The Prodrome: A Prominent Yet Overlooked Pre-Attack Manifestation of Familial Mediterranean Fever

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ABSTRACT. ***Objective.*** To identify and characterize pre-attack symptoms (prodrome) in patients with familial Mediterranean fever (FMF).

Methods. Forty-eight patients with FMF whose attacks are preceded by a prodromal period composed the study population. Clinical, demographic, and genetic characteristics of the study group were compared to those of a control group of 48 patients with FMF whose attacks begin without a premonitory phase. Patients of both groups were recruited consecutively, during their routine followup visit to the FMF clinic.

Results. A prodrome was found to be a common manifestation of FMF, experienced by about 50% of the patients. Overall, demographic, clinical, and genetic variables were comparable between study and control groups. In affected patients prodrome recurs in most attacks, lasts a mean of 20 hours, and manifests with either a mildly unpleasant sensation at the site of the forthcoming spell (discomfort prodrome), or with a spectrum of physical, emotional, and neuropsychological complaints (variant prodrome). The 2 types of prodromata are frequently accompanied by a host of constitutional symptoms.

Conclusions. A prodromal period heralding attacks is a newly defined and reliable FMF manifestation that reproducibly predicts attacks and may help prevent attacks and elucidate the pathogenesis of the disease. (J Rheumatol 2006;33:1089–92)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER PRODROME

Familial Mediterranean fever (FMF) is a systemic inflammatory disease, prevalent in populations originating in the Mediterranean basin. It is characterized by recurrent, short (1-4 days) episodes of fever and sterile serositis, associated with an increase in acute phase reactants[1-3]. AA amyloidosis, leading through proteinuria and nephrotic syndrome to end-stage renal failure, may develop in up to 60% of patients[1,4]. While daily colchicine therapy prevents attacks and amyloidosis in the majority of patients, frequent and severe attacks persist in an estimated 5%, even when receiving the maximal oral dose of 2 mg/day[3,5,6]. To date, management of this population remains inadequate[7,8].

The FMF gene, MEFV, is located on chromosome 16p13.3 and encodes pyrin, a 781 amino acid protein[2]. Pyrin is thought to be an inhibitor of inflammation, which loses its activity by structural changes caused by mutations. Although more than 40 MEFV mutations have been described thus far, only 3 are prevalent in our patient population: M694V, V726A, and E148Q[2,9-11]. Only 50-60% of patients with FMF from our population carry 2 MEFV mutations; the remainder have one or no mutations at all, suggesting a more complex pathogenesis than previously appreciated[11]. To better compare patients that manifest an extremely wide clinical spectrum, a severity score was developed, which allocates patients into mild, moderate, and severe disease categories[12].

FMF attacks are thought to be of sudden onset and to rapidly develop in an accelerating fashion, reaching a peak within 2-3 hours[1]. The prodrome of FMF has only been rarely described and in very little detail[13,14], and has never been investigated or characterized. We characterize it and discuss its importance in the diagnosis, treatment, and understanding of the pathogenesis of attack evolution.

MATERIALS AND METHODS

Study and control groups. We included patients with FMF who continued to experience attacks over the last 3 years whether or not they were receiving colchicine as preventive therapy. Our rationale was that patients who recently experienced attacks would be able to recount pre-attack manifestations in detail. All patients fulfilled the criteria for the diagnosis of FMF[15] and were recruited consecutively during their visit to the FMF clinic of the National Center for FMF at our medical center. The study was approved by the human experimentation review board of the Sheba Medical Center.

All patients underwent a clinical interview and examination. Severity of pain at the attack site was estimated using a 10 grade visual analog scale, and severity of the FMF was assessed using a severity score[12]. MEFV genetic analysis for the 3 most common mutations in our population (M694V, V726A, E148Q) was performed using acceptable techniques[16]. Patients who experienced a prodrome prior to FMF attack were included in the study group, whereas patients who did not experience a prodromal period were assigned to the control group. No adjustment was made for demographic or clinical variables, as these may potentially contribute to the actual experience of the prodrome and its various manifestations.

