Rheumatology 2009;48:395–398
Advance Access publication 4 February 2009
doi:10.1093/rheumatology/ken509

A new set of criteria for the diagnosis of familial Mediterranean fever in childhood

Fatoş Yalçınkaya[1,*], Seza Özen[2,*], Zeynep Birsin Özçakar[1], Nuray Aktay[2], Nilgün Çakar[3], Ali Düzova[2], Özgür Kasapçopur[4], Atilla H. Elhan[5], Beyza Doğanay[5], Mesiha Ekim[1], Nazlı Kara[3], Nermin Uncu[3] and Ayşin Bakkaloğlu[2]

Objectives. Several sets of criteria mainly for adults have been proposed for the diagnosis of FMF. The aim of the present study is to validate the most widely used diagnostic 'Tel Hashomer' criteria in children and to establish a new set of criteria for use in childhood.
Methods. The study group consisted of 170 recently diagnosed FMF patients who had mutations at both alleles. They were interviewed about the presence of 35 features and manifestations of FMF at the time of diagnosis. Controls were consecutive patients without FMF ($n = 141$) who had episodes of fever and clinical features mimicking that of FMF. The diagnostic performance of the candidate features was assessed by multiple logistic regression analysis.
Results. The sensitivity and specificity of Tel Hashomer criteria in our study group were 98.8 and 54.6%, respectively. The multiple logistic regression analysis showed that 5 (fever, abdominal pain, chest pain, arthritis and family history of FMF) of the 35 candidate criteria discriminate FMF from controls with a sensitivity and specificity of 88.8 and 92.2%, respectively. The presence of two or more of these five criteria diagnosed FMF with a sensitivity of 86.5% and a specificity of 93.6%.
Conclusion. It was demonstrated that although the Tel Hashomer criteria were successful in diagnosing the FMF patients in childhood, its specificity was definitely low in children. The new set of criteria has a high sensitivity and specificity for the diagnosis of FMF and is practical to use on an everyday basis.

Key words: Paediatric, FMF, Diagnostic criteria, Tel Hashomer criteria.

Introduction

FMF is an auto-inflammatory disease characterized by recurrent febrile episodes and inflammation of serous membranes. Although the gene of FMF was identified a decade ago, the diagnosis is still based on clinical criteria. Several sets of criteria for adults have been proposed [1–6] for the diagnosis of FMF before the availability of molecular diagnosis. Since the episodes of FMF typically appear in childhood, we herein validate the most widely used diagnostic 'Tel Hashomer' criteria (see supplementary data available at *Rheumatology* Online) [6] in children. As existing clinical criteria were not validated for children in many countries [7, 8] we decided to establish a new set of criteria for use in childhood and open it to discussion. Our study population was made up of only genetically confirmed cases with two *MEFV* mutations regardless of their phenotypes.

