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Review Article

Familial Mediterranean Fever: What associations to screen for? (A Review)

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Abstract

Familial Mediterranean Fever (FMF) is the most common and best known of hereditary recurrent fever or periodic fever syndromes. It was described in 1945 and genetically characterized in 1992; caused by a point mutation in the "MEFV" gene located on the short arm of chromosome 16. It is particularly frequent among Sephardic Jews, Armenians, Turks and Middle Eastern Arabs where the prevalence can reach 1/2000 to 1/1000. Recent publications objectified its frequent association with other diseases and/or syndromes, particularly those of autoimmune, genetic, and auto-inflammatory origin. The objective of this review is to familiarize healthcare professionals with the main associations to look for in patients followed for FMF. The early detection of these associations makes it possible to improve the management and the prognosis of patients with FMF.

Keywords: Familial Mediterranean Fever; Periodic fever; Diseases; Pyrine; Association; Chronic inflammation; MEFV gene

Introduction

Familial Mediterranean Fever (FMF) is an auto inflammatory disease with genetic transmission described in 1945 [1] and its characteristic mutation identified in 1992 [2,3]. It is particularly frequent among Sephardic Jews, Armenians, Turks, and Middle Eastern Arabs where the prevalence can reach 1/2000 among Jews and 1/1000 for Turks and Armenians [1,4]. It is caused by a point mutation in the "MEFV" gene located on the short arm of chromosome 16 [1,4,5]. This mutation leads to the production of a mutant protein "pyrine" and thus causes a disruption of the normal inflammatory response and cellular apoptosis [4,5]. Clinically, FMF is characterized by painful paroxysmal and febrile peritoneal, pleural, and joint attacks, which can be associated with various systemic manifestations: cutaneous, neurological, cardiac, urogenital and hematopoietic [1-4].

Several diagnostic criteria, the most used of which are those of Livneh [6], help in the positive diagnosis of this disease but the confirmation is genetic based on the demonstration of mutations in the gene "MEFV" of which there are more than twenty. The most frequent of these mutations are: M694V, M694I, V726A, and E148Q [4,7]. Recent publications have objectified its frequent association with other diseases and/or syndromes, the common denominator of which is genetic predisposition, immune dysfunction, and auto-inflammation. It is therefore important for health professionals to know these associations in order to detect them in time and initiate appropriate care without delay. This approach is the only guarantee to improve the prognosis of this disease, often reserved.

FMF and Its Most Frequent Associations

Several associations have been described with the FMF; the most frequent are: spondyloarthropathies, systemic vasculitis, and inflammatory bowel disease (IBD).

FMF and spondylarthropathies

a significant association between FMF and spondylarthropathies in general and ankylosing spondylitis in particular was reported by several authors [8-11]. In fact, 7.5% of subjects with FMF in the Akar S et al series had associated ankylosing spondylitis. The relative risk (RR) of having spondyloarthropathy and specifically ankylosing spondylitis was also very high in the first-degree parents of a subject with FMF compared to the general population (PR = 3.3 and 2.9 respectively) [11].

This association is reinforced by the particular frequency of enthesopathies in subjects with FMF [12] suggesting that the mutant MEFV gene could partially promote such an association [11,13]. In addition, a statistically significant association has been demonstrated between mutations in the MEFV gene; in particular that of type M694V, and ankylosing spondylitis (even without known FMF): 10.7% Vs only 4.2% in the general population, p=0.06 in the series of yigit S et al [10] and 22.3% Vs only 9.7 % for all "nonsense" mutations of the MEFV gene in the Cosan F et al series [14].

FMF and systemic vasculitis

The most frequent association is with Henöch-Shönlein syndrome or purpura (HSS) [15,16]. In fact, in the series of 68 patients with HSS of Altug U et al, 26% had an associated FMF [17]. This particularly frequent association between HSS and FMF seriously suggests that MEFV could be the causative gene for HSS; the etiopathogenesis of which has not yet been elucidated [18]: in the series of 72 children with HSS of Dogan CS et al. [19] 11 (14.4%) had the MEFV gene mutation in its heterozygous form, 5 (6.6%) in its homozygous form, and 2 (2.6%) in its heterozygous composite form. In addition, seven of these patients presented at the same time two distinct mutations of the MEFV gene which was clearly significant compared to the general population (9.2% Vs 1%). Other systemic vasculitides are also reported to be associated with FMF: panarteritis nodosa, Protracted Febrile Myalgia Syndrome (PFMS-syndrome), Behçet's disease [11,17,20-22], and Takayasu arteritis [23,24].

