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Evaluation of Disease Severity in Familial Mediterranean Fever

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OBJECTIVE To establish a new, objective, statistically based severity score for familial Mediterranean fever (FMF).

METHODS One hundred consecutive FMF patients were evaluated independently by 2 FMF experts for severity of their disease and were assigned to 1 of 3 severity levels: mild, intermediate, or severe. Nine candidate criteria, reflecting objective suffering and disability, were analyzed to determine their weight for patient placement in the 3 predefined severity groups.

RESULTS Candidate criteria best differentiating between the 3 patient categories were the frequency of attacks, the number of sites affected during an attack and during the course of the disease, and the duration of the attacks. These criteria were applied in a classification-tree model to establish a new FMF-severity score (F-SS). The first set of F-SS (F-SS-1) was highly sensitive and specific. Integrating F-SS-1 with clinical parameters strongly associated with disease severity resulted in a simplified score, the second set of F-SS (F-SS-2).

CONCLUSIONS New, useful, objective, and valid severity scores were established and found to distinguish between patients with mild, intermediate, and severe diseases with high sensitivity and specificity.

RELEVANCE The F-SS established may be important for treatment decisions, prognosis evaluation, and comparative analysis of patient populations.

KEYWORDS familial Mediterranean fever (FMF), severity score, criteria, mutation analysis, colchicine

Familial Mediterranean fever (FMF) is an ethnically related disease, with an autosomal recessive inheritance, and an affected population estimated as reaching approximately 120,000 individuals worldwide (1). It is characterized by acute episodes of fever and painful manifestations, usually in the abdomen, chest, joints, skin, and muscles, resulting from a massive influx of polymorphonuclear neutrophils to serosal membranes and spaces (2). Nephropathic amyloidosis of the AA type, leading to end-stage renal failure, is the gravest manifestation of the disease. Continuous treatment with colchicine in the appropriate dose prevents the attacks in most patients and amyloidosis in virtually all patients (3).

In 1997 the gene causing FMF (*MEFV*) was cloned from the short arm of chromosome 16. It encodes for a protein, termed pyrin or marenostrin, with a still uncertain function (4,5). Recently, a role for pyrin in apoptosis has been suggested based on the presence of a pyrin domain in apoptotic proteins and the finding that pyrin colocalizes with the apoptotic protein ASC in specks (6). Thus far, about 40 disease-associated mutations have been identified. Of these, only 5 (*M694V, V726A, M680I, M694I, E148Q*) account for most of

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Table 1 Severity Scoring System by Pras et al*

Parameter	Features	Score
Age of onset (years)	>31	0
	21–31	1
	11–20	2
	6–10	3
	<6	4
Number of attacks per month	<1	1
	1–2	2
	>2	3
Arthritis	Acute	2
	Protracted	3
Erysipelas-like erythema		2
Amyloidosis		3
Colchicine dose (mg/day)	1	1
	1.5	2
	2	3
	>2**	4

The overall severity of a disease in a given patient is the sum of the scores for each parameter. A score of 3 to 5 is considered to reflect mild disease, 6 to 8 intermediate disease, and ≥ 9 severe disease.

*Adopted from Ref (11).

**Unresponsive to 2 mg.

the FMF mutated alleles. The other *MEFV* carrier chromosomes either bear rare mutations or have no mutations in their pyrin coding regions (7).

The clinical heterogeneity of FMF is vast, ranging from insensible or very mild to devastating disease. This heterogeneity partially links to the *MEFV* genotypes, with more severe disease in those patients homozygous for the *M694V* and *M680I* mutations, and the complex allele *V726A-E148Q* (8,9). FMF is probably also modified by other genes (10) and yet unidentified environmental factors.

The currently used severity scoring system for FMF, which was proposed by Pras and coworkers, accounts for several features, including age of disease onset, frequency of attacks, colchicine dose, joint involvement, erysipelas-like erythema and amyloidosis, and grades each variable differently, according to its estimated contribution to the severity of the disease (Table 1). (11) However, this scoring system has several drawbacks, as follows: (1) some of the items lack a cause and effect relationship with suffering, organ dysfunction, and physical and socioeconomic disability, factors that define more severe disease; (2) parameters clearly associated with greater suffering are missing; (3) arbitrary differential scores are given to individual parameters; (4) colchicine dose employed in the score is not an authentic expression of the disease, but rather depends on absorption, side effects, accessibility, and physician attitude; and finally, (5) the validity of the score has not been statistically tested.

Because of these weaknesses, and because an index of disease severity is an important tool for the adjustment of medical treatment, determination of prognosis, analysis of clinical correlates, and comparison between surveys and patients of different ancestries, the present study was undertaken. We constructed a new FMF-Severity Score (F-SS), which eliminates the shortcomings of the former scores and includes objective and valid parameters.

Methods and Patients

Patients and Setting

The study cohort consisted of 100 consecutive FMF patients seen at the FMF clinic in Sheba Medical Center, Tel-Hashomer, during January and February 2002, and who had a clinical follow-up record of at least 5 years. The diagnosis in all patients agreed with the commonly used set FMF diagnostic criteria (12). Patients having additional diseases with manifestations that might mimic FMF, such as inflammatory bowel disease, Behçet's disease, ankylosing spondylitis, etc., were excluded because these conditions may affect the evaluation of FMF disease severity.

Determination of Disease Severity

In the absence of objective measurement, the determination of disease severity was based on subjective clinical assessment, which served as the gold standard for the establishment of the F-SS. The patients were assigned to 1 of 3 severity groups: mild, intermediate, and severe, by 2 rheumatologists experienced in treating FMF patients (N.Z. and P.L. each saw about half of the patients), and who were not aware of the candidate criteria for the F-SS (see below). Subgroup patient allocation was based on subjective understanding of the concept of disease severity by the classifying physicians as determined by interview, physical examination, data collected from patient's charts, and acquaintance with most of the patients.

Candidate Criteria for the F-SS

Candidate criteria for the severity score were chosen based on the principle that they represent genuine manifestations of FMF and logically correlate with suffering, physical disability, or organ dysfunction (Table 2). For simplicity, most candidate criteria received nominal values (yes/no) rather than ordinal values (numbers).

Determination of the Criteria suitable for F-SS

A questionnaire accounting for various disease manifestations, colchicine treatment, and the candidate criteria appearing in Table 2, was completed for each patient and used to study the applicability of the criteria. The frequencies of each criterion (in the case of yes/no answers) or the mean number of attacks or sites (as defined by the candidate criteria requiring numbers) in each subclass of severity were computed and used to determine the weight of the candidate criteria in distinguishing between the severity groups. The most discriminating criteria were used to establish the new F-SS.