Performance of Different Diagnostic Criteria for Familial Mediterranean Fever in Children with Periodic Fevers: Results from a Multicenter International Registry

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ABSTRACT. ***Objective.*** Our aims were to validate the pediatric diagnostic criteria in a large international registry and to compare them with the performance of previous criteria for the diagnosis of familial Mediterranean fever (FMF).

Methods. Pediatric patients with FMF from the Eurofever registry were used for the validation of the existing criteria. The other periodic fevers served as controls: mevalonate kinase deficiency (MKD), tumor necrosis factor receptor–associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA), and undefined periodic fever from the same registry. The performances of Tel Hashomer, Livneh, and the Yalcinkaya-Ozen criteria were assessed.

Results. The FMF group included 339 patients. The control group consisted of 377 patients (53 TRAPS, 45 MKD, 32 CAPS, 160 PFAPA, 87 undefined periodic fevers). Patients with FMF were correctly diagnosed using the Yalcinkaya-Ozen criteria with a sensitivity rate of 87.4% and a specificity rate of 40.7%. On the other hand, Tel Hashomer and Livneh criteria displayed a sensitivity of 45.0 and 77.3%, respectively. Both of the latter criteria displayed a better specificity than the Yalcinkaya-Ozen criteria: 97.2 and 41.1% for the Tel Hashomer and Livneh criteria, respectively. The overall accuracy for the Yalcinkaya-Ozen criteria was 65 and 69.6% (using 2 and 3 criteria), respectively. Ethnicity and residence had no effect on the performance of the Yalcinkaya-Ozen criteria.

Conclusion. The Yalcinkaya-Ozen criteria yielded a better sensitivity than the other criteria in this international cohort of patients and thus can be used as a tool for FMF diagnosis in pediatric patients from either the European or eastern Mediterranean region. However, the specificity was lower than the previously suggested adult criteria. (J Rheumatol First Release November 15 2015; doi:10.3899/jrheum.141249)

Key Indexing Terms:
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Familial Mediterranean fever (FMF) is the most frequent Mendelian autoinflammatory disease[1]. Clinically it is characterized by self-limited recurrent and short duration (mean 24-72 h) episodes of fever and serositis. FMF is more prevalent among 4 populations from the eastern Mediterranean region: non-Ashkenazi Jews, Turks, Armenians, and Arabs, with a prevalence of 1:250 to 1:1073[1]. FMF is caused by mutations in the *MEFV* gene, which is located on chromosome 16p13.3 and includes 10 exons[2,3]. The most severe longterm complication of FMF is AA type amyloidosis, which results in renal impairment[4,5]. Colchicine is the standard treatment option. New agents have been tried in some cases of colchicine resistance or intolerance, but daily oral colchicine remains the treatment of choice[6,7,8,9,10]. Even if the disease has an autosomal recessive pattern of inheritance, up to 30% of patients with a typical FMF phenotype carry a heterozygous mutation of *MEFV*. The diagnosis is essentially based on clinical findings, especially in countries where molecular analysis is not easily available.

Two sets of criteria have been developed for the diagnosis of FMF in adult patients: the classic Tel Hashomer criteria[11], which are the most widely used, and the more recent Livneh criteria[12]. These criteria were mainly developed before the identification of molecular analysis and in a prevalent adult population with an established disease. Thanks to the generally increasing awareness of autoinflammatory diseases in the last decade, a substantial reduction in the delay of diagnosis of these conditions has been shown[13]. For this reason, even if disease onset can be occasionally observed during adulthood, it is crucial to develop diagnostic criteria based on the characteristics of the disease at its onset, during childhood. A new set of criteria for the diagnosis of childhood FMF has been proposed by a Turkish group[14]. All the available diagnostic criteria have been developed in populations characterized by a very high prevalence of FMF. So far, information has been scarce about the accuracy of these criteria in populations that have other periodic fevers. The aim of our study was to take advantage of a large international registry for autoinflammatory disease to analyze the accuracy of the pediatric diagnostic criteria for FMF in comparison with the previously suggested 2 criteria sets.