Prodromal period. The prodrome was defined by the presence of manifesta-

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tions that precede an FMF attack and predict its arrival. The patient's description of the content of the prodrome was documented *per se*, on condition that its manifestations reproducibly herald an attack and that similar manifestations are absent during attack-free periods. For the purpose of this study and to sharply separate the patient population into 2 groups (a study population with a definite prodrome vs a control population without premonitory symptoms) an arbitrary cut-off was set at 4 hours prior to the attack. Only patients with symptoms that begin at least 4 hours before definite attack manifestations were included in the study group. Patients with acute onset of attacks without preceding manifestations were included in the control group. Patients describing a prodromal period of less than 4 hours were excluded on the assumption that their symptoms may arise from initial attack manifestations rather than prodromal manifestations heralding an attack.

Validation of the prevalence of the prodrome. The rate of patients experiencing a prodromal period of at least 4 hours' duration was reevaluated with a sample of 81 consecutive patients with FMF arriving at our clinic for routine periodic assessment. This time, all FMF patients were included without regard to the duration of remission.

Data analysis. Patients in the study and control groups were compared for differences in demographic, clinical, and genetic variables using the chi-square test for categorical variables, and the 2-tailed Student's t test for comparison of continuous variables; p values of < 0.05 were considered statistically significant. The prodrome was characterized according to its manifestations, duration, and consistency with which it occurred prior to attacks.

RESULTS

Figure 1 shows the algorithm of the study design and indicates the number of patients eventually included or excluded in each stage. There were 96 patients who could be assigned to the study or control groups (48 in each). Of these, 28 patients were newly diagnosed, 11 were poor responders to colchicine, and 57 had been in remission since they were put on colchicine (less than 3 years). Demographic, clinical, genetic, and treatment analysis showed that the 2 populations were generally comparable (Table 1). Genetic analysis was performed in most patients. Although it was found that the spectrum and distribution of MEFV in both groups was similar, the frequency of unrecognized mutations was significantly higher in the control group (18 of 84 alleles vs 29 of 78 alleles, $p < 0.05$, not shown in Table 1).

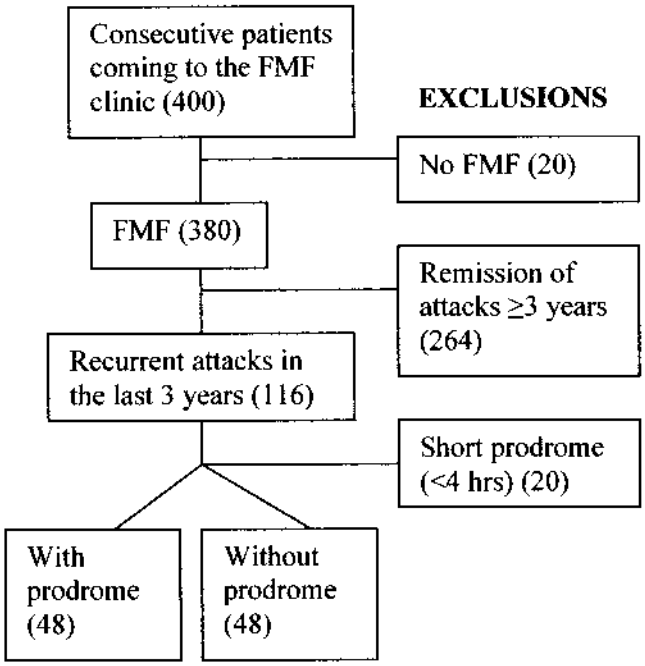

Figure 1. Algorithm of the study design, indicating the number of patients that were eventually included or excluded in each step of the recruitment procedure, as patients were assigned to the study or control groups.

Prodrome characteristics experienced by the study group are defined in Table 2. Patients could be split into 2 subgroups: those with a discomfort prodrome (about 70% of the patients), whose main manifestations were discomfort or very mild pain at the attack site; and those with a variant prodrome (about 30%), who experienced a variety of unique manifestations, none of which were localized at the site of the forthcoming attack. Of note, the prodrome, whether discomfort or

Table 1. Demographic, clinical, and genetic characteristics of patients with a prodrome. Differences between groups are statistically non-significant. Results are expressed as mean ± standard deviation, or as number (percentage).