Methods

Patients and controls

The study was performed in four major paediatric nephrology and rheumatology centres in Turkey. In each centre the same author evaluated the study group and control group, and filled out the form of the patients. All patients and controls were re-evaluated by one of the primary authors. The study group consisted of recently diagnosed (after January 2000) FMF patients who had mutations at both alleles and who presented to our outpatient clinics between August 2007 and January 2008. The diagnosis of FMF was based on the presence of two mutations and clinical findings. At least six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the *MEFV* gene were studied in all four participated centres. Exon 10 of the *MEFV* gene was screened using direct sequencing of the PCR amplified fragments. The p.E148Q mutation was analysed with a previously reported PCR restriction fragment length polymorphism (RFLP) protocol [8, 9]. One hundred and seventy FMF patients who were initially examined in one of the four main centres for paediatric nephrology and rheumatology were interviewed by one of the experienced physicians about the presence of 35 features and manifestations of FMF prior to the initiation of colchicine. The questionnaire included the following information: demographics (sex, age of onset, age at diagnosis); family history (consanguinity of parents, family history of FMF and amyloidosis or renal failure); the presence of fever, recurrent typical attacks of FMF (including peritonitis, pleuritis and arthritis); and transient inflammatory response. In addition, the presence of rare but important manifestations (i.e. erysipelas like erythema, renal biopsy proven amyloidosis, protracted febrile myalgia, leg pain and scrotal attack) of FMF and other features present in the Tel Hashomer criteria (haematuria, proteinuria and spontaneous remission) were asked. The presence of recurrent attacks ($\geqslant 3$ of the same type) was included as a mandatory criterion. The characteristics of the FMF attack were searched thoroughly in children including the duration (<6, 6–12, 12–72 and >72 h) of the attack of any type. The severity (pain score $\geqslant 6/10$ regarded as severe and $<6/10$ as mild) and localization (widespread and regional) of peritonitis and the severity of fever (axillary temperature $<38^{\circ}$C, 38–39°C and $>39^{\circ}$C) were evaluated. In addition, special features of pleuritis (unilateral *vs* bilateral) and the type (arthritis and arthralgia) of joint involvement were included in the questionnaire. We also asked the number of arthritis (monoarthritis, oligo or polyarthritis) and the involvement of particular joints (knee, ankle, hip or the other joints). As all of our patients had genetic confirmation, the diagnostic power of the response to colchicine was not incorporated in our new set of criteria.

[1]Department of Pediatric Nephrology, Ankara University School of Medicine, [2]Department of Pediatric Nephrology–Rheumatology, Hacettepe University School of Medicine, [3]Department of Pediatric Nephrology, Ministry of Health Dışkapı Children's Hospital, Ankara, [4]Department of Pediatric Rheumatology, İstanbul University Cerrahpaşa Medical Faculty, İstanbul and [5]Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkey.

Submitted 24 April 2008; revised version accepted 18 December 2008.

*Fatoş Yalçınkaya and Seza Özen contributed equally to this study.
Correspondence to: Fatoş Yalçınkaya, Çınar Sitesi 5.Blok No:62, Ümitköy 06530, Ankara, Turkey. E-mail: yalcinkaya@tr.net

© The Author 2009. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org

Downloaded from https://academic.oup.com/rheumatology/article-abstract/48/4/395/1789904 by guest on 05 March 2020

The control group ($n = 141$) included consecutive patients without FMF who had episodes of fever and clinical features mimicking that of FMF. All of the control patients were diagnosed with their primary disease based on internationally accepted criteria. The diagnosis of the control subjects were as follows: functional abdominal pain (32), recurrent urinary tract infection (UTI; 13), IBD (22), hyperimmunoglobilinaemia D syndrome (3) periodic fever aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome (3), Muckle–Wells syndrome (1), ARF (28), systemic juvenile idiopathic arthritis (JIA; 20), ReA (6), AS (1), HSP (7), Behçet's disease (1), erysipelas (1) and musculoskletal chest pain (3). Rea, ARF, systemic JIA, AS, HSP, Behçet's disease, PFAPA syndrome and functional abdominal pain were diagnosed according to the previously suggested criteria [10–17]; hyperimmunoglobilinaemia D syndrome, Muckle–Wells syndrome, recurrent UTI, IBD, erysipelas and musculoskeletal chest pain were diagnosed according to clinical and laboratory features. The same questionnaire was also completed for each control. Informed consent was obtained from the parents of each patient and the study was approved by the institutional ethics committee.

Statistical analysis

In order to define risk factors of outcome variables (FMF *vs* control) multiple logistic regression analysis was used. Prior to logistic regression analysis, the association of each independent variable with the outcome variables, a univariate estimate was performed by means of the logistic regression analysis. Upon completion of the univariate analyses we selected variables for the multivariate analysis. Any of the variables whose univariate test had a *P*-value <0.25 was considered as a candidate for the multivariate logistic model along with all variables of known biological importance. Once the variables have been identified, the final model was built with the candidate variables using likelihood ratio test.

