Early blunted cortisol response to insulin induced hypoglycaemia in familial Mediterranian fever

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ABSTRACT

Objective. *To study cortisol, adrenocorticotropic hormone and C-reactive protein responses to specific stimuli in familial Mediterranean fever (FMF).*

Methods. *For the purpose of measuring cortisol, ACTH, and CRP responses to insulin induced hypoglycaemia during attack-free periods, 14 FMF patients, 11 patients with ankylosing spondylitis or Behçet's disease as disease controls (DC), and a further 10 healthy control subjects (HC) were involved in this study. None of the subjects had ever received corticosteroids before this study. Cortisol and ACTH levels were measured by chemiluminescence enzyme immunoassay.*

Results. *No attack was observed among FMF patients during the test. No significant difference in the mean cortisol values after insulin induced hypoglycaemia was observed between the groups involved at any stage of the test. The integral cortisol response to hypoglycaemia expressed as the AUC (0-90 min) was found not to differ among the study groups (1827 ± 115.6 in FMF; 2196 ± 205.4 in DC, p = 0.12; 1771 ± 98.4 in HC, p = 0.9). The delta response of cortisol to insulin induced hypoglycaemia was found to be statistically lower (-4 ± 0.8 mg/dl vs. -1.9 ± 0.7 g/ dl; p < 0.03) only for the 0 to 30 min interval in patients with FMF compared to HC respectively. Similar results, though of no statistical significance, were also found for the 0 to 45 min interval (1.17 ± 2.2 g/dl in FMF patients vs. 3.3 ± 2 g/dl in HC; p = 0.6). The mean basal CRP level of patients with FMF was remarkably higher than that in HC. Although the mean CRP level at 90 min for FMF cases with cortisol levels under 12 g/dl at 30 min was found to be higher than those with cortisol levels over 12 g/dl at 30 min, no significant difference was observed.*

Conclusion. *An early blunted cortisol response observed in a stressful situation in FMF patients may well account for the curious relationship between stress and an inflammatory reaction and/or attack. Furthermore, the fact that the CRP level was relatively higher in FMF patients with lower cortisol levels might also highlight the importance of endogen cortisol in the inflammatory feature of this disease.*

Introduction

Familial Mediterranean fever (FMF) is a disease of unknown etiology characterised by recurrent polyserositis attacks (peritonitis, pleuritis, or synovitis) with fever. It is widely accepted that physical and emotional stress may trigger attacks of FMF (1, 2) while rest periods and vacations free from stress may provide temporary relief (3). It is not known exactly how stress precipitates attacks. Activation of the hypothalamo-pituitary-adrenal (HPA) axis is a part of the normal physiological response to both inflammatory and behavioral stress (4). The principal effectors of the generalized stress response include the corticotropin-releasing hormone (CRH) and locus coeruleus-norepinephrine (LC-NE) systems in the central nervous system. For these systems, activation releases catecholamines from nerves as well as from the adrenal medulla, which ultimately leads to the secretion of corticotropin from the pituitary. The corticotropin, in turn, mediates the release of cortisol from the adrenal cortex (5).

It was suggested that FMF might be related to abnormal catecholamine metabolism because an attack could be provoked by metaraminol infusion (6). How cortisol responds to stress in patients with FMF remains to be elucidated. Taking this into account, we investigated cortisol, ACTH, and CRP responses to insulin induced hypoglycaemia in patients with FMF in attack-free periods.

Table I. Laboratory characteristics of patients with FMF and control patients (mean ± SE) during the test.

