Paediatric rheumatology

The frequency of juvenile spondyloarthropathies in childhood familial Mediterranean fever

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Key words: familial Mediterranean fever, juvenile spondyloarthropathies, chronic arthritis, MEFV gene, M694V gene mutation

ABSTRACT

Objective. The aim of this study is to evaluate the frequency of juvenile spondyloarthropathies (JSpA) in childhood familial Mediterranean fever (FMF) patients from a single tertiary centre. Additionally, we aimed to investigate the main clinical characteristics of FMF patients with coexistence of JSpA clinical features.

Methods. We evaluated 323 paediatric FMF patients who were followed at our clinic. All of the patients were evaluated by three different investigators (EO, DS, ET) for the presence of JSpA clinical signs, according to the recently proposed JSpA criteria. Patients preliminary diagnosed as FMF+JSpA were further evaluated by the experienced paediatric rheumatologist (OK) who made the final decision on the diagnosis of the patients.

Results. The female/male ratio was 1.13 (n=172/151). Preliminarily, 33 (10.2%) out of 323 paediatric FMF patients had been classified as FMF+JSpA. An experienced paediatric rheumatologist re-evaluated the classified patients and all of them were diagnosed as definitive FMF+JSpA. The M694V mutation was the most common mutation, seen in (n=18/32) (56.3%) FMF+JSpA, and in (n=152/151) (61.1%) FMF patients without JSpA/JIA.

Conclusion. Apart from acute monoarthritis of the lower extremities, the chronic arthritis should be kept on mind among FMF patients with articular involvement. The JSpA should be considered in FMF patients with oligoarthritis, inflammatory back pain and enthesopathy complaints with onset over 6 years. Newly proposed JSpA criteria can be used to spondyloarthropathies in childhood FMF.

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease in our region, commonly presenting with fever, recurrent episodes of self-limiting polyserositis and arthritis. The disease onset appears in early childhood in 90% of patients, usually before the age of 10 (1). In a field study from Turkey, Ozen et al. (2) reported the prevalence of FMF as 9.3/10,000 among children.

FMF generally occurs as a result of autosomal recessive mutation in the MEFV gene. The MEFV gene controls neutrophil chemotaxis by encoding the pyrine protein that regulates the actin-tubulin association (3). The mutations on the exon 10 of the MEFV gene have been most frequently attributed to the disease clinical features. However, mutations in exons 2, 3 and 5 have also been associated with the disease features. Till now, the M694V, M694I, M680I, V726A and E148Q are the most commonly seen mutations in the FMF patients being described in the literature (4).

According to the data from the literature, 40% of FMF patients have acute arthritis lasting from 3–7 days (1). However, some of the patients develop different type of chronic arthritis, predominantly including oligoarticualr juvenile idiopathic arthritis (JIA) and juvenile spondyloarthropathies (JSpA). Spondyloarthropathies (SpA) is a common name for a group of inflammatory arthritides, which usually begin in the third or fourth decade of life. In general, SpA encompasses 15–20% of all children arthritides. It is characterised by arthritis and enthesitis; affecting primarily the joints of the lower extremities. Unlike those of adult SpA disorders, a JSpA disorder rarely has axial involvement (spine or sacroiliac joint) in the beginning of the disease (5).

The frequency of JSpA has been reported as increased among FMF patients, comparing to healthy children (1, 6-9).
Yigit et al. (10) reported the increased frequency of MEFV mutations among adults with SpA, comparing to healthy controls (32% vs. 15%). However, studies on JSpA among childhood FMF patients are insufficient.

Hereof, the purpose of this study is to evaluate the frequency of JSpA in childhood FMF patients from a single tertiary centre. Additionally, we aimed to investigate the main clinical features of FMF patients with coexistence of JSpA, comparing to FMF patients without signs of chronic arthritis.