We began with 35 independent variables. After univariate logistic regression, 20 of the 35 variables were eliminated. The remaining 15 variables were used to build the logistic model by likelihood ratio test. A five-variable model was selected as the final model, which discriminates best between FMF and controls. In order to calculate the number of criteria, a new classification variable was created as follows: all the patients and controls were classified as positive (FMF) if at least one of the five most discriminating variables selected by multiple logistic regression analysis was positive; otherwise as negative (control). Then crossing this new classification variable by outcome variable, sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated from this 2×2 cross-tabs. Continuous and categorical variables were evaluated by Student's *t*-test and chi-square test, respectively. *P*-values <0.05 were considered statistically significant. Analyses were done with SPSS (version 11.5).

Results

Demographic data of the study group are shown in Table 1. The age of onset was younger and consanguinity was higher in the FMF patients as compared with the control group. Mutation analyses revealed 11 different mutation combinations. Ninety-nine (58.2%) of the 170 FMF patients had homozygous p.M694V mutation, 28 (16.5%) had compound heterozygous p.M694V and p.M680I mutations, 22 (12.9%) had compound heterozygous p.M694V and p.V726A mutations and the other 21 (12.4%) patients were found to be homozygous or compound heterozygous for two of the screened *MEFV* mutations.

The frequency of vomiting, high ESR and CRP during attack-free period were similar in the FMF patients and controls. All the other selected variables for multivariate analysis were found to be significantly higher in the FMF patients as compared with the control group ($P < 0.002$) (Table 2).

Table 1. Demographic features of the study group

	FMF patients $n = 170$	Control group $n = 141$	*P*
Male/female	88/82	68/73	0.53
Age at onset, mean ± S.D., yrs	4.07 ± 3.19	7.13 ± 4.09	<0.001
Age at diagnosis, mean ± S.D., yrs	7.67 ± 4.01	7.69 ± 4.11	0.44
Current age, mean ± S.D., yrs	12.35 ± 5.17	12.09 ± 9.92	0.76
Consanguinity, *n* (%)	49 (28.8)	23 (16.3)	0.009

Table 2. Comparison of selected variables for FMF for multivariate analysis

	FMF patients *n* (%)	Control group *n* (%)	*P*	OR	95% CI
Fever	135 (79.4)	21 (14.9)	<0.001	22.04	12.17, 39.93
Abdominal pain	129 (75.9)	18 (12.8)	<0.001	21.50	11.72, 39.44
Chest pain	59 (34.7)	6 (4.3)	<0.001	11.95	4.98, 28.74
Arthritis	38 (22.4)	12 (8.5)	0.001	3.09	1.55, 6.19
Family history of FMF	80 (47.1)	3 (2.1)	<0.001	40.89	12.53, 133.44
ELE	49 (28.8)	1 (0.7)	<0.001	56.69	7.71, 416.73
Exertional leg pain	89 (52.4)	34 (24.1)	<0.001	3.45	2.12, 5.64
Heel pain	42 (24.7)	5 (3.5)	<0.001	8.92	3.42, 23.27
Vomiting	28 (16.5)	25 (17.7)	0.769	0.92	0.51, 1.66
Splenomegaly	44 (25.9)	17 (12.1)	0.002	2.55	1.38, 4.70
↑ ESR (attack)	168 (98.8)	102 (72.3)	<0.001	32.12	7.59, 135.85
↑ ESR (attack-free period)	37 (21.8)	27 (19.1)	0.57	1.18	0.67, 2.05
↑ CRP (attack)	164 (96.5)	97 (68.8)	<0.001	12.4	5.09, 30.17
↑ CRP (attack-free period)	29 (17.1)	22 (15.6)	0.73	1.11	0.61, 2.04

↑ indicates increased; OR: odds ratio; ELE: erysipelas-like erythema.

