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Multiple Sclerosis and Familial Mediterranean Fever: Myth or Reality?

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Abstract

For a long time controversial, the association between Familial Mediterranean Fever (FMF) and Multiple Sclerosis (MS) seems to be more and more obvious and confirmed. Both diseases share mainly genetic predisposition and recurrent inflammation with pro-inflammatory hypercytokinemia as contributing pathophysiological factors. The specific mutation of the MEFV gene responsible for FMF also seems to have a direct implication in the development of MS. In this mini review we discuss this association and its various plausible mechanisms.

Keywords: Familial mediterranean fever; Multiple sclerosis; Association; MEFV gene mutation; Pyrin

Introduction

Familial Mediterranean Fever (FMF), also known as "periodic disease" is a hereditary recurrent fever belonging to the family of hereditary auto-inflammatory diseases [1,2]. It is the most frequent and best known of these diseases; it was described for the first time in 1945 and genetically characterized in 1992 [3,4]. Classically described as a disease of the Mediterranean basin, particularly common among Sephardic Jews, Turks, Armenians and Arabs, the FMF is currently recognized as a ubiquitous condition [5-9] with a very variable frequency according to race and ethnicity, ranging from isolated sporadic or familial cases [8,10] to high prevalences in the order of 1/2,000 for Jews [10] and 1/1,000 for Turks and Armenians [11,12].

This disease is caused by a mutation of the gene "MEFV" located on the short arm of chromosome 16, locus 13.3 (16p13.3) and coding for a protein that is involved in the regulation of the inflammatory response, pyrin [1-4]. Several mutations responsible for this disease have been identified, the most common of which are: M680I, M694V, M694I, V726A, E148Q and K695R; the frequency of these different mutations varies according to races, and even in the same race it varies according to the ethnic groups [7,10]. Transmission of the disease is classically in an autosomal recessive mode, but "pseudo-dominant" or multi-allelic heredity forms of FMF have also been described, explaining the important genotypic and phenotypic heterogeneity of this disease [3,4,9].

Neurological manifestations of FMF and MS-like symptoms

Neurologic manifestations are rare in FMF with predominant and often severe central nervous system involvement [13,14]. Clinically, the most common manifestations are demyelinating neuropathies, reversible posterior leukoencephalopathy and cerebral vasculopathies (cerebral stroke and diffuse cerebral angiitis) [13,14]. Rarer are the pseudotumor cerebri [13] and lymphocytic aseptic meningitis [15]. Peripheral neuropathies are exceptional and the most common are classically recurrent peripheral facial paralysis [16]. Sometimes, the clinical presentation of neurological impairment during FMF can clinically and radiographically simulate the symptoms/signs of MS defining "multiple sclerosis-like" syndromes [13]. In these cases, the differentiation between the neurological manifestations of FMF and an authentic association between the two diseases (FMF and MS) represents a real diagnostic challenge for clinicians.

FMF and MS association

The association FMF and Multiple Sclerosis (MS) was reported by several authors [17-21], most often in the form of sporadic cases [19,22-29]. It has remained controversial for a long time [30], but was increasingly suggested by several cohorts [21].

The systematic screening of FMF-specific mutations in the series of 157 patients with MS had

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objectified a mutation of the MEFV gene in 19 patients (12.1%). Fifteen of these 19 patients reported at least one suggestive symptom of FMF. In addition, familial MS cases in three of these patients with FMF-specific mutations were found Kümpfel et al. [21].

Similarly, in the series of 105 patients with defined MS, the MEFV gene mutation was objectified in 37 patients (35.2%) Terzi et al. [31].

Finally, the genetic study of Yigit et al. [32] performed in 100 patients with defined MS compared to 160 matched healthy controls, showed a clearly significant association between the mutation of the MEFV gene and MS: p=0.0008.

This association has recently been proven by the large national study of Yahalom et al. [33] (one of the world's largest FMF series) where the incidence 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 M694V mutations exacerbated the clinical picture of multiple sclerosis in these patients.

On the other hand, the study by Unal et al. [18] showed 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.

Thus, it is currently accepted that the FMF frequency in Turkish patients with defined MS is 4 times that of the expected prevalence in the general population [34], and pyrin mutations are 3.5 times more common in patients with MS compared to the group of healthy controls [20].

The association between MS and FMF was also noted in the pediatric population [29] and was found to be statistically significant [35].

Pathogenic mechanisms of the FMF and MS association

The pathophysiological mechanisms explaining this association are multiple: a) Recurrent inflammation with its consequences such as mitochondrial energy deficit, demyelination, axonal damage, and disruption of blood-brain barrier, which are the factors involved in the pathogenesis of MS, are also possible during FMF [20]. Indeed, the FMF is characterized by an exaggerated and inappropriate inflammatory response (hyper-secretion of pro-inflammatory cytokines including in particular IL-1, TNF-α and IL-6, an activation of the NF-KB, and a reduction of apoptosis of inflammatory cells) [1,3,4]. These cytokines are also involved in the pathogenesis of MS. b) Genetic factor: genetic risk is currently known as a possible etiological factor of MS [32]. These two conditions (FMF and MS) thus share the genetic susceptibility [34]. FMF-specific MEFV gene mutations thus appear to be a plausible pathophysiological factor directly involved in the development of MS [32]. The exact role of these mutations is not yet fully known [31] but it has been shown that the M694V mutation significantly worsens the clinical phenotype of MS [33] and the M694V and E148Q mutations are particularly predisposing to the development of MS in patients followed for FMF [21,33].

Conclusion

The association between FMF and MS is far from a mere coincidence. Subjects followed for FMF seem to have a significantly high risk of developing MS and *vice versa*. These two conditions share genetic susceptibility and recurrent inflammation as common pathogenic factors. The specific mutation of the MEVF gene seems to play a key role in this association. This association deserves to be known and researched in any patient followed for FMF, especially since the neurological manifestations of this disease may present with clinical and radiological symptoms similar to MS (MS-like syndrome).

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