Arthritis as the Sole Episodic Manifestation of Familial Mediterranean Fever

MERAV LIDAR, RON KEDEM, ADAM MOR, DAVID LEVARTOVSKY, PNINA LANGEVITZ, and AVI LIVNEH

ABSTRACT. ***Objective.*** To clinically and genetically characterize patients with familial Mediterranean fever (FMF) in whom arthritis constitutes the only manifestation, and to establish the most important features distinguishing FMF arthritis in such a setting from other forms of mono/oligo arthritides.
Methods. The study population comprised 14 patients with episodes of arthritis as the only manifestation of FMF who nevertheless fulfilled the diagnostic criteria for FMF. The control group consisted of 28 patients with episodic mono/oligo arthritis of different disease entities (palindromic, reactive, inflammatory bowel disease, Reiter's, seronegative spondyloarthropathy, chronic juvenile, Behçet's, and gouty arthritis) who presented to the rheumatology clinic during the study period. Patients in both groups underwent clinical evaluation and donated blood for FMF gene analysis.
Results. The study and control groups shared similar age and sex distribution and experienced the monoarthritic attacks at similar sites, usually the knee and ankle joint. The 2 groups differed significantly in features of arthritis (which were febrile and of short duration in FMF), family history of FMF, mutation analysis, and response to colchicine. These differences allowed the defining of a rule, which readily distinguishes FMF arthritis from other forms of episodic mono/oligo arthritis.
Conclusion. The clinical, ethnic, and genetic features of recurrent monoarthritis of FMF are specific and may separate FMF from other entities with mono/oligo arthritis. (J Rheumatol 2005;32:859-62)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER ARTHRITIS
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Familial Mediterranean fever (FMF) is a recessive hereditary disorder, affecting around 150,000 patients globally and characterized by recurrent episodes of febrile peritonitis, pleuritis, and synovitis[1]. The majority of patients with FMF (75%) experience episodes of acute monoarthritis in addition to other FMF manifestations at some point during the disease course[1-3]. The arthritic episodes are usually associated with fever, affect the large joints of the lower extremities, and manifest with local redness, swelling and tenderness[1-3]. The arthritis typically resolves spontaneously over the course of a few days, similar to attacks at other sites. Less than 5% of the patients experience attacks of upper extremity joints[4]. About 5% of patients who have recurrent attacks develop protracted arthritis, usually of the hips or knees, with symptoms lasting from one to several months. Complete recovery is the rule, even in the protracted form of arthritis, with chronic joint damage occasionally occurring, mostly in the hips[5,6]. Additionally, FMF may be associated with HLA-B27 negative spondyloarthropathy, manifested by sacroiliitis, enthesitis, and inflammatory back pain[7,8]. Previous reports have estimated that only 1% of patients with FMF experience arthritis as their sole manifestation[3]. However, we are not aware of a published attempt to characterize this subset of patients.

Given the absence of a specific test for FMF[9], its diagnosis remains clinical and is based on highly sensitive and specific diagnostic criteria[10]. Although the criteria allow diagnosing recurrent episodes of febrile arthritis as FMF, even if it is the sole manifestation of the disease, diagnosing FMF based on arthritis alone, and distinguishing it from other palindromic-type arthritides, poses a challenge. It is usually associated with extensive investigations, multiple clinic and emergency room visits, and a huge diagnostic delay. The recent cloning of the FMF gene (MEFV) has undoubtedly increased our diagnostic ability, particularly in uncertain presentations, but has not yet been applied to patients with recurrent synovitis alone. Of note, compared to the various MEFV mutations found, the M694V mutation is more commonly associated with arthritis[11].

Our study sought to clinically and genetically characterize patients in whom arthritis forms the sole manifestation of FMF, and to define features best distinguishing FMF arthritis from other forms of mono/oligo arthritides.

From the Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer; the Department of Rheumatology, Ichilov Medical Center; and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

M. Lidar, MD; R. Kedem, PhD; A. Mor, MD; D. Levartovsky, MD; P. Langevitz, MD, Clinical Professor of Medicine; A. Livneh, MD, Associate Professor of Medicine, Heller Institute of Medical Research, Sheba Medical Center.