	(min)	FMF	DC	HC
CRP	0	0.47 ± 0.11[a]	0.53 ± 0.17	0.17 ± 0.09
(N < 0.6 mg/dl)	90	0.69 ± 0.13[b]	0.84 ± 0.38	0.29 ± 0.14
Cortisol	-10	20.8 ± 1.6	23.4 ± 2.7	18.9 ± 1.1
(N = 5-25 mg/dl)	0	18 ± 1.8	21.5 ± 2.4[c]	15.9 ± 0.8
	30	13.8 ± 1.3	18 ± 2	13.9 ± 1.1
	45	19 ± 1.6	25.6 ± 3.1	19.2 ± 1.75
	60	24 ± 2	27.9 ± 2.9	23.7 ± 2
	90	26 ± 2.4	28.4 ± 3.2	25.7 ± 2.2
ACTH	0	26.7 ± 4.1[d]	15.7 ± 1.7	16 ± 1.3
(N = 7-30 pg/dl)	90	50.5 ± 5.9	59.07 ±17.9	48.7 ± 7.3
Glucose	-10	85.6 ± 2.5	85.7 ± 2.7	80 ± 1.9
(N = 65-110 mg/dl)	0	87 ± 2.1	87.7 ± 2.6	80.6 ± 2.3
	30	34.9 ± 4.9	31 ± 4.9	23 ± 2
	45	41.7 ± 3.7	45 ± 3.7	39 ± 2.7
	60	57.8 ± 3.4	51 ± 4.2	49 ± 4.8
	90	73.8 ± 7.9	66.8 ± 7.7	58.9 ± 3.8

[a]p < 0.04, FMF vs. HC; [b]p = 0.07, FMF vs. HC; [c]p < 0.04, DC vs. HC; [d]p < 0.02, FMF vs. DC; p < 0.03, FMF vs. HC (Kruskal –Wallis test).
N: normal value; FMF: familial Mediterranean fever; HC: healthy control; DC: disease control.

Patients and methods

Patients

Fourteen patients with FMF (10 female, 4 male, median age 21 yrs, range 17-28), who were being followed in the rheumatology outpatient clinics of the Medical Faculty of Osmangazi University, voluntarily took part in our study. These patients underwent a series of tests during the remission period of the disease. All the patients had been using colchicine in doses of 1 - 1.5 mg/day, with varying periods of usage from 3 months to 7 years. No amyloidosis was observed in the involved study groups. Four patients with Behçet's disease and 7 patients with ankylosing spondylitis (8 female, 3 male, median age 22 yrs, range 16-28) were studied as the disease controls (DC). Inclusion criteria included: the absence of active synovitis or oral and genital ulcerations, and a erythrocyte sedimentation rate (ESR) < 20 mm/h. Five patients were using sulfasalazine and indomethacine, 2 only indomethacine, and 4 colchicine. These patients had at no time in the past been administered corticosteroid. Ten healthy controls (8 female, 2 male, median age 23 yrs, range 22-28) were also studied.

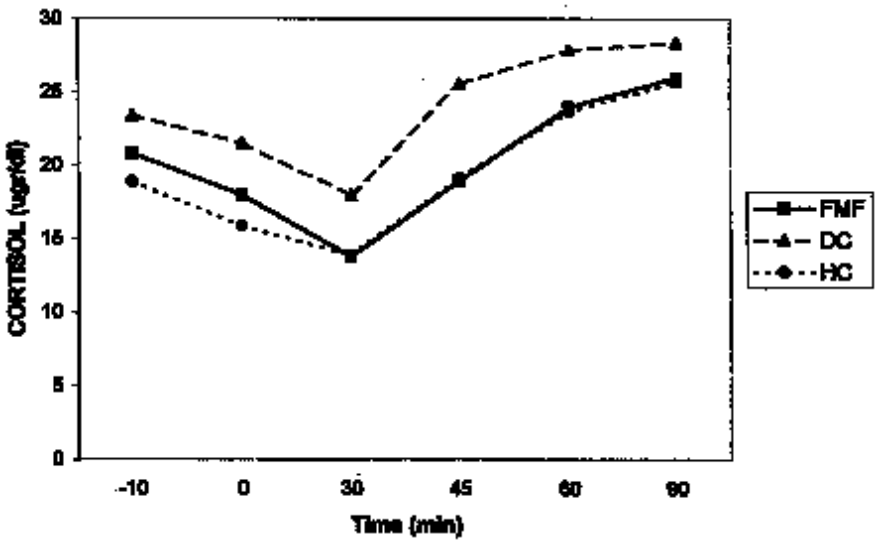

Fig. 1. Cortisol response to insulin induced hypoglycaemia in patients with FMF, DC and HC. FMF: familial Mediterranean fever; HC: healthy controls; DC: disease controls.