MATERIALS AND METHODS

Patient data analyzed in our study were extracted from the Eurofever registry. Data were collected through a secured registry on an https platform hosted in the PRINTO Website (www.printo.it). Ethical committee approval for entering patients in the registry, and informed consent, were obtained in the participating countries, depending on each country's regulations. We included consecutive pediatric patients of the different diseases for our study.

Patients with a diagnosis of FMF according to the enrolling centers were included in the registry. Patients who did not have biallelic mutations (at least 1 in exon 10) were requested to meet at least 1 of the available diagnostic criteria (Tel Hashomer, Livneh, and Yalcinkaya-Ozen)[13]. The control group included pediatric patients diagnosed with periodic fever syndromes other than FMF, such as mevalonate kinase deficiency (MKD), tumor necrosis factor receptor–associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA), or undefined periodic fever in accordance with Eurofever inclusion criteria[13]. Disease onset after the age of 18 was considered a reason for exclusion. Patients were diagnosed and entered in the registry by their local physician. Records were then reevaluated in a blinded manner (patient demographic data blinded) by independent experts (SO, MG, MF, JKD, BN, HL). The disease experts had the mandate to control the consistency and the quality of data. In case of inconsistency or other doubts, specific queries were resubmitted to the participating centers for resolution. Patients in the control group were similarly diagnosed by their physician and were checked with the same process, as described[15]. Data extracted from the Eurofever project included the following information: demographics (sex, age at onset, age at diagnosis), ethnicity, country of residence, family history (consanguinity, and family history of FMF), and clinical manifestations (fever, abdominal pain, chest pain, arthritis, fever plus serositis, erysipelas-like erythema, amyloidosis), response to the colchicine treatment, and mutation analysis.

Tel Hashomer, Livneh, and the Yalcinkaya-Ozen criteria were applied to both pediatric FMF patients and the control group. In the case of a missing or unclear variable (criterion) for the evaluation of each diagnostic tool, the patient was excluded from the calculation of sensitivity and specificity of

that given criterion. Further analyses were also performed to check sensitivity and specificity of these 3 criteria sets only in patients with FMF who have biallelic mutations in exon 10 for a homogeneous patient population. To address the effect of ethnicity and residence on the validation and the performance of diagnostic criteria in patients with FMF, 2 groups were established: (1) Eastern Mediterranean region group: patients living in Turkey, Israel, Armenia, Morocco, Saudi Arabia, Lebanon, Tunisia, or Egypt, and (2) European region group: White patients with European ancestry living in Western or Southern European countries (Italy, Greece, Spain, France, UK).

Statistical analysis. Analyses were done with SPSS (version 15.0). The validity of the Yalcinkaya-Ozen criteria and the performance of Tel Hashomer and Livneh criteria for FMF were assessed by using the data extracted from the Eurofever registry. The diagnosis confirmed by the Eurofever panel was considered as the gold standard. Frequencies and percentages were used as descriptive statistics for categorical variables. To describe scale variables, median (first, third quartiles) were used. Differences between pairwise groups were assessed by Mann-Whitney U test. Chi-square tests were applied for comparing categorical variables. The sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and accuracy of all diagnostic criteria including Tel Hashomer, Livneh, and Yalcinkaya-Ozen were calculated from the 2 × 2 crosstabs. Accuracy was used to provide sufficient information to infer clinical value if a new diagnostic test were safer or more specific than the old test[16]. P values < 0.05 were considered statistically significant.

