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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

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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.

LR+: 1,8 LR-:0,02

Prévalence: 1/200-1/1000
- Turques
- Juifs Sépharad
- Arméniens
- Africains du Nord
- Europééens

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

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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 heterozygous mutations in accordance with genetic heterogeneity [5–7]. As genetic testing may not be useful for some diagnoses of FMF, the availability of reliable tools for clinical diagnosis is still critical. The most commonly used criteria are those of Tel Hashomer, which have been established 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 retrospectively. All of them were followed at the national reference 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 the periodic fever adenitis pharyngitis and aphthosis (PFAPA) syndrome and 12 with unexplained recurrent fever. Both patient and control groups were analysed according to the Tel Hashomer criteria, the most commonly used in adults. The major criteria include: fever plus serositis, secondary amyloid A amyloidosis and response to colchicine treatment and the minor ones include: recurrent fever alone, erysipelas such as erythema and familial history. Two major or one major plus two minor criteria allow the diagnosis [8]. Both groups were also assessed by the new paediatric set proposed by Yalcinkaya *et al*., including fever (axillary temperature $>38^{\circ}$C, duration 6–72 h, three or more attacks), abdominal pain, thoracic pain, synovitis (for each sign, duration 6–72 h, three or more attacks) and family history. The diagnosis is made if at least two criteria are present [9]. The severity of FMF was assessed by the Pras paediatric modified score [10]. Subject's written consent was obtained according to the Declaration of Helsinki and all patients, when able to (and parents) gave written informed consent for genetic analyses. Our observational study does not require ethical approval in France because the genetic testing was not performed for the purpose of research but only as a diagnosis tool. In France, the genetic laboratory has to declare a biological collection and does not need ethical approval for routine testing. For statistical analyses, qualitative data were compared between genotypes using Fisher's exact test and the Kruskal–Wallis test. The 95% CIs were calculated with the binomial law.

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 according to the number of mutations are presented in Table 1. Seventy-one patients had two mutations in the *MEFV* gene, 43 were homozygotes (M694V, $n = 38$) and 28 were compound heterozygotes. Twenty-eight patients were heterozygotes (22 had M694V, 3 had V726A,

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

Signs	Two mutations ($n = 71$), n (%)	One mutation ($n = 28$), n (%)	No mutation (1)	Total ($n = 100$), %	P-value (71 *vs* 28)
Arthralgias	69 (97)	26 (92.9)	1	96	0.32
Fever	63 (89)	27 (96.4)	1	91	0.44
Chills	26 (37)	14 (50)	1	41	0.26
Abdominal pain	60 (84)	23 (82)	1	83	0.77
Diarrhoea	26 (37)	8 (29)	0	35	0.49
Constipation	10 (14)	6 (21)	1	18	0.38
Vomiting	17 (24)	6 (21)	1	24	1.00
Thoracic pain	20 (28)	3 (10.7)	0	23	0.07
Myalgias	42 (59)	18 (64.3)	1	61	0.82
Arthritis	9 (13)	2 (7.1)	0	11	0.72
Splenomegaly	15 (21)	2 (7)	0	17	0.14
Erysipela	5 (7)	0	0	5	0.32
Orchitis	6 (8)	0	0	6	0.18

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 one 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

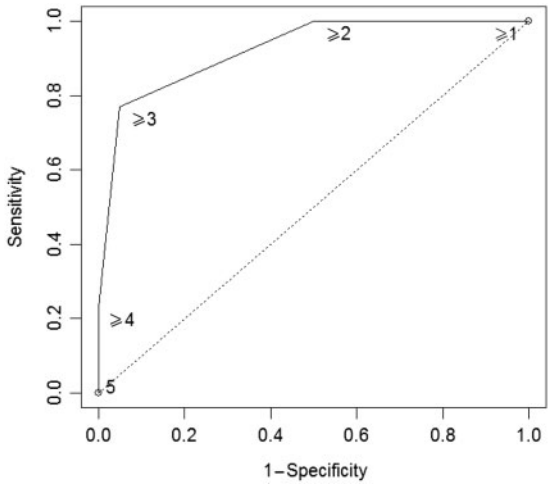
Our study group included a large population of 100 children who carried the known characteristics of paediatric FMF. Homozygosity for M694V mutation was associated with earlier age at onset: 3.2 (2.6) *vs* 5.5 (2.9) years in heterozygotes. The mean severity score of our patients was high (8) but did 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

	All FMF patients($n = 100$), %		FMF patients with two mutations ($n = 71$), %	
Criteria	Tel Hashomer	Yalcinkaya's	Tel Hashomer	Yalcinkaya's
Sensitivity	99 (0.95, 1)	100 (0.96, 1)	98.6 (0.95, 1)	100 (0.95, 1)
Specificity	45 (0.29, 0.62)	50 (0.34, 0.66)	45 (0.3, 0.5)	50 (0.35, 0.65)
PPV	81.8 (0.74, 0.88)	83.3 (0.75, 0.90)	76 (0.67, 0.85)	78 (0.69, 0.86)
NPV	94.7 (0.74, 1)	100 (0.83, 1)	95 (0.94, 0.95)	100 (0.83, 1)

Values in parentheses are 95% CI.

FIG. 1 Accuracy of the Yalcinkaya criteria in our FMF patients as a function of the number of criteria. Receiver operating characteristic (ROC) curve: this curve allows selection of the number of criteria that gives the best sensitivity and the best specificity. The point is located on the top left part of the graph corresponding to ⩾ 3 criteria.



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%).

Rheumatology key messages

- Clinical reasoning is the basis of FMF diagnosis in children.
- The new Turkish criteria have a very high sensitivity without better specificity compared with Tel Hashomer criteria.
- The use of three Turkish criteria increases specificity to 95%.

Disclosure statement: The authors have declared no conflicts of interest.

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