Address reprint requests to Prof. A. Livneh, Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer 52621, Israel. E-mail: alivneh@post.tau.ac.il

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MATERIALS AND METHODS

Study group. The study population (cases) included 14 unrelated FMF patients (9 women, 5 men) in whom arthritis constituted the only form of their FMF attacks. They were enrolled at the FMF clinic of Chaim Sheba Medical Center, Tel-Hashomer. Patients were accepted if they fulfilled the clinical criteria for the diagnosis of FMF[10]. Patients with FMF manifested at any site other than a joint were excluded from the study. Potential patients were identified using our computerized registry, which included at the time of the study 5000 patients. Initially 27 patients were identified, 3 of whom could not be contacted and 10 of whom were excluded because they had additional FMF manifestations, predominantly abdominal attacks, during the time period that elapsed since initial diagnosis. The remaining patients were invited for a clinical interview and examination. MEFV genetic analysis for the 4 most common mutations in our population (M694V, V726A, E148Q, M680I) was performed in all cases, using restriction enzyme digestion of polymerase chain reaction (PCR) amplified DNA segments of the relevant MEFV exons[12].

Control group. The control group comprised 28 unrelated patients (17 women, 11 men) with mono- or oligoarthritis due to various conditions including reactive arthritis, palindromic arthritis, inflammatory bowel disease (IBD) or other seronegative spondyloarthropathies, systemic lupus erythematosus (SLE), chronic juvenile arthritis, Behçet's disease, and gout. The patients were recruited from the rheumatology clinics of Sheba and Ichilov Medical Centers. In all controls, diagnosis of the major disease causing arthritis agreed with accepted published criteria[7,13-19]. Adjustments were made only for age and sex, as other variables could be considered disease related. The control group underwent the same clinical and genetic analysis as the study group.

FMF associated variables. Based on our experience with FMF, we selected 14 variables usually associated with typical FMF attacks or characterizing other non-attack clinical, demographic, and genetic features of FMF (Table 1) for evaluation and analysis.

Study questionnaire. A questionnaire, aimed at determining the presence of the features most typical to the arthritis of FMF (Table 1), was completed for each patient and control based on history and examination, as well as on data abstracted from clinical charts.

Data analysis. Frequency of each FMF-associated variable, either alone or in several combinations, and of the demographics for each group was computed and those best distinguishing between cases and controls were determined using Fisher's exact test or Student's t test. Sensitivity and specificity of a feature or a set of features were determined by the rates of the feature/set of features among cases and 100% minus its frequency in controls, respectively.

Table 1. Variables characterizing FMF related arthritis.

1. Fever during episodes of arthritis (≥ 38° C, rectal)
2. Large joints
3. Lower extremity
4. Monoarticular
5. Short duration, > 6 hrs, < 7 days
6. Recurrent, ≥ 3 episodes
7. Appropriate genotype, 1 or 2 FMF alleles
8. Complete response to colchicine prophylaxis
9. Family history of FMF
10. Calf or foot pain appearing after short exertions such as standing or walking 1 hr
11. Ethnic origin in which FMF is prevalent
12. Age of arthritis onset < 10 yrs
13. Consanguinity of parents
14. Proteinuria, ≥ 0.5 g/24 hrs

RESULTS

The case and control populations comprised 14 and 28 patients, respectively. The 2 populations were comparable with regard to age and sex. North-African descent predominated among cases (Table 2). Age of onset of arthritis was earlier among cases than controls with other disease entities, and as expected, family history of FMF was also more prevalent (Table 2). However, no significant differences between the groups were noted in the number of the affected generations or consanguinity.

Clinical features distinguishing cases from controls are shown in Table 2. The groups differed in the favorable response to colchicine, presence of fever, and history of leg pain associated with walking or prolonged standing. All were more common in FMF. Knee involvement better characterized the control group, while the ankles were more affected by FMF. The frequencies of the attacks (around 5 per year), as well as their duration (defined as > 6 hours, < 7 days), involvement of more than a single joint in some of the attacks (uncommon), and the presence of non-attack features, such as proteinuria (rare) and chronic low back pain (7% in cases vs 20% in the controls), were comparable between the groups.

