Concise report

Validation of the new paediatric criteria for the diagnosis of familial Mediterranean fever: data from a mixed population of 100 children from the French reference centre for auto-inflammatory disorders

Anuela Kondi1, Véronique Hentgen2, Maryam Piram1, Alexia Letierce3, Séverine Guillaume-Czitrom1 and Isabelle Koné-Paut1

Abstract

Objective. We aimed to validate the new paediatric criteria for diagnosis of FMF in a mixed population of 100 French patients.

Methods. The study group included 100 FMF children from the French reference centre for auto-inflammatory disorders. A control group of 40 patients with unexplained recurrent fever was reviewed in parallel. Both groups of patients were assessed for both the Tel Hashomer and the new paediatric criteria published by Yalcinkaya et al.

Results. Comparison of Tel Hashomer vs Yalcinkaya’s criteria in both groups gave a sensitivity of 99 vs 100%, a specificity of 45 vs 50%, a positive predictive value (PPV) of 81.8 vs 83.3% and a negative predictive value (NPV) of 94.7 vs 100%. However, when we used at least three Yalcinkaya’s criteria we obtained a sensitivity of 77% and a specificity of 95% with a PPV of 97.3% and an NPV of 62.3%. The number of mutations in the MEFV gene did not modify results for both sets of criteria.

Conclusion. The new paediatric Turkish criteria did not make a better contribution to FMF diagnosis than the Tel Hashomer criteria in our mixed population of French children while using an appropriate control group. However, if needed, they can be applied using at least three criteria, which slightly decreases their sensitivity but markedly increases their specificity.

Key words: Familial Mediterranean fever, Diagnosis criteria, Children.

Introduction

FMF is the most frequently inherited periodic fever syndrome due to recessive mutations in the MEFV gene on chromosome 16p13.3 [1, 2]. Most patients are of Mediterranean descent, especially Turkish, Sephardic-Jewish, Armenian and Northern African, but some cases have been reported in Western Europeans and also in the Japanese [3, 4]. The disease starts early in life at a median age of 4 years, characterized by 1- to 3-day-long attacks of fever accompanied with serositis. The diagnosis is made clinically and may be confirmed by identifying two homozygote or compound heterozygote mutations in the MEFV gene. Life-long colchicine treatment is effective in >90% of cases and avoids the development of secondary amyloidosis. Even though the genetic diagnosis has been available since August 1997, only a few countries can afford it. Moreover, clinically typical patients may lack one or two mutations for several reasons. First, routine screening...
cannot explore the whole gene, which may contain other rare sequence variants; secondly, mutations such as the heterozygous M694V may be expressed clinically with the same severity as other homozygous or compound hetero-
ygous mutations in accordance with genetic heterogen-

eity [5–7]. As genetic testing may not be useful for some
diagnoses of FMF, the availability of reliable tools for clin-
ical diagnosis is still critical. The most commonly used
criteria are those of Tel Hashomer, which have been estab-
lished in the Jewish adult population [8]. Recently, a
Turkish group proposed new criteria for diagnosis of
FMF in children [9]. The aim of this study is to evaluate
these new criteria in a mixed population of 100 French
children affected with FMF and in a control group of 40
patients affected with other recurrent fever syndromes.

Patients and methods

Demographic, clinical, biological and genetic data from
100 consecutive children with FMF were reviewed retro-
spectively. All of them were followed at the national refer-
ce centre for auto-inflammatory disorders in Le
Kremlin-Bicêtre and Versailles hospitals in France from
the year 2000. FMF diagnoses were made on clinical
expert opinion. Mutation analyses in the MEFV gene
were performed by routine genetic screening of exon
2 and 10 most frequent mutations (i.e. M694V, M680I,
M694I, M680V, V726A, E148Q, P369S, S683S and
A744S) using PCR and sequencing techniques reported
elsewhere. The control group included 40 children, 28 with
these new criteria in a mixed population of 100 French
children affected with FMF and in a control group of 40
patients affected with other recurrent fever syndromes.