Table 3. Criteria set for the diagnosis of FMF in childhood according to multiple logistic regression analysis

Criteria	Description
Fever	Axillary temperature of >38°C, 6–72 h of duration, ⩾3 attacks
Abdominal pain	6–72 h of duration, ⩾3 attacks
Chest pain	6–72 h of duration, ⩾3 attacks
Arthritis	6–72 h of duration, ⩾3 attacks, oligoarthritis
Family history of FMF	

The multiple logistic regression analysis showed that 5 of the 35 candidate criteria (Table 3) discriminate FMF from controls with a sensitivity and specificity of 88.8% (95% CI 83.2, 92.7) and 92.2% (95% CI 86.6, 95.6), respectively. The PPV and NPV were 93.2% (95% CI 89.7, 95.6) and 87.2% (95% CI 82.9, 90.6), respectively. Table 4 shows sensitivity, specificity, PPV and NPV according to the number of positive criteria. The presence of at least two of these five criteria had the highest sensitivity and specificity for the diagnosis of FMF (Table 4). Thus, it was decided that the presence of at least two of the selected five criteria were required for the clinical diagnosis of FMF. An equation for conditional probability of being FMF was also developed by logistic model that may guide clinicians to seek genetic analysis:

$$A = \exp(-2.55 + 1.99 \times Fever + 2.09 \times AP + 1.49 \times CP + 1.35 \times Arthritis + 3.36 \times FHFMF)$$

$$P(FMF/Criteria) = \frac{A}{1 + A}$$

where, AP: abdominal pain; CP: chest pain; FHFMF: family history of FMF.

By using this model, probability of being FMF can be calculated for any subject whose criteria are known. After calculation of this probability, subject can be assigned as FMF or not. In the

Downloaded from https://academic.oup.com/rheumatology/article-abstract/48/4/395/1789904 by guest on 05 March 2020

TABLE 4. Sensitivity, specificity, PPV and NPV of the suggested criteria compared with Tel Hashomer criteria in our series

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Suggested criteria				
⩾1 criterion	92.9 (88.1, 95.9)	64.5 (56.4, 72.0)	76.0 (70.7, 80.5)	88.3 (84.1, 91.6)
⩾2 criteria	86.5 (80.5, 90.8)	93.6 (88.3, 96.6)	94.2 (90.9, 96.4)	85.2 (80.6, 88.8)
⩾3 criteria	55.3 (47.8, 62.6)	99.3 (96.1, 99.9)	98.9 (96.8, 99.7)	64.8 (59.2, 70.1)
⩾4 criteria	21.2 (15.7, 27.9)	100.0 (97.3, 100.0)	100.0 (98.5, 100.0)	51.3 (45.6, 56.9)
5 criteria	3.5 (1.6, 7.5)	100.0 (97.3, 100.0)	100.0 (98.5, 100.0)	46.2 (40.6, 51.9)
Tel Hashomer criteria	98.8 (95.8, 99.7)	54.6 (46.4, 62.6)	72.4 (67.0, 77.2)	97.5 (94.9, 98.8)

formula, if the criterion was present in a subject, it should be coded as 1, otherwise 0 in the equation.

In our present study, 168 of our 170 FMF patients (98.8%) and 64 of our 141 control patients (45.4%) fulfilled the Tel Hashomer clinical criteria. Of the 64 control patients, 17 fulfilled at least one major criterion, 17 at least two minor and 30 fulfilled one minor plus at least five supportive criteria. The sensitivity, specificity, PPV and NPV of Tel Hashomer criteria in our study group were 98.8% (95% CI 95.8, 99.7), 54.6% (95% CI 46.4, 62.6), 72.4% (95% CI 67.0, 77.2) and 97.5% (95% CI 94.9, 98.8), respectively (Table 4).