Table 2 presents the MEFV genetic characteristics of both groups, showing, as expected, predominance of MEFV alleles and the M694V mutation in the study group. None of the genotypes (e.g., M694V/M694V or M694V/E148Q, etc.) was more common in the study group.

Because none of the studied features could by itself safely separate FMF arthritis from other forms of episodic arthritides, we assembled, based on Table 2 variables typical to FMF, 2 sets of features useful in relating episodic arthritis to FMF (Table 3). A patient experiencing episodic arthritis with features defined by one of these sets is highly likely to have FMF.

DISCUSSION

Recurrent monoarthritis is a feature of a large number of diseases including, among others, reactive arthritis, palindromic rheumatism, seronegative spondyloarthropathies, Behçet's disease, crystal induced arthritis, and FMF. Therefore, diagnosing the cause of recurrent monoarthritis may constitute a problem, particularly if other manifestations of the primary disease are subtle or missing, or the joint involvement precedes other manifestations. Under such circumstances, certain characteristics of the joint disease itself may serve as a clue for the yet invisible underlying disease. In the cohort of patients with FMF studied, these manifestations included acute inflammation of a single joint in the lower extremity associated with fever and spontaneously undergoing a complete resolution over the course of a week or less (Table 2).

Compared to other forms of episodic monoarthritis, several variables were found to be more characteristic of FMF,

Table 2. Demographic, clinical, and genetic features separating cases from controls. The controls comprised 6 patients with reactive arthritis, 5 with palindromic arthritis, 8 with inflammatory bowel disease or other seronegative spondyloarthropathies, 1 with SLE, 2 with CJA, 4 with Behçet's disease, and 2 with gout.

Variable	Cases	Controls*	p
Number of patients	14	28	—
North African Jews, %	71.4	21.4	0.002
Age at onset of arthritis, yrs ± SD	16.6 ± 10.4	28.3 ± 14.7	0.01
Onset < 10 years of age, %	28.6	3.6	0.033
Onset < 20 years of age, %	78.6	32.1	0.006
Family history of FMF, %	71.4	21.4	0.002
Colchicine responsiveness, %	100	18*	< 0.0001
Attack associated fever, %	71.4	0	< 0.0001
Exertional leg pain, %	57.1	7.1	0.0003
One or 2 FMF alleles, %**	100	25	< 0.0001
One or 2 M694V mutations, %	60	7	< 0.0008

* 11 patients received colchicine, of whom only 2 responded. ** Only 4 mutations were screened.

Table 3. Features distinguishing FMF related arthritis (cases) from other mono/oligo episodic arthritis (controls) in patients presenting with solo episodic arthritis. Arthritides not satisfying the typical criteria set are evaluated using the atypical criteria.

FMF-Related Arthritis: Criteria	Cases (n = 14) Positive (%)	Cases (n = 14) Negative (%)	Controls (n = 28) Positive (%)	Controls (n = 28) Negative (%)	Sensitivity (%)	Specificity (%)
Typical Febrile (≥ 38˚C), lower extremity, large joints, monoarticular, ≤ 7 days, recurrent (≥ 3 episodes)	64	36	0	100	64	100
Atypical Differ from typical in one feature (< 38˚C/upper extremity/small joints/ oligoarticular), but include instead one or more of the following: 1. Appropriate genotype (1 or 2 mutated alleles) 2. Favorable response to colchicine (1–3 mg/day) 3. Family history of FMF in sibs, parents, uncles, aunts, cousins, grandparents 4. Calf pain on exertion (< 30 min walk; < 60 min standing)	100*	0	0	100	100	100
Cumulative (either set 1 or set 2)	100	0	0	100	100	100

* The frequency of arthritides satisfying the atypical criteria (in cases and controls) is determined in cases and controls not fulfilling the typical criteria.

including ethnicity (North African Jewish origin), earlier age of disease onset, family history of FMF, favorable response to colchicine, fever during the attack, exertional leg pain, and a predominance of MEFV mutated alleles (Table 2). Because none of these variables appeared to be diagnostic of FMF by itself, several of them were combined into a rule, which favors FMF over other possibilities in a situation of recurrent mono/oligoarthritis (Table 3).

