THE IMPACT OF THE EUROFEVER/PRINTO CLASSIFICATION CRITERIA AND NOVEL CLASSIFICATION OF *MEFV* VARIANTS IN REAL LIFE: RESULTS FROM A LARGE INTERNATIONAL FMF COHORT

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Abstract

Introduction. A classification of genetic variants' pathogenicity associated to hereditary recurrent fevers and the novel Eurofever/PRINTO classification criteria (EPCC) have been recently developed.

Objectives: to evaluate the clinical impact of EPCC criteria and new INSAID pathogenicity classification of *MEFV* variants in the large international Eurofever FMF cohort.

Methods: baseline demographic, genetic and clinical data of FMF patients included in the Eurofever registry were analysed. Genetic and clinical EPCC criteria for FMF were applied. *MEFV* variants were classified according to the new INSAID classification.

Results: Since November 2009, clinical information was available for 1012 FMF (532 males/480 females, 827 children/185 adults) from 119 centres. For 125 patients clinical and genetic data mandatory for the application of EPCC were missing. Among the 887 remaining patients 623 (70.2%) satisfied EPCC (EPPC+), while 264 (29.8%) did not (EPPC-). Most of the EPCC- patients (172, 65.1%) displayed negative or non-informative genetics (monoallelic or biallelic benign variants, monoallelic variant of unknown significance. At baseline, Colchicine was used in most of EPCC+ patients (88%) and in a lower percentage of EPCC- patients (69 %, $p < 0.0001$), who were treated in a higher proportion with steroid or NSAID on demand ($p = 0.003$ and 0.008, respectively). Anti-IL-1 treatment was used in 4% of patients.

Conclusions: The combination of EPCC and the new classification of genetic variants' pathogenicity captured the majority of FMF patients in the Eurofever cohort in a homogeneous group. EPPC- patients were characterized by a different phenotype and therapeutic approach.

Keywords:

Total word count: 2704

Introduction

Familial Mediterranean Fever (FMF) is caused by mutations in *MEFV* located on the short arm of chromosome 16. *MEFV* encodes a protein named pyrin, which is a part of the multimeric inflammasome,(1). FMF is characterized by self-limited episodes of fever and polyserositis. The populations originating from Mediterranean basin, such as Turks, Armenians, Jews and Arabs, carry the highest prevalence of *MEFV* mutations and therefore higher incidence of the disease,(2). Colchicine is the standard treatment for the prophylaxis of FMF attacks, and to prevent the development of secondary amyloidosis—the main devastating complication of this disease,(3–5). Around 5% of patients do not respond to maximal tolerated dose of colchicine, and a variable percentage of patients display the persistence of fever episodes or sub-chronic inflammation,(6, 7). The FMF50 score has been proposed as a possible tool to define the response to treatment in FMF patients,(8). Colchicine resistant patients should be addressed with second line treatments, and the most promising ones are anti-IL1 agents, whose efficacy has been tested in randomised controlled trials,(9, 10).

FMF has been historically diagnosed clinically. The first set of diagnostic criteria for FMF was created for adults by the experts of the Tel Hashomer Hospital,(11), and subsequently refined by Livneh et al.,(12). In 2009, Yalçinkaya-Ozen criteria were developed to respond the need of criteria valid also for the paediatric population,(13). These three sets of classification criteria are indubitably useful but present some limitations: their specificity is low in populations with a lower prevalence of *MEFV* variants and where other hereditary recurrent fevers are present. Moreover, they do not consider the contribution of genetic analysis.

In 2019 a new evidence-based set of classification criteria was proposed for all hereditary recurrent fevers, including FMF, the Eurofever/PRINTO classification criteria (EPCC),(14). For the first time, a combination of genetic and clinical variables was chosen as specific classification criteria for each condition, overcoming the paradox of the absence of a role of the molecular analysis for the proper identification of patients affected by these genetic conditions. A parallel effort was performed by a group of geneticists aimed to classify the pathogenicity of all *MEFV* variants reported in the InFevers database,(15).