Results

Our FMF group included 100 patients, sex ratio M:F
(54 : 46), of whom 70% were Sephardic Jews, 11% North
Africans and 9% of Turkish origin. Familial history of FMF
and/or amyloidosis was present in 81% of them. Patients’
parents were consanguineous in nine FMF patients.
The median age at first symptom was 2.5 years (range
1.5 months to 13.1 years); the median age at diagnosis
was 4.9 years (range 5.5 months to 15.8 years) with a
mean delay of 3 (range 0–13) years. The mean disease
follow-up duration was 7.2 years (range 0.7 month to
21.9 years). All clinical characteristics of our patients ac-

TABLE 1 Clinical symptoms of 100 FMF children according to their genotypes

<table>
<thead>
<tr>
<th>Signs</th>
<th>Two mutations (n = 71, n (%)</th>
<th>One mutation (n = 28, n (%))</th>
<th>No mutation (1)</th>
<th>Total (n = 100), %</th>
<th>P-value (71 vs 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias</td>
<td>69 (97)</td>
<td>26 (92.9)</td>
<td>1</td>
<td>96</td>
<td>0.32</td>
</tr>
<tr>
<td>Fever</td>
<td>62 (89)</td>
<td>27 (96.4)</td>
<td>1</td>
<td>91</td>
<td>0.44</td>
</tr>
<tr>
<td>Chills</td>
<td>26 (37)</td>
<td>14 (50)</td>
<td>1</td>
<td>41</td>
<td>0.26</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>60 (84)</td>
<td>23 (82)</td>
<td>1</td>
<td>83</td>
<td>0.77</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>26 (37)</td>
<td>8 (29)</td>
<td>0</td>
<td>35</td>
<td>0.49</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (14)</td>
<td>6 (21)</td>
<td>1</td>
<td>18</td>
<td>0.38</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (24)</td>
<td>6 (21)</td>
<td>1</td>
<td>24</td>
<td>1.00</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>20 (28)</td>
<td>3 (10.7)</td>
<td>0</td>
<td>23</td>
<td>0.07</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42 (59)</td>
<td>18 (64.3)</td>
<td>1</td>
<td>61</td>
<td>0.82</td>
</tr>
<tr>
<td>Arthritis</td>
<td>9 (13)</td>
<td>2 (7.1)</td>
<td>0</td>
<td>11</td>
<td>0.72</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15 (21)</td>
<td>2 (7)</td>
<td>0</td>
<td>17</td>
<td>0.14</td>
</tr>
<tr>
<td>Erysipela</td>
<td>5 (7)</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0.32</td>
</tr>
<tr>
<td>Orchitis</td>
<td>6 (8)</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0.18</td>
</tr>
</tbody>
</table>
1 had E148Q, 1 had A744S and 1 had M694I). Age of onset, age at diagnosis and time to diagnosis did not differ significantly with genotypes (respective P-values: 0.9, 0.17, 0.11; data not shown). Mean Pras severity score was 8 and was influenced neither by the genotype (P = 0.46; data not shown) nor by the ethnicity (P = 0.28). Ninety-nine per cent of patients fulfilled the Tel Hashomer criteria and 100% the paediatric ones by Yalcinkaya et al.

The control group included 28 PFAPA patients and 12 with unexplained recurrent fever. The sex ratio M:F was 25:15 and only 8% of family was consanguineous. Sixty-five per cent were Caucasian Europeans, 20% were North Africans and 5% were Sephardic Jews. The median age at first symptom was 2 years; the median age at diagnosis was 5.5 years with a mean delay of 3.4 years. Fever was present in all of them. The median duration of febrile episodes was 5 (range 1–7) days. The median frequency of attacks was 1 per month (range 1 per month to 1 per 3 months). Fifty per cent had abdominal pain, 5% had arthritis; and five patients (among seven treated) responded to colchicine. None of them had rash or pleuritis. Only 3 of the 40 patients had MEFV mutation analysis; one of them, a Sephardic Jew, was heterozygous for the M694V mutation and had typical PFAPA phenotype. Fifty-five per cent (22 out of 40) of control group patients fulfilled the Tel Hashomer criteria and 50% (20 out of 40) the paediatric ones by Yalcinkaya et al.

Comparison between Tel Hashomer criteria vs Yalcinkaya’s criteria in the FMF group gave a sensitivity of 99 vs 100%, a specificity of 45 vs 50%, a positive predictive value (PPV) of 81.8 vs 83.3% and a negative predictive value (NPV) of 94.7 vs 100%. No difference was observed while selecting only patients with two mutations (Table 2).