To approach the mechanism of these associations, the study by Aytekin S et al seems very interesting by revealing a particularly high frequency of vascular anomalies on capillaroscopy during FMF (capillary enlargement and microhemorrhages). These anomalies which characterize systemic vasculitides, suggest a systemic angiitis of the small vessels as mediator of the FMF clinic [22]. This hypothesis is reinforced by the original observation of Girisgen I et al. [16] reporting the concomitant association of an FMF with two systemic vasculitides (HSS and panarteritis nodosa).

In summary, among the systemic vasculitis associated with FMF, HSS and classic panarteritis nodosa are the most frequent [11,24]; next come the PFMS-syndrome and Behçet's disease [11]. The other systemic angiitis are more exceptional [23,24].

FMF and inflammatory bowel disease (IBD)

IBD (Crohn's disease and ulcerative colitis) are far from rare during FMF [11,25-28]. In fact, 22 (15.4%) in the series of 78 patients suffering from FMF of Beser OF et al, had concomitant endoscopically and histologically confirmed IBD [26]. Likewise, the presence of the MEFV gene mutation was significantly found in patients with histologically confirmed IBD: 28% in ulcerative colitis, and 22.6% in Crohn's disease Vs only 9.9% in the healthy controls; p=0.006 [27].

FMF and multiple sclerosis (MS)

This association reported by several authors [11,29-32] but too long controversial [33] has just been recently proven by the large national study of Yahalom G et al. [34] (one of the largest series of FMF) where the frequency of multiple sclerosis in patients with FMF was 0.075%=three times that of the general population (p= 0.0057); in addition, the presence of the M694V mutation worsened the clinical picture of multiple sclerosis in these patients. On the other hand, the study of Unal A et al. [29] had shown a significant frequency of the mutation of the MEFV gene in patients with multiple sclerosis compared to the general population: 38% Vs only 11%, p <0.0001. These findings suggest the mutation of the MEFV gene as a potential predisposing factor for multiple sclerosis; in particular the E148Q type mutation [32].

FMF and rheumatoid arthritis

This association is increasingly reported in the world literature [35-39], and a significantly higher frequency of anti-citrullinated protein (anti-CCP) autoantibodies (specific for rheumatoid arthritis) has been found in patients with FMF: 14.5% Vs only 4.7% in the general population (3 times higher); their presence was significantly associated with arthritis during FMF [40].

FMF and jvenile idiopathic arthritis (JIA)

This association is also far from rare. It has been reported by several authors [41-43]. It has been shown that the frequency of the specific M694V mutation of the MEFV gene during JIA is around 10%, and its presence makes the JIA more severe and more resistant to the usual treatment requiring the use of biotherapy [41]. Also, the presence of all types of MEFV mutations was significantly higher during JIA compared to the general population: 14.28% Vs only 5%, p<0.01% [41]. Therefore, it is recommended to screen for MEFV gene mutations in children presumed to have JIA, especially those of male sex, if enthesopathies and if negative anti-nuclear antibodies [44].

FMF and non-alcoholic fatty liver disease (NAFLD)

in the series of Rimar D et al, 74% of patients with FMF presented NAFLD ranging from simple hepatic steatosis (5 patients/21) to non-alcoholic steatohepatitis (NASH): 3 patients/21, and cirrhosis on NASH: 7 patients/21; and this apart from any underlying metabolic syndrome suggesting a strong association between FMF and NAFLD [45].

FMF and its rarer associations

Other rarer associations have been reported, with: systemic lupus erythematosus [46-48], sarcoidosis, Blau syndrome [49], Kartagener syndrome [50], Gitelman syndrome [51],

Fabry syndrome [52], celiac disease [53], polymyositis [54], juvenile dermatomyositis [55], beta-thalassemia [56], atrophic polychondritis [57], fibromyalgia [58], eosinophilic gastroenteritis [59], and tumour necrosis factor receptor-1 syndrome (TRAPS syndrome).

Conclusion

Knowledge of these associations, especially the most common, is very useful for healthcare professionals caring for patients with FMF. Their diagnosis is not always easy since many of these diseases can cause the same symptoms or have similar clinical presentations. The early detection of these associations makes it possible to improve the management and the prognosis of patients with FMF.

Conflicts of Interest

None.

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