MEFV mutations are increased in Behçet’s disease (BD) and are associated with vascular involvement

P. Atagunduz, T. Ergun, H. Direskeneli

ABSTRACT

Objective. A high prevalence of Behçet’s disease (BD) among familial Mediterranean fever (FMF) patients has been described recently and a weak association of BD and certain MEFV gene mutations, originally linked to FMF, has been reported in an ethnically mixed population from France. We further investigated the presence of MEFV mutations in BD patients from Turkey, a country with a high prevalence of both disorders.

Methods. The frequencies of three FMF-related MEFV mutations (M694V, M680I and V726A) were investigated in BD patients (n = 57) by molecular genetic studies using a polymerase chain reaction with the ARMS method. All patients fulfilled the International Study Group Criteria for the diagnosis of BD and patients with FMF-like symptoms or a chronic inflammatory disease were excluded.

Results. Fifteen BD patients were found to carry one single MEFV mutation (26%), compared to 9.1% in the control group (p = 0.003, OR: 3.5, 95% CI: 1.6-7.6). Among 20 BD patients with vascular involvement, 11 (55%) had MEFV mutations compared to 4 patients (11%) in the non-vascular group (p = 0.001, OR: 10, 95% CI: 2.5-39.3). M694V was the dominant mutation in our study group (11 out of 15 patients with mutated alleles). Six out of 7 female patients with vascular involvement carried MEFV mutations in contrast to 5 out of 13 male patients (85.7% versus 38.4%, p = 0.07, OR: 0.1, 95% CI: 0.009-1.14). No association with other clinical manifestations was observed.

Conclusion. MEFV mutations, originally linked to FMF, may act as a genetic susceptibility factor for other inflammatory disorders such as vascular BD.

Introduction

Mutations of the MEFV gene, which encodes the neutrophil protein pyrin (marenostrin) was recently linked to familial Mediterranean fever (FMF), an autosomal recessive, inflammatory disease characterized by recurrent episodes of febrile serositis attacks. Behçet’s disease (BD) is a multi-systemic vasculitic disorder with mucocutaneous, ocular, arthritic, vascular and central nervous system involvement. A clinical relationship between FMF and BD has been described in Israel, with a slightly higher prevalence of BD among FMF patients compared to the general population (1). Recently, a weak association of certain MEFV mutations and BD has also been reported in an ethnically mixed population from France (2). We further investigated the presence of MEFV mutations in BD patients from Turkey, a country with a high prevalence of both BD and FMF.

Materials and methods

Patients

We investigated the presence of MEFV mutations in BD patients from Turkey (n = 57, 26 males, 31 females, mean age 38 ± 11 years) recruited from the Behçet’s disease outpatient clinics of Marmara Medical Faculty, Istanbul. All BD patients had oral ulcers. Genital ulcers were present in 86%, skin manifestations in 75%, ocular involvement in 21% (all posterior uveitis except for one patient) and vascular involvement in 35%. The pathergy test was positive in 53% of the study patients. At the time of the study, 23% of the patients were receiving immunosuppressive treatment. The study was approved by the University of Marmara Institutional review board and informed consent was obtained.

Inclusion and exclusion criteria

Consecutive patients were screened for
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Table I. The distribution of MEFV mutations in BD patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Mutation</th>
<th>Oral ulcer</th>
<th>Genital ulcer</th>
<th>Positive pathergy test</th>
<th>Uveitis</th>
<th>Cutaneous signs</th>
<th>Venous involvement</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD patients with vascular involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M694V / M694V</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>EN</td>
<td>DVT, V Cava infl. syndrome</td>
<td>AZA, MP, Warfarin</td>
</tr>
<tr>
<td>6</td>
<td>M680I / -</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>DVT</td>
<td>COL, ASA</td>
</tr>
<tr>
<td>13</td>
<td>M694V / -</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>BC syndrome</td>
<td>AZA, MP, Warfarin</td>
</tr>
<tr>
<td>14</td>
<td>V726A / -</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>EN</td>
<td>DVT, BC syndrome</td>
<td>AZA, MP, Warfarin</td>
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<td>20</td>
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<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>DVT, BC syndrome</td>
<td>CYC, AZA, MP</td>
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<td>24</td>
<td>M694V / -</td>
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<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>DVT, CNS involvement</td>
<td>AZA, Warfarin, COL</td>
</tr>
<tr>
<td>33</td>
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<td>YES</td>
<td>YES</td>
<td>EN</td>
<td>NO</td>
<td>Nodular vasculitis</td>
<td>COL</td>
</tr>
<tr>
<td>34</td>
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<td>YES</td>
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<td>NO</td>
<td>NO</td>
<td>EN</td>
<td>DVT</td>
<td>ST</td>
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<tr>
<td>53</td>
<td>M694V / -</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>EN</td>
<td>ST</td>
<td>COL</td>
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<tr>
<td>54</td>
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<td>YES</td>
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<td>NO</td>
<td>NO</td>
<td>EN</td>
<td>DVT</td>
<td>COL, NSAID</td>
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<tr>
<td>57</td>
<td>M694V / -</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>EN</td>
<td>ST</td>
<td>COL</td>
</tr>
<tr>
<td>BD patients without vascular involvement</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>25</td>
<td>V726A / -</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>EN</td>
<td>NO</td>
<td>NSAID</td>
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<tr>
<td>29</td>
<td>M694V / -</td>
<td>YES</td>
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<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>DVT</td>
<td>NSAID</td>
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<tr>
<td>30</td>
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<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>EN</td>
<td>NO</td>
<td>NSAID</td>
</tr>
<tr>
<td>38</td>
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<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>ST</td>
<td>NSAID</td>
</tr>
</tbody>
</table>