Material and method

Study population

A total of 323 paediatric patients diagnosed as FMF according to Turkish Paediatric FMF criteria (11) were included consecutively in the study. Turkish Paediatric FMF criteria include the presence of two or more of the following: ≥3 attacks with 6-72 hours duration of fever, abdominal pain, chest pain, oligoarthritis, and positive family history. Arthritis lasted <6 weeks was considered as acute and that lasting for >6 weeks as chronic.

Afterwards, patients were blindly questioned according to recently proposed criteria for JSpA (5, 12, 13) by 3 researchers (EO, DS, ET) who were previously educated for FMF and JSpA. Patients who were preliminarily diagnosed as FMF + JSpA were reevaluated by an expert in paediatric rheumatology (OK) and finally divided in two groups: FMF with and without coexisting JSpA.

Data collection

A standardised case report form (SCRF) including patients’ demographic, clinical features and presence of classification criteria for JSpA was fulfilled for each of patient. Demographic data include gender, age at time of the study, age of disease onset, date of diagnosis, MEFV mutation, treatment modality, presence of colchicine treatment resistance, concomitant disease, familial history for FMF and familial rheumatologic disease history. Clinical data includes FMF arthritis’ onset age-duration and localisation, age at the onset of oligoarthritis, presence of inflammatory lumbar pain, enthesitis, hip arthritis, sacroiliitis, tarsometatarsal arthritis, male gender, response to non-steroidal Anti-Inflammatory Drugs (NSAIDs), Human Leukocyte Antigen (HLA) B27 positivity, limitation in Schober test (<4 cm) and a family history of SpA group of disease or dactylitis or psoriasis or presence of Inflammatory Bowel Disease (IBD).

Mutations analysis

The genetician form the Department of Medical Genetics at our institution has performed all mutation analysis. The DNA was extracted from peripheral blood leukocytes using standard protocols. Molecular analyses were performed within the framework of routine genetic testing for FMF patients. The presence of MEFV mutation was investigated in exons 2, 3, 5, and 10, as previously suggested in the literature (1, 2, 4).

Statistical analysis

We performed descriptive statistics in this study. The ratios and mean values are calculated with SPSS 21.0 program (SPSS Inc., Chicago, IL., USA). The mean ± SD values were used for variables with normal distribution, while the median (IQR) values were used for variables that were not normally distributed. The categorical variables are expressed by frequency.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

Demographic characteristics

A total of 323 FMF patients were included in the study; 172 (53.25%) of them were females.

Mean age at disease onset was 6.76±3.88 years for FMF+JSpA patients and 5.14±3.49 years for FMF patients without coexisting features of JSpA/JIA. The frequency of male gender was higher in FMF patients compared to JSpA or JIA (69.70% vs. 46.75%) (23/33 to 123/275). Resistance to colchicine treatment was similar in both groups (3.03% and 2.54%), (1/33 to 7/275 respectively). Main demographic characteristics of patients are shown in Table I.

Clinical characteristics

M694V was the leading MEFV mutation in patients with FMF. MEFV mutation distribution is summarised in Table II. The frequency of juvenile spondyloarthropathies according to recently proposed JSpA criteria was 10.21% (n:

Table I. The demographic characteristics of study groups.

<table>
<thead>
<tr>
<th></th>
<th>Total FMF</th>
<th>FMF + JSpA</th>
<th>FMF + JIA</th>
<th>FMF without JSpA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=323</td>
<td>n=33 (10.2%)</td>
<td>n=15 (4.6%)</td>
<td>n=275 (85.1%)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>172 (53.3%)</td>
<td>10 (30.3%)</td>
<td>10 (66.7%)</td>
<td>152 (55.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean age at disease onset (mean ± SD years)</td>
<td>5.1 ± 3.5</td>
<td>6.8 ± 3.4</td>
<td>4.9 ± 3.3</td>
<td>4.9 ± 3.4</td>
<td>0.019</td>
</tr>
<tr>
<td>Mean age at the time of study (mean ± SD years)</td>
<td>12.6 ± 4.4</td>
<td>14.6 ± 3.6</td>
<td>10.73 ± 3.6</td>
<td>12.5 ± 4.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean duration of follow-up (mean ± SD years)</td>
<td>7.5 ± 4.05</td>
<td>7.9 ± 4.3</td>
<td>5.9 ± 2.9</td>
<td>7.6 ± 4.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Family history of FMF, n (%)</td>
<td>156 (48.3%)</td>
<td>13 (39.4%)</td>
<td>6 (40%)</td>
<td>137 (49.8%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Resistance to colchicine treatment, n (%)</td>
<td>9 (2.8%)</td>
<td>1 (3%)</td>
<td>1 (6.7%)</td>
<td>7 (2.5%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