RESULTS

Demographic, clinical, biological, and genetic data of both groups are shown in Table 1. At the time of the study, 438 FMF patients had been submitted to the Eurofever registry. A total of 339 patients (183 males, 156 females) were included in the study (Table 1). Ninety-nine patients were excluded because of a lack of complete information (75 out of 99) or disease onset in adulthood (24 out of 99 excluded patients). The median age at disease onset was 2.6 years (1st-3rd quartiles: 1.2-4.9) with a mean age at diagnosis of 5.9 years (1st-3rd quartiles: 3.7-9.2). Parents were consanguineous in 36 patients (10.6%). A family history of FMF was present in 110 patients (32.4%). Of the patients with FMF, 276 (81.3%) were carriers of 2 mutations in the *MEFV* gene: 117 of them were homozygous for mutations in exon 10, 6 were homozygous for E148Q and satisfied at least 1 FMF criterion (Supplementary Table 1, available from the authors on request), 152 were compound heterozygotes (148 with at least 1 mutation in exon 10). Fifty-three heterozygous patients and 10 patients not genetically screened fulfilled at least 1 of the 3 diagnostic criteria and were considered affected by FMF by the enrolling centers. After stratification of patients according to their ethnicity and residence, 211 (62.2%) of them were assigned to the Eastern Mediterranean region group [84 from Turkey, 101 from Armenia, 12 from Israel, 14 from Arabic countries (9 from Saudi Arabia, 2 from Egypt, 1 from Lebanon, 1 from Morocco, 1 from Tunisia)], and 54 (15.9%) to the European region group (mainly from Italy, Spain, and Greece). Seventy-four patients (21.9%) with Arab, Turkish, Jewish, or Armenian origin were living in Western European countries. This last group was not included

Table 1. Demographic features of our control and FMF group. Data are n (%) unless otherwise indicated.

Characteristics	FMF Group, n = 339	Control Group, n = 377	p
Male/female	183/156	195/182	0.298
Age at onset, yrs, median (1st–3rd quartiles)	2.6 (1.2–4.9)	1.5 (0.7–3.4)	< 0.001
Age at diagnosis, yrs, median (1st–3rd quartiles)	5.9 (3.7–9.2)	4.9 (3.0–8.2)	0.008
Consanguinity	36 (10.6)	18 (4.8)	0.005
Fever	279 (82.3)	356 (94.4)	< 0.001
Fever*	201 (59.3)	297 (78.8)	< 0.001
Abdominal pain	310 (92.4)	188 (49.9)	< 0.001
Chest pain	183 (54.0)	22 (5.8)	0.002
Arthritis	87 (25.7)	24 (6.4)	< 0.001
Family history	110 (32.4)	70 (18.6)	0.001
Fever plus serositis	78 (23.0)	6 (1.6)	0.017
Amyloidosis	2 (0.6)	1 (0.3)	0.194
Erysipelas-like erythema	43 (12.7)	1 (0.3)	0.167
Colchicine treatment	294 (86.7)	29 (7.7)	< 0.001
Response**			
Complete response	192 (56.7)	4 (1.1)	
Partial response	102 (30)	25 (6.6)	
Mutations in FMF group			
Homozygous	123 (36.2)	None	
Compound heterozygous	153 (45.1)		
Heterozygous	53 (15.8)		
Unknown	10 (2.9)		
Ethnicity/residence			< 0.001
Eastern Mediterranean region group	211 (62.2)	41 (10.9)	
European region group	54 (15.9)	331 (87.8)	

* Definition of fever according to the Yalcinkaya-Ozen. ** Complete or partial response. FMF: familial Mediterranean fever.

in the analysis of the effect of ethnicity and residence on the diagnostic criteria.

The disease control group consisted of 377 patients (Table 1). Among them, 53 (14.1%) had TRAPS, 45 (11.9%) MKD, 32 (8.5%) CAPS, and 160 (42.4%) PFAPA, and 87 (23.1%) had undefined periodic fevers (Supplementary Table 2, available from the authors on request). Overall, 182 females and 195 males were in the control group. Consanguinity was reported in 18 patients (4.8%). The median ages at disease onset and age at diagnosis were 1.5 years (1st-3rd quartiles: 0.7-3.4) and 4.9 years (1st-3rd quartiles: 3.0-8.2), respectively. Family history of periodic fever was present in 70 (18.6%) of the whole control group. None of them displayed *MEFV* mutations. After categorization of patients according to their ethnicity and residence, 41 (10.9%) and 331 (87.8%) of the control group were assigned to the Eastern Mediterranean and European region group, respectively (Table 1).