To our knowledge, this study forms the first series of FMF patients in whom arthritic attacks constitute the sole manifestation of the disease. The course of the joint attack as an isolated manifestation is identical to the course described in patients who exhibit the full disease spectrum. However, compared to the commonly used diagnostic criteria[10], our rule appears to be more specific: 2 controls in our study fulfilled standard criteria for FMF, but were differentiated by our proposed criteria (data not shown). In this respect, our study may be considered as fine tuning of the already established criteria, and also as a validity analysis for these criteria, particularly with respect to their specificity. Most important, by focusing on this subset of patients, our study underscores the typical presentation of FMF arthritis attacks that, in contrast to abdominal attacks, is being ignored by practitioners when joint attacks are the only expression of the FMF.

All cases in our series carried at least one MEFV mutation (Table 2). The comparable genetic background of our patients, as depicted by MEFV allelic distribution between the study group and patients with classic FMF, implies that we are dealing with an isolated aspect of the same disease. It should be emphasized that in FMF, the identification of only a single MEFV mutation or no mutation at all does not exclude the diagnosis. The diagnostic sensitivity of genetic analysis is about 60%[9]. It is assumed that the cryptic alleles carry an as yet unidentified MEFV mutation, a promoter mutation, or another modifier gene that allows expression of

the FMF phenotype[9]. Moreover, due to a large number of asymptomatic individuals carrying a double MEFV mutation, the diagnostic specificity of genetic analysis is also low. Hence, typical arthritic attacks suffice to confirm the diagnosis of FMF, as do incomplete attacks, which respond favorably to colchicine, or are associated with a positive family history and/or calf pain on exertion regardless of the results of genetic analysis. On the other hand, the finding of an MEFV mutation carrier is not diagnostic of FMF[9]. Indeed, 25% of the controls had MEFV mutations, which is comparable to the general population[20].

In theory, the features described should allow the identification of FMF related arthritis, even in a setting where FMF coexists with another disease that may also cause monoarthritis, for example, Crohn's disease or Behçet's disease[21,22]. However, incomplete attacks of FMF arthritis in the presence of another disease that may also cause arthritis may result in diagnostic dilemmas not answered by our findings. Another limitation of our study is the absence from our control group of several rare recurrent monoarthritides such as crystal-induced other than gout, certain infectious diseases such as brucellosis and lyme, and malignant diseases such as non-Hodgkin's lymphoma or synovial metastasis. Also, rheumatic fever with its large spectrum of joint manifestations may rarely simulate FMF. Yet theoretically, again based on published data, the common presentation of the above rare recurrent monoarthritides would not fit the 2 sets of established rules.

The prevalence of arthritis as a single manifestation of FMF was lower in this study than the published rate of 0.5–1% as only 14 patients were identified from a cohort of 5000 FMF patients. However, it may be that patients with FMF arthritis are misdiagnosed, are not referred to the FMF clinic, and are treated instead by family physicians or rheumatology services. If this assumption is correct, then they may be subjected to needless investigations and overtreated with nonsteroidal antiinflammatory drugs, disease modifying antirheumatic drugs, and intraarticular steroids, exposing them to unnecessary side effects.

The importance of identifying FMF as the basis for recurrent attacks of acute arthritis extends beyond the achievement of earlier diagnosis and treatment of joint attacks. By starting colchicine we can prevent FMF related amyloidosis that may develop unhindered if the arthritis is treated by alternative means. Although no patient in this study had amyloidosis, or even proteinuria, it should be noted that it was a young cohort with relatively short disease duration and all were treated with colchicine.

Our study highlights the importance of FMF in the differential diagnosis of acute monoarthritis in young adults. The diagnosis can be made promptly, based on a set of distinguishing features that are highly indicative of FMF as the underlying disease. The only expensive laboratory test, genotype analysis, may yield a feature of only secondary importance, and therefore, it is not essential. Longterm followup is needed to determine if these cases of monoarthritis are truly the sole or rather only the initial manifestation of FMF.

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