FMF: familial Mediterranean fever; JIA: juvenile idiopathic arthritis; JSpA: juvenile spondyloarthropathies.
Juvenile spondyloarthropathies in childhood FMF/ E. Ozer et al.

Table II. M694V mutation distribution in study group.

<table>
<thead>
<tr>
<th></th>
<th>Total n=323</th>
<th>FMF + JSpA n=33 (10.2%)</th>
<th>FMF + JIA (other than JSpA) n=15 (4.6%)</th>
<th>FMF without JIA/ JSpA n=275 (85.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M694V mutation, n(%)</td>
<td>181/298 (60.7%)</td>
<td>18/32 (56.3%)</td>
<td>11/15 (73.3%)</td>
<td>152/251 (60.5%)</td>
</tr>
<tr>
<td>Homozygous, n(%)</td>
<td>68/181 (37.6%)</td>
<td>8/18 (44.4%)</td>
<td>8/11 (72.7%)</td>
<td>52/152 (34.2%)</td>
</tr>
<tr>
<td>Heterozygous, n(%)</td>
<td>61/181 (34.8%)</td>
<td>7/18 (38.9%)</td>
<td>2/11 (18.2%)</td>
<td>54/152 (35.5%)</td>
</tr>
<tr>
<td>Compound heterozygous, n(%)</td>
<td>50/181 (27.6%)</td>
<td>3/18 (16.7%)</td>
<td>1/11 (9.1%)</td>
<td>46/152 (30.3%)</td>
</tr>
<tr>
<td>Mutation not found</td>
<td>26/298 (8.7%)</td>
<td>4/32 (12.1%)</td>
<td>0</td>
<td>22/251 (8.7%)</td>
</tr>
<tr>
<td>Not Available, n(%)</td>
<td>25/323 (7.7%)</td>
<td>1/33 (3%)</td>
<td>0</td>
<td>24/275 (8.7%)</td>
</tr>
</tbody>
</table>

FMF: familial Mediterranean fever; JIA: juvenile idiopathic arthritis; JSpA: juvenile spondyloarthropathies.

Table III. Presence of JSpA criteria in patients.

<table>
<thead>
<tr>
<th></th>
<th>FMF + JSpA n=33 (10.2%)</th>
<th>FMF + JIA (other than JSpA) n=15 (4.6%)</th>
<th>FMF without JIA/ JSpA n=275 (85.1%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease onset &gt;6 years, n, (%)</td>
<td>27 (81.8%)</td>
<td>6 (40%)</td>
<td>32 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oligoarthritis, n(%)</td>
<td>21 (63.6%)</td>
<td>14 (93.3%)</td>
<td>10 (3.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inflammatory back pain, n(%)</td>
<td>19 (57.6%)</td>
<td>0</td>
<td>10 (3.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enthesopathy, n(%)</td>
<td>21 (63.6%)</td>
<td>0</td>
<td>37 (13%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>18 (6%)</td>
<td>0 (0)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip arthritis, n(%)</td>
<td>21 (63.6%)</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tarsometatarsal sensitivity, n(%)</td>
<td>10 (30.3%)</td>
<td>1 (6%)</td>
<td>8 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA-B 27 Positivity, n(%)</td>
<td>10 (31.3%)</td>
<td>0</td>
<td>1 (0.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>23 (69.7%)</td>
<td>5 (33.3%)</td>
<td>123 (44.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Response to NSAIDs, n(%)</td>
<td>19 (73.1%)</td>
<td>2 (28.6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Limitation in Schober test (&lt;4 cm), n(%)</td>
<td>8 (24.2%)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Family history of SpA group of disease, dactylitis, psoriasis or presence of IBD, n(%)</td>
<td>8 (24.2%)</td>
<td>1 (12.5%)</td>
<td>10 (3.6%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