	Study (prodrome) Group	Control Group
No. of patients	48	48
Male	27 (56)	25 (52)
Age, yrs	32 ± 13	30 ± 11
Age of onset, yrs	15 ± 13	16 ± 12
Age of diagnosis, yrs	23 ± 5	23 ± 13
Ethnic origin		
Ashkenazi	1 (2)	1 (2)
Iraqi	11 (23)	5 (10)
North-African	15 (31)	12 (25)
Other/mixed	21 (44)	30 (63)
Family history of FMF	29 (60)	34 (70)
Attack site		
Abdomen	43 (90)	44 (92)
Chest	30 (63)	27 (56)
Joint	22 (46)	21 (44)
Other (fever, skin, muscle)	17 (35)	23 (50)
Chronic manifestations	2 (4)	3 (6)
No. of attacks/yr (prior to colchicine therapy)	23 ± 18	27 ± 21
Severity score	7 ± 3	7 ± 3
Colchicine treatment*		
No. (%) assessed	35 (73)	33 (69)
Average dose, mg	1.4 (± 0.6)	1.6 (± 1.5)
Complete/partial response	29 (83)	28 (85)
Genotype**		
No. of patients	42	39
M694V/M694V	8 (19)	7 (18)
M694V/Other	24 (57)	14 (36)
V726A/V726A	3 (7)	3 (8)
V726A/other	2 (5)	6 (16)
E148Q/0	3 (7)	2 (5)
0/0	2 (5)	7 (18)

* Some patients were diagnosed with FMF on day of study entry or shortly before, therefore, their response to colchicine therapy could not be assessed. ** Genotype frequency is calculated as percentage of patients. The V726A/other genotype does not include V726A/M694V accounted for in the M694V/other category.

Table 2. Characterization of the prodrome in FMF in 48 patients with FMF. Discomfort prodrome denotes manifestations that include also mild pain at the attack site; variant prodrome denotes any manifestation excluding pain at the attack site. Constitutional symptoms are any or a combination of: malaise, weakness, fatigue, anorexia, nausea, vomiting, headache, generalized muscle or joint pain. Unique manifestations are any physical, emotional or psychological manifestation other than constitutional symptom or discomfort at the attack site.

	Discomfort Prodrome	Variant Prodrome
No. (%) of patients with the specific prodrome	34 (71)	14 (29)
Duration, h	17 ± 13	24 ± 20
Severity of pain, VAS 1–10	2 ± 2	—
Rate of attacks preceded by a prodrome, %	93 ± 16	88 ± 21
No. (%) with fever	6 (18)	3 (21)
No. (%) with constitutional symptoms during the prodrome	26 (76)	9 (64)
No. (%) with unique manifestations during the prodrome	22 (65)	10 (71)

VAS: visual analog scale for pain.

Table 3. Characterization of prodrome in patients with unique manifestations*.

Manifestation	Duration Prior to Attack, h	No. of Patients with Unique Manifestations	No. of Patients with Other Manifestations**
Anxiety or irritability	19 ± 15	10	9
Dizziness	18 ± 6	2	1
Chills without fever	12	1	1
Diarrhea	12	1	1
Constipation	12	2	1
Bulimia	48	1	0
Dyspnea without pain	12	2	1
Altered taste sensation	6	1	1
Burning of skin sensation	24	1	1
Sore throat	6	1	1
Back or low back pain	19 ± 13	10	7
Forearm pain	24	1	1
Leg heaviness/pain	12	2	1

* Includes all manifestations other than discomfort at the site of the forthcoming attack. ** Either discomfort or constitutional or both.

variant, preferentially preceded abdominal attacks (not shown): 60% of patients in the study group with abdominal attacks experienced prodrome, versus only 20% of patients with chest attacks and 14% of patients with joint attacks.

In patients experiencing a discomfort prodrome, the prodrome heralded the majority (93%) of their attacks. An attack would reliably follow the prodrome in almost 100% of the cases (not shown). The prodrome was lengthy, about 17 hours, during which time the patient typically experienced discomfort at the site of the impending attack. Pain or discomfort was usually mild, about 2 on a scale of 10, as compared to an average of 9 on the same pain scale, during an acute attack. The prodrome could be accompanied by a host of constitutional symptoms, including weakness, fatigue, malaise, myalgia, arthralgia, headache, nausea, and vomiting. It could also be linked to one or more of the unique manifestations characterizing the variant prodrome (Table 2). In contrast to an acute attack, the discomfort prodrome was only rarely accompanied by fever, and when fever developed it was usually of low grade (< 38°C).

Patients without pain at the impending attack site (variant prodrome) could experience one or more constitutional symptoms or have unique physical, emotional, and psychological phenomena (Table 3). These unique prodromal manifestations could also appear as the sole characteristic of the variant prodrome or be accompanied by constitutional symptoms (Table 2).