The aim of this study was to evaluate the clinical impact of EPCC criteria and new INSAID classification of *MEFV* variants in a large international FMF cohort. As a second aim we also described the baseline clinical features and disease outcome of this cohort.

Patients and Methods

Data were collected from the Eurofever registry and extracted through a secured platform hosted on the Pediatric Rheumatology International Trials Organization (PRINTO) website (http://www.printo.it). Twenty-eight centers included patients in the registry. The study was approved by the Gaslini ethical review board. Informed consent was obtained from each patient before enrolment; patients were identified by a private alphanumeric code.

Since 2009, Eurofever collect patients with different Autoinflammatory diseases in a cross-sectional registry,(16,17). All patients with a clinical and/or genetic diagnosis of FMF according to the participating center were included in the study. Clinical manifestations, molecular diagnosis, laboratory findings from disease onset to enrollment were analyzed, considering the clinical feature observed before the initiation of any treatment. In patients which were receiving a treatment at enrollment (baseline visit), information on efficacy of therapy were also analyzed. The dataset was closed in February 2020.

The EPCC for FMF are the following: (a) presence of confirmatory *MEFV* genotype (biallelic pathogenic or likely pathogenic variants) and at least one clinical criterion or (b) presence of non confirmatory *MEFV* genotype (in trans compound heterozygous for one pathogenic *MEFV* variant and one variant of unknown significance (VUS), or biallelic VUS, or heterozygous for one pathogenic *MEFV* variant) and at least two clinical criteria. The clinical criteria are duration of episodes 1-3 days, arthritis, chest pain, or abdominal pain,(14).

MEFV variants were defined according to the INSAID classification, as: i) pathogenic, ii) likely pathogenic, iii) VUS, iv) likely benign, v) benign, vi) unclassified,(15).

Only those patients who had a complete demographic, clinical, genetic and therapeutic profile were considered eligible for the study. Baseline data included: age, gender, country of birth, country of residence, ethnicity, consanguinity, age at the time of disease onset and diagnosis, and date of first and last visit to the referring center. Besides, molecular diagnosis was integrated with information on the mutations found (according to the InFever database, http://fmf.igh.cnrs.fr/ISSAID/infevers), the type of the molecular analysis performed (point mutations, more informative exons, or complete gene sequencing) and the laboratory having carried out the tests.

As already reported in previous studies, response to treatment was defined as i) complete (absence of clinical manifestations and normal laboratory parameters), ii) partial response (persistence of some clinical manifestations and/or some elevation of acute phase reactants, with reduction of at least 50% of fever episodes); iii) failure (absent of any substantial impact on disease activity or worsening) (18,19).

Statistical analysis was performed using STATA software. General statistics are reported as frequencies and percentages for categorical variables and median and range for numerical variables. All descriptive results are given with 95% confidence intervals (95% CIs). Analyses involved the chi-square test for categorical variables and t-test for continuous variables. $P < 0.05$ was considered statistically significant.

Results

Until February 2020, complete baseline information was available for 1182 FMF patients enrolled in the Eurofever registry by 28 countries (Supplementary Table 1). Out of the 1182 FMF patients, 887 had complete clinical and genetic data for the evaluation of EPCC and were eligible for the study (Figure 1).

Clinical characteristics at baseline

Among the 887 patients included (471 male), median age at time of enrollment was 7.9 years (range 0.2 - 82.8 years), one fifth of patients were adults (174 adults vs 713 children). The median age at disease onset and at diagnosis were 3.7 (range 0 - 66.8) and 7.9 years (range 0.2 – 72.2) respectively (Table 1). Six-hundred twenty-five patients satisfied the EPCC (EPCC+), while 262 patients did not satisfy the criteria and were defined as EPCC-. In the EPCC- group we found a significant lower diagnostic delay and disease duration than in the EPCC+ group (Table 1). Around 40% of patients of the entire cohort were from south-east Mediterranean and were classified as high-risk ethnicity.

