Amyloidosis in Behçet's disease and familial Mediterranean fever

Sir, Familial Mediterranean fever (FMF) is a genetic disease with autosomal recessive transmission, occurring mainly in Middle-Eastern and eastern Mediterranean populations. Haplotype and mutation analysis has helped us trace the origins of this disease to the Fertile Crescent, located in the eastern Mediterranean [1]. Another rheumatological disease that is common in this area is Behçet’s disease (BD). However, it is assumed that the genetic seeding of BD has been through the Silk Route and Japan. Both diseases may be complicated with amyloidosis of the AA type; however, this is much rarer in BD than in FMF [2]. In recent years, the possible association between FMF and BD has been of interest [3–5]. In order to evaluate the possible role of mutations of the MEFV (gene for FMF) in BD-related amyloidosis and to investigate the association between BD and MEFV mutations, we studied the common mutations in three patients with BD.

Case 1, a 45-yr-old man, had nephrotic syndrome and renal biopsy revealed amyloidosis. Case 2, a 41-yr-old man, had nephrotic syndrome and renal failure, and amyloidosis was demonstrated by rectal, gastric and bone marrow biopsies. Case 3, a 51-yr-old man, was the brother of case 1 and did not have any renal or intestinal problems indicating amyloidosis. All patients fulfilled the diagnostic criteria of the International Study Group for Behçet’s disease [6]. Cases 1 and 2 have been reported previously [7–8]. All patients and first-degree relatives denied recurrent abdominal pain and fever attacks during childhood and appendectomy was not performed.

Our strategy for mutation analysis included two steps. The hotspot exon 10, which harbours 14 mutations, was first analysed by denaturing gradient gel electrophoresis. According to the band pattern, subsequent analysis was done either by restriction endonuclease enzyme digestion or sequencing. Furthermore, E148Q in exon 2 was analysed by restriction endonuclease enzyme (BstNI) digestion. Case 1 was found to be homozygous for the M680I mutation. No MEFV mutations were present in the remaining two patients.

In 2000, Schwartz et al. [3] reported 39 patients with BD and FMF and concluded that BD, like polyarteritis nodosa (PAN) and Henoch-Schönlein purpura, is a vasculitis complicating FMF. Although 10 of the 39 patients had proteinuria greater than 0.5 g/day, amyloidosis was not reported in these patients. A preliminary study of these patients had shown that most of them were homozygous or heterozygous for the M694V mutation [3, 5]. The case presented here is the first demonstration of homozygosity for the M680I mutation in a patient with BD. This case lacked the clinical features of FMF, unlike the cases reported in the study of Schwartz et al. [3]. Furthermore, our patient is the first to have developed amyloidosis secondary to BD and to have a mutation in both alleles of the MEFV gene.

Recently we have reviewed cases with FMF and PAN [9], and there are some differences between BD and PAN as a vasculitis complicating FMF: (i) all patients with PAN had sufficient clinical features for the diagnosis of FMF before the diagnosis of PAN; (ii) genotypic FMF disease has not been described in a patient with PAN who did not have phenotypic FMF; and (iii) none of the siblings of patients with FMF and PAN had only PAN. However, in the siblings presented here, the patient who had BD and amyloidosis had no symptoms of FMF, although he had a genotypic diagnosis. His sibling had only BD, lacked a MEFV mutation (which his brother had) and did not develop amyloidosis. Thus, BD seems to be segregating in a different way in this family. These data show that the relationship between FMF and BD may be more complex than is implied by the description of BD as a vasculitis complicating FMF.

Unlike FMF, BD is not a single-gene disease: it seems to be a multigenetic disease with contributing environmental factors. The clinical features of BD show variation according to geographic area and/or ethnic group. Most cases with BD and amyloidosis have been reported from the Middle East and Mediterranean countries rather than Japan [2, 10]. On the other hand, FMF and MEFV mutations have never been reported from Japan. The familial form of BD is also more frequent in the Middle East than in Japan [11]. The MEFV gene codes for pyrin and is expressed in neutrophils and monocytes, and it is believed that mutations of pyrin affect neutrophil inflammation. Because neutrophils and monocytes are also involved in the pathogenesis of BD, it is conceivable that mutations in the pyrin gene affect the expression of the disease, at least in certain populations. It may be suggested that MEFV mutations are among the risk factors for more severe disease in the ethnic groups in which it is present, whereas other ethnic groups require other genetic predisposing factors for the development of amyloidosis. Although the MEFV gene was mutated in only one of our cases, it may be speculated that MEFV-related mutations may explain why amyloidosis due to BD and the familial form of BD is more common in Middle-Eastern and Mediterranean countries than in Japan. Recently, some MEFV mutations were shown to be more frequent in BD than in controls, suggesting that they act as additional susceptibility factors in BD [4]. None of the patients was homozygous for an MEFV mutation and amyloidosis was not reported in these cases [4].

It is tempting to speculate that two doses of an MEFV mutation may be a risk factor for the development of amyloidosis in BD. Further studies are needed to test this hypothesis. In the meantime, prescription of colchicine may be useful in BD patients homozygous.
for an MEFV mutation. The possible beneficial effects of colchicine in patients heterozygous for MEFV mutations remain to be defined. Identification of new MEFV mutations or MEFV-related genes will clarify the relationships between FMF, BD and amyloidosis.

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