Sensitivity and specificity of the 3 criteria. All the variables for each criteria set were available in 286 out of 339 patients with FMF for the Yalcinkaya-Ozen criteria, 271 for the Tel Hashomer criteria, and 286 for the Livneh criteria. By applying the Yalcinkaya-Ozen criteria, 250 out of 286 patients with FMF were correctly diagnosed as FMF with a sensitivity of 87.4% (Table 2). Tel Hashomer were able to correctly identify 122 out of 271 patients with FMF, and Livneh criteria, 221 out of 286, with a sensitivity of 45.0 and 77.3%, respectively (Table 2).

Tel Hashomer criteria displayed the highest specificity (97.2%), with a very low number of false-positive results (Table 2 and 3). Conversely, the Yalcinkaya-Ozen and Livneh criteria displayed a high rate of false positivity (Table 2). Notably, a relevant number of patients classified as undefined periodic fever by the enrolling centers fulfilled at least 1 set of FMF criteria, namely the Livneh (60.9%) and the Yalcinkaya-Ozen criteria (43.7%; Table 2). We also analyzed the performance of the Yalcinkaya-Ozen criteria using 3 positive criteria as cutoff. The sensitivity obtained was 52.4%, with a specificity of 88.2% (Table 3). Sensitivity, specificity, PPV, NPV, and accuracy of the Yalcinkaya-Ozen criteria compared with Tel Hashomer and Livneh criteria are shown in Table 3. The overall accuracy (percentage of true positive and true negative patients in the whole group of patients analyzed) for the Yalcinkaya-Ozen criteria was 65.0% and 69.6% (using 2 and 3 criteria, respectively), compared to 59.9% for Livneh criteria and 71.8% for Tel Hashomer criteria (59.2%, not considering the response to colchicine).

We also evaluated which combination of Yalcinkaya-Ozen criteria had the highest accuracy in the identification of patients with FMF. The effect of any combination of 2 among the 5 (fever, abdominal pain, chest pain, arthritis, positive family history for FMF) Yalcinkaya-Ozen criteria was assessed (Supplementary Table 3, available from the authors on request)[13]. The combination of fever and abdominal pain was found to provide the highest sensitivity (58.7%), whereas the combination of chest pain and arthritis was found to have the highest specificity (99.5%). The combination of abdominal pain and chest pain (sensitivity 50.9%, specificity: 95.1%, PPV: 90.5%, NPV: 67.9%) provided the best accuracy (73%; Supplementary Table 3, available from the authors on request).

Of any combination of 3 Yalcinkaya-Ozen criteria, fever, abdominal pain, and chest pain displayed the highest accuracy of 65.9%, with a sensitivity of 34.5% and a specificity of 97.3% (PPV: 92.4%, NPV: 61.3%). The combination of chest pain, arthritis, and positive family history for FMF was found to provide the highest specificity of 99.7% (Supplementary Table 3, available from the authors on request).

For the Tel Hashomer criteria, the response to colchicine treatment displayed the highest sensitivity (86.7%), whereas the presence of amyloidosis had the highest specificity (99.7%), but owing to its very low incidence in the pediatric age group, it had a low sensitivity (0.6%; Supplementary Table 4, available from the authors on request). When we evaluated the performance of Tel Hashomer criteria without considering the response to colchicine, we observed that the sensitivity dropped to 16.6% (Table 3).

Sensitivity and specificity of the 3 criteria in patients with biallelic mutations in exon 10. To evaluate the performance of the 3 criteria in patients with genetically confirmed FMF, we performed a subanalysis involving the patient carriers of biallelic mutations in exon 10. Biallelic mutations in exon 10 were found among 198 of 286 patients with FMF who fulfilled the pediatric and Livneh criteria, and 183 of the 271 patients who fulfilled the Tel Hashomer criteria (Table 4).