Insulin hypoglycaemia test

Cortisol secretion was assessed in response to insulin induced hypoglycaemia by giving crystalline insulin 0.15 units/kg body weight intravenously as a bolus. Samples for cortisol and glucose were taken at -10, 0, 30,45, 60, and 90 min after stimulation. We performed the test at 9 am under standard fasting and bed rest conditions. The test was deemed valid if the glucose level decreased to less than 40 mg/dl, associated with hypoglycaemia symptoms. Cortisol was measured by chemiluminescence enzyme immunoassay (Immulite, Cortisol, Diagnostic Products Corporation, Los Angeles, CA).

ACTH determination

Samples for ACTH were obtained at 0 and 90 min after stimulation. Blood samples for ACTH were drawn into tubes with EDTA and brought to the laboratory and frozen without delay. ACTH was measured by chemiluminescence assay (Immulite, ACTH,Diagnostic Products Corporation, Los Angeles, CA).

C-reactive protein (CRP)

CRP levels were determined at 0 and 90 min. The CRP level was determined by rate nephelometry (Beckman,Image Immunochemistry System).

Statistical analysis

The Kruskal Wallis or Mann Whitney-U test was used to compare the study groups. The cortisol response to hypo-

Table II. Interval-specific delta cortisol responses to insulin induced hypoglycaemia (mean ± SE).

	minutes						
	0-30	0-45	0-60	0-90	30-45	30-60	30-90
FMF	-4.3 ± 0.33	1.1 ± 0.43	5.4 ± 0.54	8.2 ± 0.65	5.5 ± 0.31	10.5 ± 0.39	12.6 ± 0.47
HC	-1.9 ± 0.19	3.3 ± 0.30	7.8 ± 0.34	8.9 ± 0.38	5.29 ± 0.39	9.82 ± 0.47	10.7 ± 0.52
DC	-3.2 ± 0.94	4.0 ± 1.	6.38 ± 1.36	6.85 ± 1.5	7.3 ± 1.21	9.6 ± 1.13	10 ± 1.25
P*	0.03	0.63	0.51	0.83	0.93	0.95	0.63

*Difference between FMF delta vs HC delta (Kruskal-Wallis test).
FMF: familial Mediterranean fever; HC: healthy control; DC: disease control.

glycaemia was integrated over time and expressed as area under the response curve (AUC) from 0 to 90 min as mentioned before by Matthews *et al.* (7). Results were expressed as mean ± SE. P values below 0.05 were considered statistically significant.

Results

Insulin induced hypoglycaemia (Table I)

The lowest glucose levels were determined at 30 min in all groups (34.9 ± 4.9 mg/dl in FMF patients; 31 ± 4.9 mg/dl in DC; 23 ± 2 mg/dl in HC). Although basal serum glucose levels were higher in FMF and DC than those in HC, they were of no significant difference.

ACTH response (Table I)

The basal ACTH levels in patients with FMF were significantly higher than DC and HC (26.7 ± 4.1 pg/dl in FMF patients versus 15.7 ± 1.7 pg/dl in DC and 16 ± 1.3 pg/dl in HC; $p < 0.02$, $p < 0.03$ respectively). The levels of ACTH at 90 min compared to basal ACTH levels were significantly higher in each of the three groups. There was no difference between the groups at 90 min (50.5 ± 5.9 pg/ml in FMF group vs. 59.07 ± 17.9 pg/ml in DC and vs. 48.7 ± 7.3 pg/ml in HC; $p = 0.3$, $p = 0.7$ respectively).

Cortisol response (Table I, Fig. 1)

Although the basal serum levels of cortisol in FMF and DC were higher than in HC, a significant difference was found only between DC and HC (21.5 ± 2.4 g/dl in DC vs. 15.9 ± 0.89 g/dl in HC; $p < 0.04$). The lowest cortisol levels were determined at 30 min in the groups; therefore, the mean increment levels between the basal value and 30 min value were negative in the groups (Table II). The peak cortisol levels after hypoglycaemia were observed at 90 min in the groups. No significant difference in the mean cortisol values after insulin induced hypoglycaemia was determined between the groups involved at any stage of the test The cortisol responses were analyzed by the incremental elevation above the baseline (Table II). The delta response of cortisol to insulin induced hypoglycaemia was found to be statistically lower (-4 ± 0.8 g/dl vs. -1.9 ± 0.7 g/dl; $p < 0.03$) only for the 0 to 30 min interval in patients with FMF compared to HC. Similar results, though of no statistical significance, were also found for the 0 to 45 min interval (1.17 ± 2.2 g/dl in FMF patients vs. 3.3 ± 2 g/dl in HC; $p = 0.63$). The blunted delta cortisol response at 30 min disappeared after 45 min. No significant difference was observed between FMF and DC at any time during the test.

