subgroup of FMF amyloidosis patients who had undergone renal transplantation. The effect of FMF, a disease with a robust systemic inflammation, on the cardiovascular system is enigmatic because, contrary to expectations, the rate of atherosclerosis and coronary artery disease in FMF is normal. Still, there is evidence for more subtle changes in the cardiovascular sys-

FMF = familial Mediterranean fever
IL-1 β = interleukin-1 beta

tem in FMF, such as increased intima-media thickness [5]. In the work of Nussinovitch et al. [3], QT interval variability, a marker of increased risk for ventricular arrhythmia, was normal in non-complicated FMF but significantly higher in FMF amyloidosis patients, suggesting a possible susceptibility to ventricular arrhythmia in these patients. However, it remains to be determined whether this finding is due to cardiac amyloidosis or to long-term exposure to inflammation.

It is still unclear why only a fraction of FMF patients develop amyloidosis. Over the years, some risk factors have been identified, such as carriage of the M694V *MEFV* mutation, male gender, joint involvement, and family history, among others. Unexpectedly, in the study presented at that meeting by Kivity et al. [4], these risk factors were shown not to differ between the amyloidosis cohort and sequential FMF patients who were assigned to the control group. The only significant factor in this study for the development of amyloidosis was non-compliance with colchicine treatment for many years prior to the development of amyloidosis. The finding that non-genetic factors are stronger than genetic factors in the development of amyloidosis is reinforced by a previous work of Touitou and collaborators [6] who have shown that country of residence, rather than *MEFV* mutations or other epidemiological factors, is the seminal risk factor for the development of amyloidosis. Such factors, including non-compliance, are amenable to change through patient education and improved health services.

An interesting case presented at the meeting and to the readers of this issue of *IMAJ* [7] is an autoinflammatory disorder, different from FMF, called tumor necrosis factor receptor-associated periodic syndrome. TRAPS is the new name for the disease known for many years in England and northern Europe as familial Hibernian fever. The name was changed to TRAPS following identification of the disease-causing mutation in the TNF receptor and the realization that the disease prevails worldwide. The case described by Arad et al. [7] is important because it shows for the first time that this rare autoinflammatory disease may be present in the Jewish population living in Israel. Extra care should be exercised before classifying an atypical case with febrile attacks as FMF. Genetic laboratories involved in the identification of autoinflammatory diseases should extend their expertise to include tests for all the new autoinflammatory syndromes.

Following from the previous paragraph, another important issue regarding diagnosis of FMF, to which a session of the meeting was devoted, is quality assurance of genetic testing for FMF and other hereditary periodic fevers. Yael Shinar from Sheba Medical Center presented the proposed quality assurance scheme of the European Quality Assurance Molecular Genetics Network. However, there is still a long way to go

TRAPS = tumor necrosis factor receptor-associated periodic syndrome
TNF = tumor necrosis factor

before these recommendations will become a formal rule that must be followed by laboratories that study hereditary periodic fevers.

Of note, unrelated to the FMF conference, but still in the same area, the current issue of *IMAJ* features a case history by Ori et al. [8] of an FMF amyloidosis patient in whom amyloid goiter developed 6 years after initiation of renal replacement therapy for amyloid nephropathy. While this manifestation of amyloidosis is part of the natural history of the disease, it is rare and occurs at a late stage of the disease. Its unique features, such as accelerated thyroid growth, clinically significant compression of neck structures, with impairment of their function and yet preservation of thyroid function, makes the diagnosis of this entity straightforward. This case report aptly serves as a reminder of this entity. It also suggests the possible involvement of the parathyroid glands in this process.

In conclusion, although FMF is a rare disease worldwide, it is highly prevalent in Israel, and primary care physicians and internists alike should be comfortable with the approach to these patients and their management. To date, only a minority of physicians are familiar with the 'little secrets' of FMF, including heterogeneity of its presentation, and the treatment of all its manifestations. The education of patients about their disease will be the topic of the next annual meeting in an attempt to bridge some of these knowledge gaps.

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