Table 2. No. patients who met FMF diagnosis in our series according to different diagnostic tools. Data are n/N (%).

	Yalcinkaya-Ozen Criteria	Tel Hashomer Criteria	Livneh Criteria
FMF patients positive for FMF	250/286 (87.4)	122/271 (45.0)	221/286 (77.3)
CAPS false-positive for FMF	10/32 (31.3)	0/32 (0.0)	12/32 (37.5)
MKD false-positive for FMF	25/45 (55.6)	2/45 (4.4)	35/45 (77.8)
TRAPS false-positive for FMF	30/53 (56.6)	3/53 (5.7)	42/53 (79.2)
PFAPA false-positive for FMF	53/160 (33.1)	2/160 (1.1)	62/160 (38.8)
Undefined patients	38/87 (43.7)	1/87 (1.1)	53/87 (60.9)

FMF: familial Mediterranean fever; CAPS: cryopyrin-associated periodic syndrome; MKD: mevalonate kinase deficiency; TRAPS: tumor necrosis factor receptor–associated periodic syndrome; PFAPA: aphthous stomatitis, pharyngitis, adenitis syndrome.

Table 3. Sensitivity, specificity, PPV, and NPV of the suggested criteria compared with previous criteria.

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Yalcinkaya-Ozen					
1 criterion	99.3	5.7	53.4	88.2	54.5
2 criteria	87.4	40.7	61.6	74.8	65.0
3 criteria	52.4	88.2	82.9	63.0	69.6
4 criteria	24.1	99.6	98.6	54.7	60.3
5 criteria	5.6	99.6	94.1	49.2	50.6
Tel Hashomer criteria	45.0	97.2	93.8	65.0	71.8
Without colchicine response	16.6	99.6	97.8	55.7	59.2
Livneh criteria	77.3	41.1	58.8	62.4	59.9

FMF group (n = 286), control group (n = 263), for Yalcinkaya-Ozen criteria. FMF group (n = 271), control group (n = 285), for Tel Hashomer criteria. FMF group (n = 286), control group (n = 263), for Livneh criteria. FMF: familial Mediterranean fever; PPV: positive predictive values; NPV: negative predictive values.

Table 4. Sensitivity, specificity, PPV, and NPV of the suggested criteria compared with previous criteria (including only patients with biallelic mutations in exon 10).

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Yalcinkaya-Ozen					
1 criterion	99.5	5.7	44.3	93.8	46.0
2 criteria	90.4	40.7	53.4	84.9	62.0
3 criteria	64.1	88.2	80.4	76.6	77.8
4 criteria	33.3	99.6	98.5	66.5	71.1
5 criteria	8.1	99.6	94.1	59.0	60.3
Tel Hashomer criteria	49.7	97.2	91.9	75.1	78.6
Without colchicine response	24.0	99.6	97.8	67.1	70.1
Livneh criteria	77.3	41.1	49.7	70.6	56.6

FMF group (n = 198), control group (n = 263), for Yalcinkaya-Ozen criteria. FMF group (n = 183), control group (n = 285), for Tel Hashomer criteria. FMF group (n = 198), control group (n = 263), for Livneh criteria. FMF: familial Mediterranean fever; PPV: positive predictive values; NPV: negative predictive values.

With any combination of 2 or 3 criteria, the sensitivity of the Yalcinkaya-Ozen criteria were 90.4 and 64.1%, respectively. Sensitivity of the Livneh criteria revealed as 77.3% and specificity, 41.1%. When we evaluated the performance of Tel Hashomer criteria we found a very high specificity (97.2%), with a sensitivity rate of 49.7% considering the response to colchicine (Table 4).