Table 1 Demographics and clinical features* of Eurofever FMF cohort at baseline visit

	Total	EPCC +	EPCC -	*p*
N	887	625 (70.5%)	262 (29.5%)	-
Gender (M : F)	471:416	338:287	133:129	*NS*
High risk ethnicity,** *N (%)*	357 (40.6%)	294 (47.2%)	63 (24,6%)	< 0.0001
Age at onset, median years (range)	3.7 (0 - 66.8)	3.7 (0 - 66.8)	3.9 (0 - 59.1)	*NS*
Age at diagnosis, median (range)	7.9 (0.2 – 72.2)	7.9 (0.2 – 72.2)	7.9 (1 - 66.7)	*NS*
Age at enrolment, median (range)	7.9 (0.2 – 82.8)	8.1 (0.2 – 82.8)	7.5 (1 - 68.4)	*NS*
Episodes per year, median (range)	12 (1 – 25)	12 (1 – 25)	12 (1 – 25)	*NS*
Duration of episodes, *median day (25th – 75th p)*	3 (2-3)	3 (2-3)	3 (2-4)	*NS*
Abdominal pain, *N (%)*	757 (85.3%)	591 (94.6%)	166 (63.4%)	< 0.0001
Chest pain, *N (%)*	345 (39.1%)	307 (49.4%)	38 (14.5%)	< 0.0001
Arthritis, *N (%)*	223 (25.1%)	186 (29.8%)	37 (14.1%)	< 0.0001
Arthro-myalgia, *N (%)*	473 (53.3%)	355 (56.8%)	118 (45.0%)	*NS*
Erysipelas-like rash, *N (%)*	77 (8.7%)	72 (11.5%)	5 (1.9%)	< 0.0001
Amyloidosis, *N (%)*	6 (0.7%)	3 (0.5%)	3 (1.1%)	*NS*

* clinical features observed before the initiation of any treatment; ***South-East Mediterranean origin

The clinical manifestations and characteristic of fever episodes at the time of the enrollment in the registry and before any treatment are reported in Table 1. Patients experienced a median of 12 episodes per year (range 1 – 25) with a median duration of episodes of three days (25th percentile 2 days – 75th percentile 3 days). As expected, the most frequently reported symptom associated with fever was abdominal pain (85.3%), while chest pain and arthritis were reported in a third and a quarter of patients respectively. Patients satisfying the EPCC criteria showed a significantly higher frequency of the aforementioned symptoms. Arthro-myalgia was a rather common symptom in both EPCC + and EPCC groups. On the contrary erysipelas-like rash was relatively uncommon and was significantly more reported in EPCC+ patients. Amyloidosis was reported only in 6 patients, equally distributed between the two groups.

Genotype

Overall, 39.5% of patients had two high penetrance/pathogenic mutations in the two copies of the *MEFV* gene; 10.3% had one high penetrance mutation with a VUS in the other allele; 25.5% one high penetrance mutation in heterozygosity or with a benign or likely benign variant in the other allele; finally, 19.4% harbored only VUS or benign variant in one single allele (Supplementary Table 2); 42 patients (4.7%) were negative for *MEFV* variants at genetic analysis. As expected, the patients fulfilling the Eurofever/PRINTO criteria showed a much higher frequency of pathogenic variants, and patients who were wild type for *MEFV* were automatically classified as EPCC-.

The most frequent genotypes in the cohort were the heterozygosity and homozygosity for M694V variant, 14.7% and 14.3% respectively. The most frequent other genotypes are shown in Supplementary Table 3.

Treatment at baseline

We analyzed the treatment received by the patients at baseline (Table 2 and Supplementary Figure 2). Colchicine was administrated in 82.4% patients and was the most frequent treatment, as expected. Out of these patients, 41 discontinued colchicine because of remission (20), decision of the patient/family (8), inefficacy (5), mild adverse events (2). No reasons were reported for 6 patients. Around 7% of patients were off continuous therapy and received NSAID or steroids on demand. Thirty-one patients were treated with anti-IL1, anakinra or canakinumab. Out of them, 24 patients received anti-IL-1 in association with colchicine, while 10 patients received biologic treatment alone.