FMF: familial Mediterranean fever; HLA: human leukocyte antigen; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; JSpA: juvenile spondyloarthropathies; NSAID: nonsteroidal anti-inflammatory drugs.

33/323). Sixty percentage (n: 18/30) of FMF patients with JSpA had radiological confirmed sacroilitis. Thirty one percentage (n: 10/32) of FMF patients with JSpA was HLAB-27 positivity. In FMF+JSpA patients, disease onset over 6 years of age, oligoarthritis, inflammatory back pain and enthesisopathy were more frequent, comparing to FMF patients without JIA and JSpA. We have tried to establish the frequency of JSpA among FMF patients, by using the recently proposed criteria for JSpA patients, using by the recently proposed criteria for JSpA (5, 12, 13).

In general, the prevalence of JIA varies from 3.8 to 4.00 per 100.000 children. Spondyloarthropathies include the 18% of all JIA patients (14). Data from literature suggest the common inflammatory mechanisms take role in familial Mediterranean fever and spondyloarthropathies, due to activation of common inflammatory interleukin cytokine pathway (15).

Studies on JSpA frequency in FMF are insufficient. In FMF patients, JSpA is reported in 3-10% frequency (1, 6-9).

Discussion

FMF is a chronic, autoinflammatory disease characterised by recurrent episodes of fever and polyserositis. Articular involvement generally includes the acute monarthritides of the lower extremities, without sequealae. We have tried to establish the frequency of JSpA among FMF patients, by using the recently proposed criteria for JSpA patients, using the recently proposed criteria for JSpA (5, 12, 13).

In general, the prevalence of JIA varies from 3.8 to 4.00 per 100.000 children. Spondyloarthropathies include the 18% of all JIA patients (14). Data from literature suggest the common inflammatory mechanisms take role in familial Mediterranean fever and spondyloarthropathies, due to activation of common inflammatory interleukin cytokine pathway (15).

Studies on JSpA frequency in FMF are insufficient. In FMF patients, JSpA is reported in 3-10% frequency (1, 6-9).

As we mentioned in the results, we defined 33 childhood FMF patients with JSpA in a large cohort of 323 patients (10.21%). In FMF patients with JSpA, disease onset of age was significantly higher comparing to FMF patients without JSpA and JIA (6.76±3.88 age to 4.95±3.43 age). This result is not surprising, since the JSpA generally appears among male patients older than 6 (5).

Again, male gender was in a higher ratio in FMF+JSpA patients comparing to FMF patients without coexistence of JSpA features. These results also could be expected due to generally predominance of spondyloarthopathies among males. We did not find further significant differences between FMF patients with and without coexistence of JSpA features.

Additionally, we tried to explore the relation between MEFV mutation and clinical presentations. The MEFV was screened in 92.2% (n: 298/323) of total FMF patients. The M694V mutation was documented in 60.73% (n: 181/298) of total patients: homozygous in 37.56% (n: 68/181), heterozygous in 34.80% (n: 61/181) and compound heterozygous in 27.62% (n: 50/181). The M694V was dominantly present in both patient groups: those with and without co-existing JSpA: 56,25% (n: 18/32) vs. 37.56%, 63.63% (other than JSpA) without JIA/JSpA 3.93%, 63.63% (other than JSpA) without JIA/JSpA vs. 3.95%, 57.57% (n: 10/253; 19/33).

