Periodic Fever in Infants: Familial Mediterranean Fever Only?

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Key words: familial Mediterranean fever, infants

IMAJ 2003;5:739–740

Familial Mediterranean fever is a hereditary autosomal recessive disease characterized by recurrent episodes of fever with peritonitis, pleuritis, arthritis or erysipelas-like skin erythema [1]. In some cases fever may be the sole manifestation of the disease. Although not all hereditary diseases are manifested in infancy or childhood, FMF is one of the genetic disorders known to appear in young infants [2,3]. However, reaching a diagnosis of FMF in early infancy may sometimes be difficult due to the inability of infants to verbally express their pain, its source or exact location. Infants may display unusual behavior, with restlessness and irritability as an expression of abdominal, pleuritic or joint pains. Thus, the only objective and measurable finding is fever, which becomes the main clue for an underlying active disease in the infant. In families where elder siblings have already been diagnosed as having FMF either clinically or genetically, the parents are the first to raise the possibility of FMF in their infant based upon their previous experience. In many FMF clinics it is not infrequent to encounter a mother who claims that her infant may also have FMF since the child's behavior reminds her of the behavior of her elder son or daughter suffering from FMF.

In this issue of the Journal, Brik et al. [4] describe three infants under the age of 2 with recurrent episodes of fever and non-specific clinical symptoms. In two cases either the father or their brothers had FMF, whereas the third patient did not have any family history of FMF. A diagnosis of FMF was established in the three infants by genetic analysis searching for the *MEFV* mutations [4]. This manuscript is timely and should alert pediatricians in the community and physicians in the emergency room to the possibility of FMF in infants with episodic fever and no obvious etiology. Furthermore, availability of the relatively new tool of genetic testing may help physicians to confirm this diagnosis quite easily. Since FMF is common among non-Ashkenazi Jews and Arabs in Israel, it is mainly infants from these ethnic groups who should be suspected as suffering from FMF and evaluated accordingly.

Fever of unknown origin has already been reported as the main manifestation of FMF in adults [5]. Therefore, the current work-up plan for fever of unknown origin in populations at risk should include genetic analysis for the *MEFV* mutations. The same approach should be adopted in infants with episodic fever with no known cause.

With respect to the patients presented by Brik et al. [4], the question is raised regarding the approach that should be taken in infants with recurrent fever with no apparent cause but with a well-documented family history of FMF (as in the first two cases). Should they undergo a colchicine trial before the genetic analysis, or even if they do not bear *MEFV* mutations? In my opinion, a therapeutic trial with colchicine is crucial because the possibility of them having FMF (especially in the first two infants) is quite high. Furthermore, in such patients the lack of *MEFV* mutations does not exclude this diagnosis since we know that the five most frequent mutations sought do not cover all FMF patients in Israel. There is still the possibility that mutations yet unknown or genetic heterogeneity for FMF can be traced.

In their paper, Brik et al. mention that for infants with recurrent fever the differential diagnosis of other hereditary periodic syndromes should be considered, such as: hyper-immunoglobulin D syndrome, tumor necrosis factor receptor-associated periodic syndrome (TRAPS, formerly called "familial Hibernian fever"), familial cold urticaria and Muckle-Wells syndrome [6]. In addition, they claim that in the cases presented, only FMF and HIDS "were applicable to their patients" and since their serum IgD was not elevated, only a diagnosis of FMF was proposed [4].

It is true that in the cases presented, HIDS is the less likely diagnosis, due to the fact that the disease has been described only in northern and western European patients. None of the patients reported had a Mediterranean ancestry. However, low IgD serum levels do not exclude the diagnosis of HIDS, and neither is elevated IgD specific for this syndrome. Serum IgD level may also be high in FMF and TRAPS during acute attacks. Thus, an accurate diagnosis of HIDS requires sequence screening of the mevalonate-kinase gene [6].

Regarding the applicability of the rest of the hereditary periodic fever syndromes, in the presented cases it seems that our concepts should be modified in light of recent publications. Dode et al. [7] looked for *TNFRSF1A* mutations (associated with TRAPS) in individuals with recurrent inflammatory syndromes in a series of 394 patients from various ethnic groups. Surprisingly, they found *TNFRSF1A* mutations in a population of persons of Mediterranean ancestry who are usually at risk for FMF, such as Armenians, Arabs and Sephardic Jews. Furthermore, Aganna et al. [8] described an Israeli Arab patient with a *de novo TNFRSF1A* mutation causing TRAPS. These studies suggest that TRAPS should also be suspected in Israeli infants with recurrent fever episodes as it is present

FMF = familial Mediterranean fever

HIDS = hyper-immunoglobulin D syndrome

IgD = immunoglobulin D

TRAPS = tumor necrosis factor receptor-associated periodic syndrome

among the Mediterranean population. Furthermore, *de novo* mutations causing TRAPS may also arise – in Israel – as sporadic cases. The phenomenon of *de novo* rising mutations was also reported recently in patients with FCU/MWS [9]. Four of six patients with these syndromes bore new mutations in the *CAIS1* (gene associated with FCU/MWS) that were not found in their parents [9]. Again, this observation supports the possibility that even in Israel there is a chance that *de novo* mutations could cause hereditary periodic syndromes. Therefore, it seems that patients (including infants) with fever of unknown origin should be evaluated not only for FMF but also for other periodic fever syndromes.

These emerging new data may justify the establishment of a national center in Israel for hereditary periodic fever syndromes. In such a center facilities for molecular and genetic diagnosis of the hereditary periodic syndromes should be established.

In summary, FMF is still the most common hereditary periodic fever syndrome in Israel and should be sought in every case of recurrent fever episodes with no known cause. The presence of a family history for FMF further supports this diagnosis. However, in infants with atypical presentation of recurrent fever attacks with no family history of FMF and no known explanation, it is feasible to search for one of the hereditary periodic syndromes, especially TRAPS.

FCU-MWS = familial cold urticaria/Muckle-Wells syndrome

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