ASA: Acetyl salicylic acid; AZA: Azathiopirin; BC Synd: Budd-Chiari syndrome; CNS: Central nervous system; COL: Colchicum dispert; CYC: Cyclophosphamide; DVT: Deep vein thrombosis; EN: Erythema nodosum; MP: Methylprednisolone; NSAID: Non-steroid anti-inflammatory drugs; ST: Superficial thrombophlebitis

the diagnostic criteria of the International Study group for BD and the Tel-Hashomer criteria for FMF (3, 4). Patients fulfilling the Tel-Hashomer criteria for FMF or patients with symptoms resembling those of FMF were excluded. Patients with a chronic inflammatory disease other than FMF also were excluded from the study. A non-inflammatory group of both healthy (n = 50, M/F 23/27) and disease controls (n = 136, M/F 62/74) with cardiovascular system disorders (n = 48), metabolic disorders (n = 58), renal disease (n = 16), or pulmonary disease (n = 14) were also studied. Mutational analysis with PCR was done according to a protocol described earlier by Eisenberg et al. (5).

Statistical analysis
The allele frequencies were compared by the Fisher’s exact test.

Results
Fifteen BD patients were found to carry one single MEFV mutation (26%), compared to 9.1% in the control group, with a statistically significant difference between the groups (p = 0.003, OR:3.5, 95% CI:1.6–7.6). All patients were heterozygous for MEFV mutations except for one who was homozygous for M694V (Table I). M694V was the dominant mutation in our study group. Among 20 BD patients with vascular involvement, 11 (55%) had MEFV mutations compared to 4 patients (11%) in the non-vascular group (p=0.001, OR:10.0, 95% CI:2.5–39.4). The allele frequencies in the non-vascular group did not differ from the control group (11% vs. 4.5%) (p = 0.76). All four patients with severe vascular involvement (Budd-Chiari syndrome, vena-cava superior thrombosis and vascular neuro-BD) were mutation positive (p=0.004, OR: 33.2, 95% CI: 1.6–664.2). MEFV mutations were also more frequent in the pathergy positive group (40% vs. 11%, p = 0.02, OR: 5.3, 95% CI: 1.3–21.7). The frequency of mutations did not differ in patients with uveitis (31% vs. 25%, p = 1.0, OR: 1.2, 95% CI: 0.3–4.7) and no association between other clinical manifestations of BD and MEFV mutations was observed. Six out of 7 female patients with vascular involvement carried at least one MEFV mutation compared to 5 out of the 13 male patients (85.7% vs. 38.4%. p = 0.07, OR:0.1, 95% CI: 0.009 – 1.14). Similar to two recent reports by Yilmaz et al. and Ozdogan et al. we found a carrier rate of 9% for the M694V, M680I and V726A mutations in the Turkish population (6, 7).

Discussion
Epidemiological similarities and the neutrophilic nature of the inflammatory infiltrates suggest that a common factor may be present in BD and FMF (8). Touitou et al. first suggested the possible implication of MEFV mutations in BD, reporting slightly higher frequencies of M694V, V726A and E148Q mutations (2.6%, 2.6%, and 5.2%, respectively) compared to the controls (0%, 0%, and 2.2%) (2). However, Touitou et al. studied BD patients with diverse ethnical backgrounds, possibly including some from populations with low MEFV penetration. Only 6 patients were of Turkish origin in their study and 2 of them were positive for MEFV mutations. On the other hand, a similar frequency of MEFV mutations to our study among BD patients (30%) has been reported by Ben-Chetrit et al. from Israel (9). An association of MEFV mutations with the severity of rheumatoid arthritis and multiple scler-
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rosis has also been reported recently, suggesting that MEFV mutations might be a severity marker for other inflammatory disorders, a question not addressed by the previous studies (9-12).

Although vascular complications are an exception in the course of FMF, an important observation of our study is the high prevalence of MEFV mutations in BD patients with vascular involvement. Severe vascular complications such as Budd-Chiari syndrome, vena-cava superior thrombosis and vascular neuro-BD were found to be present only in the mutation positive group of BD patients. Factor-V Leiden and prothrombin 20210 mutations have also been linked to vascular thrombosis in BD previously (13). However, whether the increased propensity to thrombosis in BD is intra-vascular or linked to the endothelial damage is still controversial. Recently, neutrophilic infiltration of the vasa vasorum has been described as the main pathologic feature in the vascular specimens of BD patients (14). Although controlled studies are not available, immunosuppressives are also the first choice treatment for vascular BD by most experts (15).

Male BD patients are described to have a more severe clinical course and vascular involvement is also more common in male patients (13/26 versus 7/31) in our study (16). However, the higher prevalence of MEFV mutations among female patients with vascular complications (6/7 versus 5/13) suggests that the presence of the MEFV gene might be a more crucial genetic factor in female patients for vascular involvement. Ben-Chetrit et al. did not report any association of MEFV mutations with the clinical manifestations of BD or gender (9). However, there was only one patient of Turkish origin in their study and the differences between the two studies could be explained by the differences in ethnic background. In conclusion MEFV mutations, especially of M694V, may act as another genetic susceptibility factor, especially for vascular BD, in Turkish BD patients. Further studies evaluating the role of MEFV mutations in BD patients from other ethnic populations and on different neutrophilic disorders such systemic neutrophilic vasculitides will further help to elucidate the exact role of MEFV gene on neutrophil-related inflammatory mechanisms.

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References