The integral cortisol response to hypoglycaemia expressed as the AUC (0-90 min) differed in none of the groups (1827 ± 115.6 in FMF; 2196 ± 205.4 in DC, $p = 0.1$; 1771± 98.4 in HC, $p = 0.9$).

C-reactive protein (Table I)

The basal mean CRP level in patients with FMF did not differ from those in DC (0.47 ± 0.11 mg/dl in FMF vs. 0.53 ± 0.17 mg/dl in DC; $p = 0.8$), but it was higher than in HC (0.17 ± 0.09 mg/dl in HC; $p = 0.01$). The CRP levels at 90 min in FMF patients were not higher than those of HC (0.69 ± 0.13 mg/dl in FMF vs. 0.29 ± 0.14 mg/dl in HC; $p = 0.07$). Likewise, there was not a significant difference between FMF and DC at 90 min (0.84 ± 0.38 in DC; $p = 0.5$). The basal CRP levels in patients with DC were higher than in HC ($p = 0.03$). However, this difference did not appear at 90 min ($p = 0.06$).

Before setting about doing this study, we argued that if the cortisol response to insulin induced hypoglycaemia was blunt, then the CRP levels at 90 min in patients with lower cortisol levels would most probably be higher. For this reason, patients with cortisol levels below 12 g/dl (group I) and above 12 g/dl

Table III. CRP levels at 90 min in the status of cortisol level below 12 mg/dl and above 12 mg/dl at 30 min in groups.

	Cortisol levels (30 min)				
	< 12 g/dl (Group I)		> 12 g/dl (Group II)		p*
FMF	0.93 ± 0.1	(7)	0.43 ± 0.1	(7)	0.94
DC	4	(1)	0.49 ± 0.16	(10)	0.11
HC	0.16 ± 0.12	(3)	0.34 ± 0.2	(7)	0.88

*Group I vs. Group II (Mann Whitney-u test)
Values between parentheses refer to the number of patients.
FMF: familial Mediterranean fever; HC: healthy controls; DC: disease controls.

(group II) at 30 min were compared with each other for their CRP levels at 90 min (Table III). The choice of 12 g/dl as the threshold level was arbitrary, thinking that this level would correspond to the nearly half of the maximum level in healthy people. Although the mean CRP level at 90 min in group I was found to be higher than in group II, no significant difference was observed within or between the groups (Table III).

Discussion

The HPA axis and adrenomedullary (sympathetic) systems are peripheral limbs of the stress system. It is widely accepted that physical and emotional stress may trigger attacks of FMF (1, 2). There exist some studies on catecholamine metabolism in patients with FMF (6). To the best of our knowledge, no HPA axis studies have been carried out in FMF patients to date. For this reason, we investigated cortisol, ACTH and CRP responses to insulin induced hypoglycaemia (IIH), which is a rational test of the HPA response to stress (8), in patients with FMF. By the way, it should be noted that CRH and ACTH stimulation tests are the other alternatives for HPA axis evaluation (8). Although the baseline ACTH levels were found to be significantly higher in FMF than in DC and HC, baseline serum cortisol levels were not higher in FMF compared to DC and HC. No significant difference in cortisol was observed between the groups during the test. Nevertheless, interval-specific delta analysis revealed a lower cortisol response to IIH in FMF patients when compared to HC, which was significant for the 0 to 30 min interval of hypoglycaemia stimulus. These results suggest that, despite increased basal levels of ACTH in FMF, the early cortisol response to hypoglycaemia stimulation is deficient. Regarding this, we may postulate the existence of some degree of HPA axis dysfunction in the FMF patients.

