CONCISE REPORT

Acute phase response in familial Mediterranean fever

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Objective: To test the hypothesis that not all acute phase reactants respond in the same way during attacks of familial Mediterranean fever (FMF) and that there is a subclinical acute phase response (APR) in a proportion of patients during the interval between attacks.
Methods: Blood and urine samples were obtained from 49 patients with FMF during an attack and the attack-free period that followed, to test for erythrocyte sedimentation rate, C reactive protein (CRP), fibrinogen, white blood cell count, platelet count, factor VIII related antigen, haptoglobin, protein electrophoresis, ferritin, proteinuria, and haematuria. Control groups comprised 29 patients with juvenile idiopathic arthritis, 10 patients with various infectious diseases, and 19 healthy subjects.
Results: A marked APR was seen during the FMF attacks which was comparable with that obtained in the diseased control groups. CRP was the only acute phase protein that was raised during all attacks. Neither thrombocytosis nor an increase in ferritin levels (except one) was noted in any attack. Serum albumin levels remained unchanged. In two thirds of the patients with FMF a continuing APR was seen in between the attacks.
Conclusion: Platelet, ferritin, and albumin responses are not part of the significant APR seen during short lived attacks of FMF, and inflammation continues in about two thirds of the patients during an attack-free period.

The typical clinical course of familial Mediterranean fever (FMF) is that of exacerbations and remissions, and the increased acute phase response (APR) seen during these attacks usually returns to normal in attack-free periods.[1] However, we had the clinical impression that not all acute phase proteins (APPs) respond in the same way during FMF attacks, and, moreover, not all APPs return to normal levels in between attacks. To determine the characteristics of the APR during attack and attack-free periods of FMF, we studied a set of acute phase reactants in patients with FMF and controls.

METHODS

Patients

The study group comprised 49 consecutive patients who presented to Cerrahpasa Medical Faculty rheumatology outpatient clinic with a diagnosis of an FMF attack. Twenty nine patients with juvenile idiopathic arthritis (JIA), 10 inpatients with various infectious diseases, and 19 normal healthy subjects were studied as controls (table 1). Blood and urine samples were obtained from all the patients and controls to test for the APR. This procedure was repeated at two different times in the FMF group: (*a*) within the first 72 hours after the onset and (*b*) at least two weeks after the end of the attack (mean (SD) 21 (5.4) days (range 14–30)). The erythrocyte sedimentation rate (ESR), C reactive protein (CRP), fibrinogen, haptoglobin, protein electrophoresis, white blood cell (WBC) count, platelet count, factor VIII related antigen (FVIIIRAg), and albumin were tested in the initial 24 patients with FMF during and after an attack, 16 with JIA, 10 with infectious diseases, and 10 normal controls. Because ferritin was available later in the course of the study, only ferritin, ESR, CRP, and platelet count were examined in the subsequent 25 patients with FMF during and after an attack, 13 with JIA, and nine normal controls.

Table 1 Age and sex distribution of patients with FMF and controls

Groups	No	F/M	Mean (SD) age (years)
FMF	49	23/26	22 (8)
Positive control	39	17/22	18 (7)
JIA	29	14/15	17 (5)
Infection	10	3/7	22 (9)
Healthy control	19	5/14	21 (2)

Thirty nine patients with FMF were receiving regular colchicine treatment, and 10 were diagnosed for the first time. Twenty six of the patients who were using colchicine were not able to take the drug at the time of the study because colchicine was not available in Turkey for a period of time. The type of attack was abdominal in 46, articular in two, and protracted febrile myalgia in one.

The inclusion criteria for JIA were active synovitis in more than two joints and an ESR of over 20 mm/1st h. Of the 29 patients with JIA, 13 had systemic, 13 polyarticular, and three oligoarticular onset disease. Among the 10 patients with infectious diseases, five had tuberculosis, one each had septicaemia, pneumonia, emphysema, endocarditis, and cellulitis.

Acute phase reactants

The ESR was determined by the Westergren method; CRP by the turbidimetric method (Behring, Germany); fibrinogen by the clotting time method (Biopool, USA); haptoglobin by the single radial immunodiffusion method (Kallestad, USA); FVIIIRAg by the enzyme linked immunosorbent assay (ELISA) method (Malakit, Belgium); ferritin by chemiluminometric (sandwich) immunoassay (Ciba Corning ACS Ferritin assay kit); and protein electrophoresis by the cellulose acetate method. The salicylsulphonic acid method was used to test for urine protein. Trace and higher levels were accepted as proteinuria. Haematuria was defined as five or more erythrocytes per high power field.