Effect of ethnicity and residence on the validation of diagnostic criteria. For Yalcinkaya-Ozen criteria, based on 2 criteria, no difference in the sensitivity (87.6 vs 90.2%, p = 0.594) and specificity (40.7% vs 35.5, p = 0.373) were observed when patients from the Eastern Mediterranean region and from Europe were compared (Table 5).

When the Livneh criteria were analyzed, we found a higher sensitivity (88.9%) for the European patients, compared to patients coming from the Eastern Mediterranean region (75.4%, p = 0.075), with a specificity of 39.0 vs 45.9%, respectively (p = 0.323; Table 5).

In the Eastern Mediterranean region, Tel Hashomer criteria were significantly more sensitive than for the European patients (56.9 vs 34.5%, p = 0.007), with no difference for specificity (97.9 vs 95.9%, p = 0.422; Table 5).

DISCUSSION

In our present study we validated the Yalcinkaya-Ozen criteria for the diagnosis of FMF in a large international registry (Eurofever), including different ethnic groups from a number of countries in Europe and the eastern Mediterranean basin. Moreover, we compared the performance of the Yalcinkaya-Ozen criteria with the classic Tel Hashomer and Livneh criteria.

There were 2 previous attempts to validate the Yalcinkaya-Ozen criteria. Kondi, *et al*[17] had included 70% of Sephardic Jews in an FMF group of patients living in France. Yalcınkaya, *et al*[14,18,19] had included only Turkish patients living in Turkey. However, neither of the 2 previous studies had compared other periodic fevers syndromes with a heterogeneous ethnic background and country of residence, as in our present study[14,17]. Despite the limitation of a retrospective analysis and the lack of complete information for all FMF criteria in all patients, the registry allowed us to analyze the largest number of pediatric patients with different periodic fevers and with a heterogeneous geographical and ethnic distribution.

We found that the positivity of at least 2 Yalcinkaya-Ozen criteria were associated with the highest sensitivity (87.4%) among the 3 available criteria. Indeed, high sensitivity is

Table 5. Sensitivity, specificity, PPV, and NPV of the suggested criteria compared with previous criteria (regarding ethnicity and residence).

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
European region group				
Yalcinkaya-Ozen				
≥ 1 criterion	100	5.3	36.3	100
≥ 2 criteria	90.2	35.5	43.0	87.1
≥ 3 criteria	53.7	86.8	68.8	77.6
≥ 4 criteria	9.8	100	100	67.3
5 criteria	0	100	100	65.0
Tel Hashomer criteria	34.5	95.9	44.0	73.3
Livneh criteria	88.9	39.0	44.0	86.7
Eastern Mediterranean region group				
Yalcinkaya-Ozen				
≥ 1 criterion	99.0	5.7	43.3	88.2
≥ 2 criteria	87.6	40.7	52.1	81.7
≥ 3 criteria	56.2	88.2	77.9	73.2
≥ 4 criteria	29.4	99.6	98.3	65.7
5 criteria	8.2	99.6	94.1	59.5
Tel Hashomer criteria	56.9	97.9	93.8	80.2
Livneh criteria	75.4	45.9	43.8	76.9

In European region group: FMF group, n = 54→41; control group, n = 100→76. In Eastern Mediterranean region group: FMF group, n = 211→196; control group, n = 377→266.

rather crucial when the diagnostic test is used to identify a serious and treatable disease[16]. The sensitivity rate in our study was lower compared to Kondi, *et al* (100%)[17], but similar (86.5%) to the results obtained in a study from Turkey[14]. The main limitation of the Yalcinkaya-Ozen criteria (using at least 2 criteria) was the low specificity (40.7%). As already observed by Kondi, *et al*, the use of at least 3 positive criteria as a cutoff increased the accuracy (70%), thanks to a much higher specificity.