Discussion

This is the first attempt to develop classification criteria for FMF to be used in childhood based on a cohort of genetically confirmed group. We have also attempted to validate the Tel Hashomer criteria, which is the most widely used adult criteria for the diagnosis of FMF. Although the Tel Hashomer criteria were very successful in diagnosing the patients, the specificity was low (54.6%) in children (Table 4). This was not unexpected since a number of features expressed in the Tel Hashomer criteria pose differences in childhood. In the Tel Hashomer criteria, typical attacks were defined by the presence of all the following features: pain, recurrence of the attacks (⩾3 of the same type), fever in most attacks (rectal temperature ⩾38°C), short duration (12 h to 3 days) and the presence of one or more of the following conditions: peritonitis (generalized, severe, requiring bed rest), pleuritis (unilateral), pericarditis, monoarthritis of the knee, ankle or the hip joints, erysipelas-like eruption in the calf and/or symmetric myalgia. In our study, we have noticed that the child is often not able to express the severity and location of the pain and the chest pain is not always unilateral in children. The duration is somewhat shorter extending the lower limit to 6 h instead of 12. To make the issue more complicated, fever axillary temperature of 38°C or higher was not present in 20% of our patients. These are handicaps for the major criteria of Tel Hashomer. On the other hand, axillary temperature is accepted as less sensitive than rectal temperature and can miss febrile patients. Therefore, the high proportion of afebrile FMF patients in our study could be related to this. The minor or supportive criteria of Tel Hashomer included the features of the disease not associated with the attacks, such as the ethnic origin (Jew, Turk, Arab, Armenian), the presence of age ⩽20 yrs at disease onset, removal of appendix and consanguinity of the parents. All of our patients were Turkish and children, which makes the age and susceptible ethnic origin criteria redundant. Children are often diagnosed before appendectomy and consanguinity of the parents in our country is ~21% [18], which decreases the power of other supportive criteria. In fact, 75% of the 64 control patients fulfilled minor or supportive criteria, which decreases the specificity and PPV of the Tel Hashomer criteria in childhood; these data reflect the fact that the differential diagnosis is more problematic in childhood.

With the suggested childhood criteria in this article we have misdiagnosed 23 FMF patients and 9 controls. All FMF patients with two mutations were included in our study. For example, one of the patients had no abdominal pain, no fever, no arthritis and no chest pain. Seven patients had atypical symptoms, such as abdominal pain with a duration of <6 h. That is why the sensitivity of our diagnostic criteria decreased to 88.8%. In fact, we chose the 'control group' based on our paediatric experience, covering the diseases that we encounter when we approach the child with fever. Childhood is the era when we encounter the microbes, hence one would need to consider the infections of childhood in the differential diagnosis. Childhood is when the symptoms of the other periodic fever syndromes such as hyperimmunoglobulinemia syndrome (HIDS) or the cryopyrinopathies or the common PFAPA syndrome manifest themselves, hence one needs to include these diseases in the differential diagnosis. In addition, the common rheumatic diseases of childhood such as systemic JIA and some vasculitides also complicate our practice in paediatrics. We believe that the control group in this study addresses these problems.

However, a drawback of this study was that it was confined to a group of Turkish children. This has limited the number of periodic fever syndromes among controls as well. Thus, these criteria need to be validated in other ethnic groups where FMF is not frequent but other hereditary periodic fever syndromes are frequent. These criteria also need to be validated among heterozygous patients with clinical features of FMF in future studies. Since febrile episodes are frequent in infancy, a future study comparing very young children with FMF to others may also be warranted.

We have shown that the presence of two of the five suggested criteria has a high sensitivity and specificity for the diagnosis of FMF. These criteria are practical to use on an everyday basis and they thoroughly define the characteristics of the attack. The number of attacks is as defined by Dr Livneh's group and they are helpful in discarding other diseases.

We had originally thought that the history of FMF in the family would not be specific in a population with very high FMF frequency. However, it has turned out to be statistically significant. We believe that it will be even more specific in ethnic groups where FMF is not frequent.