Table 2 Treatment received at baseline according to EPCC fulfillment

	Total N (%)	**EPCC + N (%)**	**EPCC – N (%)**	***p***
Colchicine	731 (82.4%)	548 (87.7%)	183 (69.8%)	0.0006
Anti-IL1	34 (3.8%)	23 (3.7%)	11 (4.3%)	*NS*
Anakinra	17 (1.9%)	12 (2.6%)	5 (1.9%)	*NS*
Canakinumab	17 (1.9%)	11 (1.9%)	6 (2.3%)	*NS*
NSAIDS on demand	20 (2.3%)	3 (0.5%)	17 (6.5%)	0.008
Steroids on demand	42 (4.7%)	18 (2.9%)	24 (9.2%)	0.003
Off treatment	88 (9.2%)	53 (8.8%)	35 (13.4%)	0.04
Other treatments (with or without colchicine)	22 (2.5%)	12 (1.8%)	10 (3.8%)	*NS*

The treatment received was then analyzed according to EPCC fulfilment: colchicine was significantly more administered in the EPCC+ group respect to the EPCC- group (87.7% and 69.8% respectively). On the other hand, NSAIDS and steroids on demand were significantly more frequent in the EPCC- group than in the EPCC+. Around 4% of patients received anti-IL1, with no differences between the two groups (Table 2). Around 10% of patients were completely off-treatment.

Twenty-two patients were receiving other treatments: 4 methotrexate (MTX), 4 anti-TNF, 4 sulfasalazine, 3 cyclosporine, 2 azathioprine, 1 thalidomide, 4 a combination of MTX, anti-TNFalfa and sulfasalazine. Colchicine was also administered in 19 of them, while 3 were not receiving neither colchicine neither anti-IL1. A concomitant disease was reported for 10 patients (4 Juvenile Idiopathic Arthritis, 2 spondyloarthropathy, 1 Rheumatoid Arthritis, 1 Behçet disease, 1 inflammatory bowel disease, 1 received liver transplantation for non-specified reasons).

Among the 3 patients not treated with colchicine, one patient was affected by systemic lupus erythematosus, while no concomitant disease was reported in the other two. All of these 3 patients were not fulfilling the EPCC criteria and were carrying one heterozygous benign or VUS variant (R202Q, P369S and E148Q).

Information about response to colchicine and anti-IL-1 at baseline was available for 667 patients, 501 EPPC+ and 167 EPPC-. The distribution of responders to colchicine was different between EPCC+ and EPPC- groups ($p = 0.006$), with a higher percentage of response in EPCC+ FMF patients. (Figure 2 and Table 3).

Information about response to anti-IL-1 treatment was available for only 22 patients. Among these patients, 12 (54%) had a complete response to anti-IL1 treatment while only 4.5% was considered non-responder. No difference between EPPC+ and EPPC- patients was observed (Table 3).

Table 3 Response to treatment according to EPCC fulfilment

		Total N (%)	EPCC+ N (%)	EPCC– N (%)	*p*
Colchicine	**Complete responders**	378 (56.7%)	300 (60%)	78 (46,7%)	*0.006*
	Partial responders	225 (33.7%)	159 (31,8%)	66 (39,5%)	
	Non responders	64 (9.6%)	41 (8,2%)	23 (13,8%)	
Anti-IL-1	**Complete responders**	12 (54.5%)	10 (58.8%)	2 (40%)	*0.49*
	Partial responders	9 (40.9%)	6 (35.3%)	3 (60%)	
	Non responders	1 (4.5%)	1 (5.9%)	0 (0%)	

In Figure 3 and Supplementary Table 4 we reported data on treatment response according to genotype. We found a tendency towards a difference among the 5 groups (p = 0.07) for the response to colchicine. Patients with pathogenic mutations (2 pathogenic or likely pathogenic mutation in homozygous or compound heterozygosity) displayed a higher proportion of complete responder in comparison to patients with benign or VUS mutations or even to patients' wild type for *MEFV* mutations. Concerning anti-IL-1 treatment, the rate of complete responders was markedly higher in patients with pathogenic mutations (80%) compared to patients with other genotypes. The difference was not statistically different because of the limited number of patients receiving anti-IL-1 treatment.