Considering the 18% of all JIA patients (14). Data from literature suggest the common inflammatory mechanisms take role in familial Mediterranean fever and spondyloarthropathies, due to activation of common inflammatory interleukin cytokine pathway (15).
compound heterozygous M694V mutations were more common than in FMF patients with JSpA (30.3% vs. 16.7%, 46/152 vs. 3/18). Homozygosity and heterozygosity of M694V mutations were more common in FMF patients with JSpA. Additionally, M694V mutation is more associated with sacroiliitis in FMF patients compared to other MEFV mutations (17).

HLA-B27, which is thought to be capable of presenting potentially arthritogenic peptides to immunity is a strong marker for spondylitis (5). HLA B27 has been shown to be associated with severity of disease, in the previous studies (16, 18). In the populations originating from Mediterranean basin its frequency has been reported as 3-12% (16). In recent studies, HLA B27 positivity was found in 26% to 47% of FMF patients with sacroilitis (9, 19).

In our study, HLA B27 was positive in 31.3% of FMF+JSpA patients (n: 10/32). It is important to mention that HLA B27 positivity and sacroilitis are less frequent among children, comparing to adults SpA patients (5, 18).

Although the acute monoarthritides of the lower extremities is the typical presentation of the articular involvement in FMF, the chronic arthritis could be seen in 4-5% of patients (1). In our cohort, the frequency of JIA (other than JSpA) was 4.6%, according to ILAR criteria for JIA (20).

The frequency of sacroilitis was quite high in our FMF+JSpA patients group, comparing to FMF+JIA patients (other than JSpA), 60% vs. 0% (Table III). This high percentage could be explained by some common characteristics of FMF and JSpA, which are raising a possibility for the overdiagnosis of JSpA in FMF. The FMF patients with radiological confirmed sacroilitis are more prone to be classified as JSpA, than those without sacroilitis. Further studies with higher number of patients from different regions would give more clear data on this topic. The exertional leg pain has been explained as a characteristic musculoskeletal manifestation of FMF (1, 2). Eshed et al. (21) suggested that exertional leg pain should be considered as a new feature of SpA, since it has been frequently associated with sacroilitis and an underlying ankle enthesopathy. Exertional leg pain has not been questioned in our patients, since it does not take a place in the JSpA criteria that we used for classification. Further studies among juvenile patients would give answer whether this finding could be considered as a relevant marker of JSpA. Tufan et al. (22) reported the increased frequency of enthesopathy in adult FMF patients, especially among those who were carries of M694V variant of MEFV mutation. We also found increased frequency of enthesopathy among patients with FMF+JSpA, comparing to the rest of our FMF patients. However, we haven’t find any correlation between MEFV gene mutation and presence of enthesopathy.

The association between MEFV gene mutations and variety of inflammatory conditions has been demonstrated (23-26). Bayram et al. (23) reported that MEFV mutations are more frequent in patients with Henoch-Schonlein purpura (HSP) than in the general population. Furthermore, patients with HSP that were mutation carriers had more severe clinical findings with higher inflammatory response compared to those who were mutation-negative. Ozcakar et al. (24) showed that inflammatory diseases including vasculitis, chronic arthritis and inflammatory bowel disease were more frequently detected in patients with FMF during childhood in Turkey. Again, findings of another study suggest that MEFV mutations may represent a susceptibility factor for enthesitis related arthritis in the populations of the eastern Mediterranean (26).

The main limitation of our study is its retrospective nature with possibility of recall bias. Additionally, our hospital is the tertiary medical centre with most of patients having severe clinical presentation. Also the frequency of FMF-JSpA association is high: this underlines the point that there is an intrinsic over-estimation due to overlap between clinical features of FMF and JSpA in our country. Prospective, multicentric study with higher number of patients would reveal more data on the described topic.

In conclusion, chronic arthritis should be kept on mind among FMF patients with articular involvement. The JSpA should be considered in FMF patients with oligoarthritis, inflammatory back pain and enthesopathy complaints with onset over 6 years. Newly proposed JSpA criteria can be used to spondyloarthropathies in childhood FMF. Prospective, multicentric studies with higher number of patients would support our findings.

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