The Tel Hashomer criteria displayed overall the highest accuracy in discriminating pediatric patients with FMF from controls. This was mainly due to their high specificity (97.2%). However, the major limitation of these seminal criteria was their low sensitivity (45%). Indeed, few pediatric patients display amyloidosis and erysipelas-like erythema. More importantly, clinical features clearly consistent with a serositis are only occasionally referred in pediatric FMF, where chest pain and abdominal pain are more frequently reported. Finally, in pediatric FMF, it is important to diagnose the patient before starting the treatment with colchicine. It is widely debated whether the response to colchicine should be properly considered part of a diagnostic criteria set. Treatment should follow the diagnosis of a given disease. The diagnosis of FMF should be uniquely based on the clinical and genetic variables found in the patients. The response to colchicine plays a relevant role in the final confirmation of a diagnosis of FMF in daily practice, especially in populations in which FMF is predominant. However, it should be noted that the response to colchicine is not uniquely observed in FMF, but other periodic fevers might benefit from this treatment[20,21]. It should be discussed whether response to treatment more than a diagnostic criterion should be considered as a supportive criterion for the final classification in some patients, especially those with an uncertain clinical definition or without a confirmatory genetic test. Livneh criteria showed rather good sensitivity (77.3%), with specificity (40.7%) similar to that observed with the Yalcinkaya-Ozen criteria. Compared to the Tel Hashomer criteria, the Livneh criteria are indeed very useful and have proven their performance in adult series. However, in young children the presence of peritonitis may be difficult to evaluate, especially with a retrospective analysis of personal history. For this reason, simpler criteria such as chest pain and abdominal pain have been included in the Yalcinkaya-Ozen criteria with the aim to make them easier to use in everyday pediatric clinical practice. These latter symptoms are surely less specific than serositis, and it is conceivable that the low specificity observed for the Yalcinkaya-Ozen criteria is due to the frequent presence of these symptoms in other periodic fevers. Notably, the presence of both symptoms increased significantly the specificity in pediatric patients with FMF. Our study points out the need to provide a more detailed description of the clinical variables used as diagnostic criteria (duration, frequency, influence on daily activities, etc.) to avoid the subjectivity associated with their use.

Yalcinkaya-Ozen criteria for the diagnosis of FMF were created and validated in patients from eastern Mediterranean ancestry and residence[14]. Our study revealed that neither the ethnicity nor the residence affected the accuracy of the Yalcinkaya-Ozen criteria. The same was true for the Livneh criteria. Conversely, Tel Hashomer criteria displayed a lower sensitivity in patients with FMF who were from European countries. This result is in line with the previous studies showing that European pediatric patients with FMF display

a less severe disease course, with much lower incidence of severe serositis in comparison to patients living in Eastern Mediterranean countries[22].

When we reevaluated the performance of the 3 criteria in genetically confirmed patients with FMF carrying biallelic mutations in exon 10, we observed that the Tel Hashomer criteria continued to have the highest accuracy. Interestingly, the performance of the Livneh criteria was not affected noticeably. The positivity of any 3 combinations of Yalcinkaya-Ozen criteria revealed a rate of accuracy similar to the Tel Hashomer criteria.

In our present study we also identified a number of limitations for each diagnostic tool regarding sensitivity and/or specificity. This may be because these diagnostic tools were originally elaborated and validated in countries where FMF has a very high prevalence and where other monogenic periodic fevers are extremely rare. Although the Yalcinkaya-Ozen criteria display good sensitivity, their poor specificity represents a limitation, especially in those countries where FMF is relatively rare (Italy, Spain, Greece) and where other autoinflammatory diseases are frequently observed. Therefore we suggest the inclusion of additional variables, such as duration of fever episodes and ethnicity, in new clinical diagnostic criteria.

It is conceivable that the availability of a large international registry collecting data on all periodic fevers diseases provides a perfect tool to evaluate the specificity of the existing diagnostic criteria[23]. The multiethnic and multinational character of the registry allows a reliable validation of the criteria.

Our study shows that the new Yalcinkaya-Ozen criteria set can be used for the diagnosis of FMF, but that it had low specificity, whereas the Tel Hashomer criteria had better specificity but lower sensitivity.

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