We note that a prodromal period prior to an FMF attack is an extremely common phenomenon. To determine the precise prevalence of a prodrome in FMF, another group comprising 81 consecutive patients with FMF was recruited during their routine clinic visit, and these patients were interviewed regarding the occurrence of a prodromal period. Slightly more than half of the patients (44/81 patients) were found to sustain a prodrome of more than 4 hour duration prior to their attacks.

DISCUSSION

Premonitory symptoms or a prodrome, a common phenomenon in FMF experienced by about 54% of patients, include discomfort at the impending attack site and various constitutional, emotional, and physical complaints. In affected patients, a prodrome heralds an attack in almost 100% of occurrences and can be considered a valid sign of impending attack. Thirty percent of patients with a prodrome did not describe discomfort at the impending attack site but rather a variety of constitutional, physical, and neuropsychological complaints including irritability, dizziness, increased appetite, and altered taste sensation (Table 3).

Differences in clinical manifestations, ethnic origin or genetic background, family history of FMF, or response to therapy between the study group and the control group were not significant (Table 1), suggesting that the prodrome is a common phenomenon not restricted to a specific patient population. Moreover, the study population was demographically, clinically, and genetically representative of the general FMF population, including the 6:4 male preponderance, the 10 year diagnostic delay, family history of FMF in about 60% of cases, and a preponderance of patients of Jewish non-Ashkenazi and mixed descent[1,3,17]. The percentage of colchicine non-responders, which was similar in the study and control patients (15%), is actually higher than that reported for the general FMF population (5%)[6] and reflects our inclusion criteria that favored non-responders who may recall pre-attack manifestations more vividly. The preferential inclusion of non-responders did not significantly affect the attack manifestations, in accordance with our previous study[6].

The prevalence of unknown alleles was higher in the control than in the study group (37% vs 21%, $p < 0.05$). As the

only exception in the 2 highly analogous populations, this difference could be fortuitous, or it may suggest that a prodrome is experienced by a patient population with a somewhat different genetic makeup. The relatively few patients with 2 mutated alleles in both the study and control groups is in line with reported data and serves to emphasize that FMF is still a disease preferentially diagnosed based on clinical criteria[11,16,18].

The experience of a prodrome may serve as a credible early marker of attack onset. As such, it allows prompt institution of preventive therapy. Indeed, administration of interferon-α (IFN-α) during the early phases of acute FMF attacks was found to shorten attack duration and result in a depressed inflammatory response in some patients, suggesting that in the early phase the attack may still revert to normal, subject to appropriate intervention[8]. It is plausible that the institution of IFN-α therapy during the prodrome will prove more efficacious in suppressing both clinical and laboratory signs of inflammation. Other modes of therapy, such as high dose colchicine, anti-tumor necrosis factor (TNF) (etanercept), and nonsteroidal antiinflammatory drugs (NSAID) administered during the prodrome may also prove beneficial.

Further understanding of the prodrome phenomenon may shed light on the pathogenesis of FMF. It has been shown that significant changes take place between acute attacks of FMF. For example, mononuclear cell content of TNF-α and interleukin (IL)-1 levels is lower during attacks than in remission[19,20], a finding attributed to exhaustion of the secreting cells due to over-excretion between attacks. Assessing cellular and serum cytokine levels during the prodrome period may clarify the early steps of the evolving inflammatory storm and help establish appropriate therapies.

Although most patients experience the prodrome at the site of impending attack, they clearly differentiate it from the attack because of its low severity, relatively limited focus, and their ability to undertake everyday activities; in contrast an acute attack will confine patients to bed. Arguably, the prodrome may not represent a separate entity but rather the initial manifestation of the attack. However, the observation that 50% of patients experience a prodrome argues in favor of regarding it as a separate entity, as does the fact that the patients themselves recognize a clear demarcation between the symptoms of the prodrome to those of the attack.

In summary, we describe in detail an overlooked phenomenon in FMF, a pre-attack prodrome, experienced by 50% of the patients up to 24 hours prior to an attack and characterized by discomfort at the site of impending attack and/or by various constitutional, physical, emotional, and psychological symptoms. Although based on a retrospective analysis, our findings appear to be firm and valid. The importance of recognizing the prodrome as a disease manifestation in FMF lies in the ability to institute specific preventive measures at its onset, as well as in the information it gives us about the early stages of the attack, from which the inflammatory pathogenesis of the disease may ultimately be construed.

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