The effects of glucocorticoids include inhibiting production and release of cytokines, such as interleukin-1, interleukin-6 and tumor necrosis factor alpha (9). Stress-induced physiologic concentrations of glucocorticoids suppress neutrophil activation (10). The primary role of glucocorticoids in a stress state is to restrain or counter-regulate behavioral mechanisms, as well as many of the peripheral adaptive mechanisms of the stress response, including the inflammatory and immune responses that, if left unchecked, may produce disease.

Endocrine dysfunction involving the HPA axis might contribute to the development or the persistence of inflammation (11, 12). A dysfunction of the HPA axis in some chronic inflammatory diseases, such as rheumatoid arthritis (RA) and Sjögren's syndrome, has been reported, as well as having been a subject of discussion for polymyalgia rheumatica (13-15). Recent studies of patients with RA have shown that overall activity of the HPA axis remains inappropriately normal and is apparently not sufficient to inhibit ongoing inflammation, at least in early untreated patients (16). In addition, high basal ACTH levels, without the presence of expected hypercortisolemia, have been observed in patients with active RA (17). Research reveals that neuroendocrine and immune mechanisms mediate the inter-relations between stress-inducing factors and rtheumatic disease-related outcomes (18).

FMF is also a chronic inflammatory disease, considering the fact that there is a subclinical inflammation even between attacks in some FMF patients (19). The well-recognized association of FMF with chronic vasculitis also suggests a persisting inflammation in some FMF patients (20). Furthermore, the first degree relatives of FMF patients, who are free of this clinical disease, have also shown evidence of an acute phase response (21).

Although we did not observe any attacks during the test in our patients using colchicine regularly, patients with cortisol levels below 12 g/dl at 30 min showed higher CRP levels at 90 min than those with above 12 g/dl at 30 min, which was not of a statistical significance. This may well account for the importance of the endogen cortisol response to an acute phase response in a stressful condition.

The basal CRP levels were significantly higher in FMF in comparison with those in DC, but this significance disappeared at 90 min. We therefore believe that if a serial measurement had been undertaken over a longer period of time, the CRP levels might well have reached a marked level in FMF in comparison with DC because, as is known, a rise in CRP levels generally appears only after 4 to 6 hours following the inflammatory stimuli (22).

These results raise the question as to whether the administration of glucocorticoids at an early stage of an attack could prevent the progression of the attack. Many contradictory studies exist regarding the influence of glucocorticoids on FMF. Some French (23) and Israelis (24) have reported no benefit from steroid therapy. Contradictory to these studies,Sieagal suggested (3) that if the steroid is administered promptly, and in an adequate dosage, it can control acute attacks, but if the drug is discontinued too soon, attacks can recur at much shorter intervals, or in greater intensity, the total effect being an aggravation of the course of the disease. This was explained by the post-treatment inhibition of endogenous pituitary-adrenal hormonal activity, which results in lessened control of the attacks (3).

Matzner *et al.* have reported the C5a inhibitor to be deficient in peritoneal fluids obtained from FMF patients (25), as a result of which the uninhibited C5a activity leads to the influx of neutrophils into serosal membranes, with the ultimate result being an inflammatory reaction and/or attack (26). Another speculation made is that FMF mutations might contribute to the downregulation of granulocyte-mediated inflammation, either by downregulating inflammatory mediators, or adhesion molecules, or by upregulating anti-inflammatory mediators such as the C5a inhibitor (2).

Assuming from the fact that steroids might play a part in the inhibition of C5a production (27,28), we can speculate that, aside from MEFV gene mutations and a deficiency of the chemotactic inhibitor, an early blunted cortisol response to a stressful situation might well contribute to a failure to prevent

the development of a full-blown inflammatory reaction and/or attacks. Relying on our results, we suggest that long-term low dose corticosteroids combined with colchicine may prove beneficial for colchicine-resistant FMF patients. We also suggest that this should be supported by further studies into this subject.

We did not deal with the status of the LC-norepinephrine system in patients with FMF in this study. Therefore, we believe that further studies featuring a larger number of patients are required in order to assess the LC-norepinephrine system, together with the HPA axis, and to point out the stress relationship of this disease.

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