The diagnosis of FMF is still a clinical one. We and others have shown that the mutation analysis of the *MEFV* gene may fail to show two mutations in some patients [8, 19]. Furthermore, it is not always possible to obtain this analysis and it is expensive. On the other hand, certain data may need to be shown for the justification of genetic testing for insurance companies in countries where the disease is not as endemic as in Turkey or in Israel. Although colchicine testing is frequently employed in countries like ours, it may not be practical for ethnic groups where other periodic fever diseases are more frequent. Thus the paediatricians need reliable clinical criteria to guide them. By proposing those criteria to be used in childhood FMF we want to open a discussion among paediatricians who are dealing with children having FMF throughout the world. We would very much appreciate the validation of these criteria in ethnic groups where FMF is not frequent.

Rheumatology key messages

- This is the first attempt to develop classification criteria for FMF to be used in childhood.
- The new set of criteria has a high sensitivity and specificity for the diagnosis of FMF.

Downloaded from https://academic.oup.com/rheumatology/article-abstract/48/4/395/1789904 by guest on 05 March 2020

Acknowledgement

The authors thank Prof. N. Akar and Engin Yılmaz for genetic analysis.

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

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Heller H, Sohar E, Sherf L. Familial Mediterranean fever. Arch Intern Med 1958;102:50–71.
2 Sohar E, Gafni J, Pras M *et al.* FMF: a survey of 470 cases and review of the literature. Am J Med 1967;43:227–53.
3 Eliakim M, Levy M, Ehrenfeld M. Recurrent polyserositis (familial Mediterranean fever, periodic disease). Amsterdam: Elsevier/North-Holland Biomedical Press, 1981:16–17.
4 Armenian HK. Genetic and environmental factors in etiology of familial paroxysmal polyserositis. An analysis of 150 cases from Lebanon. Trop Georg Med 1982;34: 183–7.
5 Pras M, Sohar E. Familial Mediterranean fever. In: Klippel JH, Dieppe PA, eds. Rheumatology. St. Louis: Mosby, 1994:30.1–30.4.
6 Livneh A, Langevitz P, Zemer D *et al.* Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40:1879–85.
7 Tunca M. Familial Mediterranean fever diagnostic criteria: comment on the article by Livneh et al. Arthritis Rheum 1998;41:1516–7.
8 Samuels J, Aksentijevich I, Torosyan Y *et al.* Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations and survey of 100 American referrals to the National Institutes of Health. Medicine 1998;77:268–97.
9 Akar N, Misiroglu M, Yalcinkaya F *et al. MEFV* mutations in Turkish patients suffering from familial Mediterranean fever. Hum Mutat 2000;15:118–9.
10 Kingsley G, Sieper J. Third international workshop on reactive arthritis. 23–26 September 1995, Berlin, Germany. Report and abstracts. Ann Rheum Dis 1996;55: 564–84.
11 Dajani AS, Ayoub EM, Bierman FZ *et al.* Guidelines for the diagnosis of rheumatic fever: Jones Criteria, updated 1992. J Am Med Assoc 1992;87:302–7.
12 Petty RE, Soutwood TR, Baum J *et al.* Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991–4.
13 Dougados M, van der Linden S, Juhlin R *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218–27.
14 Mills JA, Michel BA, Bloch DA *et al.* The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. Arthritis Rheum 1990;33: 1114–21.
15 International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1070–80.
16 Thomas KT, Feder HM Jr, Lawton AR *et al.* Periodic fever syndrome in children. J Pediatr 1999;135:15–21.
17 Rasquin A, Di Lorenzo C, Forbes D *et al.* Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527–37.
18 Tunçbilek E, Koç I. Consanguineous marriage in Turkey and its impact on fertility and mortality. Ann Hum Genet 1994;58:321–9.
19 Yalçınkaya F, Çakar N, Mısırlıoğlu M *et al.* Genotype-phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatol 2000;39:67–72.

Downloaded from https://academic.oup.com/rheumatology/article-abstract/48/4/395/1789904 by guest on 05 March 2020