**Discussion**

Our study group included a large population of 100 children who carried the known characteristics of paediatric FMF. Homozygosity for M694V mutation was associated with earlier age at onset: 3.2 (2.6) vs 5.5 (2.9) years in heterozygotes. The mean severity score of our patients was high (8) but did not vary with the genotype. Patients with PFAPA and unexplained recurrent fever were chosen as controls because these conditions are commonly seen in most parts of the world. The symptoms of our control group resembled as much as possible those of FMF. Indeed, we reasoned that serositis, as specified in the Tel Hashomer criteria, might not be distinguished from acute abdominal pain by most parents and even by a lot of physicians. Moreover, patients with other conditions including serositis i.e. TNF receptor associated periodic syndrome and mevalonate kinase deficiency, were too few (even in a reference centre) to perform accurate statistical analyses. Our control group was matched in terms of age at first symptom and age at diagnosis, but was not perfectly matched in terms of ethnicity (majority of Caucasian French patients). Our study aimed at validation of the new paediatric criteria for FMF recently proposed by a Turkish group, Yalcinkaya et al. This group has suggested a set of five criteria (listed in ‘Patients and methods’ section). The combination of at least two gave in their patients a sensitivity of 86.5% and a specificity of 93.6%, while the Tel Hashomer criteria gave a sensitivity of 98.8% and a specificity of 54.6%. Our results were concordant for the Tel Hashomer criteria, but quite different for the Turkish ones with a higher sensitivity of 100% and a lower specificity of 55%. However, when we used at least three Yalcinkaya’s criteria (instead of two) we obtained a sensitivity of 77% and a specificity of 95% with a PPV of 97.5% and an NPV of 62.3% (Fig. 1). In addition, while selecting only patients with two MEFV mutations, our results remained similar between the two sets of criteria. There are three main reasons for differences between our study and Yalcinkaya’s one. First, Yalcinkaya’s group used Livneh’s criteria instead of the Tel Hashomer ones, in comparison with the paediatric criteria [11]. According to their experience, Livneh’s criteria had low specificity in the paediatric population where recurrent fevers are more frequent than in adults. Secondly, our study group included a mixed population reflecting our French ethnic background with a majority of Sephardic Jews, some North Africans and only few Turkish patients. The different ethnicity could explain the accuracy of the Tel Hashomer criteria in our population. Thirdly, our control group reflected more recurrent fever syndromes resembling FMF than the group chosen for Yalcinkaya’s analyses. Indeed, Yalcinkaya’s control group included 141 patients in whom only 7 had recurrent fever syndromes, all the others had very different conditions such as IBD, functional abdominal pain, systemic

**Table 2** Application of the Tel Hashomer and Yalcinkaya’s criteria in the whole group of FMF patients and in patients with two mutations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>All FMF patients (n = 100), %</th>
<th>FMF patients with two mutations (n = 71), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tel Hashomer</td>
<td>Yalcinkaya’s</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>99 (0.95, 1)</td>
<td>100 (0.96, 1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>45 (0.29, 0.62)</td>
<td>50 (0.34, 0.66)</td>
</tr>
<tr>
<td>PPV</td>
<td>81.8 (0.74, 0.88)</td>
<td>83.3 (0.75, 0.90)</td>
</tr>
<tr>
<td>NPV</td>
<td>94.7 (0.74, 1)</td>
<td>100 (0.83, 1)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI.
juvenile arthritis and urinary tract infections [9]. As we diagnosed our FMF patients on a clinical basis, we could not find any difference according to their genotypes. Similarly, patients in the control group had a diagnosis other than FMF, i.e. PFAPA or unexplained recurrent fever, on the basis of their clinical signs without a systematic search for MEFV mutations being made. Indeed, genetic testing for MEFV mutations in non-Mediterranean patients (75% in the control group) is of particularly weak diagnostic value as shown by Tchernitchko et al. [12]. While genetic testing is not universally available or contributive for each FMF patient, making an accurate clinical diagnosis remains crucial. Our study has shown that the Tel Hashomer criteria gave high sensitivity in our FMF children; however, their major drawback is their low sensitivity due to the presence of the supportive (minor) criteria. However, since the consequence of not diagnosing FMF is severe, high sensitivity is probably more important than high specificity.

In conclusion, the new paediatric Turkish criteria did not make a better contribution to FMF diagnosis than the Tel Hashomer criteria in our mixed population of French children while using an appropriate control group. However, if needed, they can be applied with at least three criteria, which slightly decreases their sensitivity (77%) but markedly increases their specificity (95%).