Discussion

In the present study we evaluated the actual impact of the Eurofever/PRINTO classification criteria (EPCC) and the new classification for the pathogenicity of *MEFV* variants in a large international cohort of FMF patients enrolled in the Eurofever registry.

The application of EPCC was able to identify two subsets of patients with different clinical presentation, genetic features and therapeutic approach.

Patients fulfilling the EPCC showed significantly more frequently abdominal pain, chest pain and arthritis. That is quite self-explanatory since these symptoms are included in the classification criteria. However, other features like high-risk ethnic origin and erysipelas-like rash were significantly more common in EPCC+ patients. Arthro-myalgia was rather common in both groups, probably because it is a common and non-specific symptom. The low incidence of amyloidosis in respect to previous studies is related to the prevalence of pediatric population in this cohort and probably to the improvement in the recognition and institution of a proper treatment in the last 10 years (1, 2).

Interestingly, even if the enrolling centers made a formal diagnosis of FMF in all patients for the inclusion in the registry, the therapeutic approach was significantly different when comparing EPCC+

from EPPC- patients with a much lower percentage of patients treated with colchicine and a wider use of steroids and NSAIDs on demand in EPCC- patients. This observation supports the impact of the genotype on the clinical presentation and the therapeutic choices by the centers.

The molecular analysis of *MEFV* gene has gained increasing importance in the last years, since its discovery,(21). Genetic diagnosis is definite when two pathogenic mutations are present in the two *MEFV* alleles. However, the presence of at least one *MEFV* pathogenic variant has been considered as supportive for a proper classification for FMF patients with a consistent phenotype,(14). The growing evidence of a dose-effect of the *MEFV* variants is supported by the observation of a phenotypic crescendo of FMF-associated symptoms according to the *MEFV* genotypes, increasing from genetically negative patients to those carrying two pathogenic *MEFV* mutations,(22,23). In this context the actual impact of VUS and benign and likely benign *MEFV* variants is confirmed to be rather limited.

In the present paper, patients fulfilling the EPCC displayed a clear trend towards a higher rate of compete response to colchicine, in respect to EPCC- patients, with a relevant number of non-responders patients in the EPCC- group. This observation suggests that the presence of an inconclusive genotype has an overall negative impact on the response to colchicine.

The limited number of patients treated with anti-IL-1 at the moment of the enrollment does not allowed a proper evaluation of possible difference for the response to anti IL-1 agents among the different groups analyzed.

This issue raises the main limitation of the present study, that is linked to the absence of a longitudinal evaluation of the response to treatment of the patients analyzed. This part of the study is ongoing. The longitudinal evaluation over 5 years of this cohort will provide clues on the overall long-term outcome in term of efficacy, safety and tolerability of different treatments.

In conclusion, our study provides data on the largest international cohort of FMF patients described so far. Classification criteria are essentially meant as a highly specific tool for the identification of patients to be included in clinical trials or in studies on pathogenesis of the disease, and not as a diagnostic tool for the everyday clinical activity. However, the application of EPCC in real life defines two homogenous group of patients, which differ in clinical characteristic, therapeutic approach and response to treatment. The present data suggest that the negativity of EPPC criteria should alert the physicians for the possibility of an alternative diagnosis in the context of an inflammatory phenotype.

This study confirms that the genetic analysis should be considered as mandatory for a better definition of each case of suspected FMF, especially in all cases presenting with an atypical presentation, even in

countries with a high incidence of this condition. The longitudinal evaluation of the Eurofever cohort of FMF patients is ongoing and will provide detailed evidence on the efficacy and safety of the different treatments used in this condition.

Legend to the figures

Figure 1 Colchicine efficacy according to EPCC fulfilment (*CR: complete responders, PR: partial responders, F: failure*)

Figure 2 Response to treatment according to genotype *(WT: wild type, NC: not classified, B: benign, LB: likely benign, P: pathogenic, LP: likely pathogenic).*

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