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. AA amyloidosis, leading through proteinuria and nephrotic syndrome to end-stage renal failure, may develop in up to 60% of patients. 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. To date, management of this population remains inadequate.

The FMF gene, MEFV, is located on chromosome 16p13.3 and encodes pyrin, a 781 amino acid protein. 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. 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 pathogene-

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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).

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

![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.](image-url)
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.

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. 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, 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 inflammatory response in some patients, suggesting that in the early phase the attack may still revert to normal, subject to appropriate intervention. 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.

In summary, we describe in detail an overlooked phenomenon in FMF, a pre-attack prodrome, experienced by 50% of 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.