Statistical analysis

Values are expressed as the mean (SD). Statistical evaluations were performed by Pearson's correlation coefficient (*r* values), Wilcoxon test, and the Mann-Whitney U test.

Abbreviations: APPs, acute phase proteins; APR, acute phase response; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; FVIIIRAg, factor VIII related antigen; IL, interleukin; JIA, juvenile idiopathic arthritis; TNFα, tumour necrosis factor α; WBC, white blood cells

Table 2 Levels of acute phase response during the attack and attack-free periods in patients with FMF in comparison with those in the control groups (mean (SD))

APR and urine analysis	FMF, during attack (n=49)	FMF, attack-free (n=49)	Positive controls (n=39)	Healthy controls (n=19)
ESR (>20 mm/1st h)	52 (27)[a] (43/49)+ (88)++	20 (12) (22/42) (52)	75 (32)[g] (39/39) (100)	5 (0. 03) (0/19)
CRP (>6 mg/l)	139 (110)[a] (49/49) (100)	22.1 (38) (15/44) (34)	118 (100) (36/39) (92)	5 (0.3) (1/19) (5)
Fibrinogen (>4 g/l)	4.13 (1.11)[b] (15/24) (63)	2.82 (0.83) (1/24) (4)	3.72 (1.37) (8/26) (31)	2.50 (0.79) (0/10)
Haptoglobin (>2.70 g/l)	2.67 (0.81)[c] (10/24) (42)	1.74 (0.85) (3/24) (13)	2.92 (1.01) (17/26) (65)	1.43 (0.68) (0/10)
WBC (>10×10⁹/l)	10.6 (3.9)[c] (12/24) (50)	7.5 (2.3) (3/24) (13)	10.3 (5.4) (12/26) (46)	7.3 (1.3) (0/10)
Platelets (>400×10⁹/l)	255.8 (62.1) (0/45)	246.5 (64.9) (0/42)	395.7 (163.2)[i] (17/39) (44)	248.0 (59.1) (0/19)
Ferritin (ng/ml)¶	127 (113)[d] (1/25) (4)	72 (52) (0/25)	1159 (1775)[h] (8/13) (62)	80 (59) (0/9)
FVIIIRAg (>200%)	147 (130)[e] (3/17) (18)	61 (43) (0/17)	197 (212) (7/21) (33)	78 (43) (0/7)
Protein electrophoresis*				
α_1 Globulin (g/l)	1.8 (0.7)[f]	1.3 (0.6)	1.7 (0.7) (1/26) (4)	1.3 (0.4)
α_2 Globulin (g/l)	9.6 (2)[b] (4/24) (17)	7.4 (1) (0/24)	8.1 (2.1)[j] (2/26) (8)	6 (0.9)
β Globulin (g/l)	3.7 (3) (3/24) (13)	8.6 (1) (1/24) (4)	8.1 (2.5) (2/26) (8)	8.3 (1.3)
γ Globulin (g/l)	12.1 (3) (2/24) (8)	12.2 (3) (2/24) (8)	14.1 (6.2) (6/26) (23)	9.8 (2.5)
Albumin (<35 g/l)	45 (6) (1/23) (4)	46 (6) (2/22) (9)	34 (9)[k] (10/26) (38)	52 (4) (0/10)
Proteinuria ⩾ trace	10/24 (42)	1/24 (4)	9/26 (35)	1/10 (10)
Haematuria ⩾5RBC	3/24 (13)	0/24	5/26 (19)	0/10

[a]p<0.0001; [b]p<0.001; [c]p<0.0001; [d]p<0.002; [e]p<0.01; [f]p<0.05 attack *v* attack-free periods by Wilcoxon test. [g]p<0.0005; [h]p<0.03; [i]p<0.002; [j]p<0.02; [k]p<0.001 positive control group *v* attack by Mann-Whitney U test. After the value (SD) the next parentheses+ give the number, of patients with levels above normal/to the number of patients tested; ++ the final parentheses give the percentage of patients above normal. For albumin, it is the number of patients below normal levels. *The number of patients undergoing protein electrophoresis was 24. Parentheses refer to percentage of patients with levels above normal. ¶Normal values for ferritin: 10–292 ng/ml for women; 22–322 ng/ml for men).

RESULTS

APR during FMF attacks

Table 2 (first column) gives the mean values of the APPs noted during FMF attacks. CRP was the only APP that was increased in all attacks. It was followed in frequency by ESR (88%), fibrinogen (63%), and WBC (50%). Albumin did not behave as a negative acute phase reactant in the FMF attacks compared with the diseased controls.

The two most striking findings were the normal platelet counts noted in every attack and the normal ferritin response in all attacks but one. The only patient with a raised ferritin level had an attack of protracted febrile myalgia. Thrombocytosis was noted in 13/29 patients with JIA and 4/10 with infectious diseases. Ferritin levels were increased in 8/13 (62%) patients with JIA, compared with 1/25 FMF attacks.

APR in an attack-free period

There was a significant fall in the levels of APPs after the attack was over. However, the level of at least one APP was still above normal in 15 (63%), and two or more APPs were above normal in six cases (25%) among the initial 24 patients with FMF. Values above the normal were detected for CRP in 34% and for ESR in 52%. However, the raised fibrinogen levels returned to normal during the attack-free period, except in one patient.

Urine analysis

During attacks 10 patients had proteinuria and three haematuria. All were transient and disappeared after the attack was over except in one patient who had amyloidosis secondary to FMF. CRP was significantly higher in patients who had proteinuria ($p<0.03$).

Colchicine effect upon acute phase response

The only significant difference between the 13 patients who were receiving regular colchicine and 36 patients who were either currently not taking the drug (n=26) or diagnosed for the first time (n=10) was the lower CRP response during attacks seen in the first group (74 (49) *v* 164 (117) mg/l; $p<0.006$).

DISCUSSION

As expected, the APR during FMF attacks was compatible with that found in other inflammatory diseases like JIA and infections. However, not all APPs increased concomitantly and only CRP was raised in all attacks.

There were several interesting observations. Thus normal platelet counts were noted during acute attacks, whereas thrombocytosis was noted in the inflammatory control groups. The relation between synovitis and thrombocytosis has been well described. Thrombocytosis has been correlated with interleukin 6 (IL6) levels and joint involvement in JIA,[2] and with disease activity in rheumatoid arthritis.[3] In this study almost all the attacks were abdominal, except two which were short lived articular attacks and protracted febrile myalgia in one. Therefore the possibility that increased platelet counts may be found in protracted FMF arthritis still exists.

Ferritin behaves as an acute phase reactant in various disease states like rheumatoid arthritis,[4] both adult and juvenile Still's disease,[5] infections,[6] and systemic lupus erythematosus.[7] The slight increases seen in ferritin levels during FMF attacks were within normal limits in all except one patient with protracted febrile myalgia.

It has been reported that the synthesis of ferritin by hepatocytes is induced by IL1, IL6, or tumour necrosis factor α (TNFα).[8 9] It can be speculated that this blunted ferritin response may be due to either insufficient synthesis of IL1 and TNFα and/or increased synthesis of sTNFr p55, sTNFr p75 in patients with FMF.[10] This finding may help in the differential diagnosis of FMF attacks.

Serum albumin, a well known negative acute phase reactant,[11] remained normal during the FMF attacks in contrast with the increase seen in diseased controls. This is probably because the duration of intense inflammation in FMF is limited to the brief periods of the attacks.

The change in the magnitude of the APR between attack and attack-free period has been used as a means of diagnosis of FMF for some time.[12] However, some early reports noted that in some patients with FMF, the ESR remained high during intervals between attacks.[13] The possibility of continuing subclinical inflammation in at least 25% of patients during attack-free periods has been previously discussed.[14] Splenomegaly was also present during attack-free intervals in about 25% of the patients without amyloidosis, again implying an APR.[15] Similar observations have been made more recently by other groups.[16] Interestingly, the first degree relatives of the patients with FMF showed evidence of an APR,[17] suggesting a genetic component.

In conclusion, this study shows that lowered serum albumin levels and the augmented platelet and ferritin responses are not part of the significant APR seen during short lived attacks of FMF, and there is a continuing inflammation

in about two thirds of the patients when they are clinically well. The persistence of the APR in the attack-free periods in FMF provides a strong argument for uninterrupted lifelong colchicine use in this disease.

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