Low Serum Levels of DHEAS in Untreated Polymyalgia Rheumatica/Giant Cell Arteritis

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ABSTRACT. ***Objective.*** To address a controversy regarding the existence of a relative adrenal hypofunction in patients with untreated polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) we evaluated baseline serum levels of ACTH, cortisol, and DHEAS in a cohort of patients with recent onset PMR/GCA not previously treated with glucocorticoids, in comparison with healthy controls. Possible correlations between baseline DHEAS levels and laboratory measures of disease activity were also explored.

Methods. Basal serum levels of these hormones were prospectively investigated in 25 patients with active untreated disease and compared with those of 25 age- and sex-matched control subjects.

Results. Of the 25 patients, 19 had isolated PMR and 6 had biopsy-proven GCA + PMR. Basal levels of cortisol and ACTH in PMR/GCA patients did not differ from control subjects; in relation to inflammatory status, lower than expected basal production of cortisol was observed in active untreated PMR/GCA. Baseline serum DHEAS levels were significantly lower in all patients compared with controls. In these patients, a significant correlation was found between baseline DHEAS values and laboratory measures of disease activity. The percentage of DHEAS reduction and the severity of inflammatory response were higher in women than in men.

Conclusion. Patients with PMR/GCA with new-onset active disease before steroid treatment have inappropriately normal cortisol levels regarding the ongoing inflammation, and significantly lower levels of DHEAS compared to the age- and sex-matched healthy control subjects. These data support the existence of a relative adrenal hypofunction in PMR and GCA. (First Release June 15 2006; J Rheumatol 2006;33:1293–8)

Key Indexing Terms:
POLYMYALGIA RHEUMATICA GIANT CELL (TEMPORAL) ARTERITIS
ACTH CORTISOL DEHYDROEPIANDROSTERONE SULFATE INFLAMMATION

Temporal arteritis, or giant-cell arteritis (GCA), and polymyalgia rheumatica (PMR) are 2 closely related conditions that seem to represent different clinical expressions of the same underlying vasculitic disorder[1]. Corticosteroids are the drugs of choice for treating both these diseases because they rapidly relieve symptoms and prevent blindness and other ischemic complications.

One of the most striking features of these conditions is that they develop almost exclusively in older people: rarely occurring before age 50 years, their incidence rises steadily thereafter. Despite this close association with age, the pathogenic mechanisms to explain this age-related predisposition are unknown. The natural decline in production of androgens, especially dehydroepiandrosterone sulfate (DHEAS), during the process of aging[2] may represent such a factor. Indeed, several studies have documented the existence of a relative adrenal hypofunction in patients with untreated PMR, as evidenced by the presence of low serum levels of DHEAS and a lower than expected basal production of cortisol in relation to the ongoing inflammation[3-8]. Since DHEAS has a well documented immunomodulatory role in humans[9-12], this observation has suggested a possible link between endocrinosenescence and immunosenescence in the pathogenesis of PMR. However, the most recent study to explore the hypothalamic-pituitary-adrenocortical (HPA) axis function in PMR/GCA did not confirm these or other data relative to adrenal hypofunction, as no differences were found in serum DHEAS levels between patients with PMR/GCA and healthy controls[13]. Results of this study bring into question the proposed role for HPA axis impairment in the pathogenesis of this disease.

In view of these contradictory observations, we conducted a prospective study to evaluate baseline serum levels of ACTH, cortisol, and DHEAS in patients with recent onset PMR/GCA not previously treated with glucocorticoids in

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comparison with age- and sex-matched healthy controls. Possible correlations between baseline DHEAS levels and laboratory measures of disease activity were also explored.

MATERIALS AND METHODS

Twenty-five consecutive male and female patients with PMR/GCA with new-onset active disease before steroid treatment and 25 age- and sex-matched control subjects entered the study. All patients were clinically evaluated by a rheumatologist; PMR was diagnosed based on criteria proposed by Healey, *et al*[14], and GCA was diagnosed on the basis of positive temporal artery biopsy that shows interruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall, with or without giant cells[15]. As controls, 25 patients with osteoarthritis attending our outpatient clinic were selected after giving informed consent. All were healthy according to accurate clinical investigations and to hematologic and biochemical characteristics, and none had a history of neoplasia, infection, or autoimmune disease. Patients and controls were not taking hormone replacement therapy.

The main demographic and routine laboratory data of the study cohort are summarized in Table 1. Nineteen patients had isolated PMR and the remaining 6 patients had biopsy-proven GCA + PMR; the mean disease duration at the time of the first visit was 2.7 ± 2.5 months. Patients and controls did not differ in age or sex but, as expected, patients with active untreated PMR/GCA had a significant increase in those variables that reflect the severity of the inflammatory response.

All patients and controls had fasting blood samples taken between 8:00 AM and 10:00 AM at the time of clinical assessments and stored at –80°C. Serum levels of ACTH and DHEAS were quantified by commercially available specific direct radioimmunoassays, and serum levels of cortisol were assayed by chemiluminescence assay. According to the manufacturer's data (Diagnostic Products Corp., Los Angeles, CA, USA) intra-assay and interassay coefficients of variation were below 10% in each test.

Statistical analysis. Continuous data were described as mean ± standard deviation and categorical variables as percentages. Comparisons were made using the Student t test for independent continuous variables or the Mann-Whitney U test when the assumption of normality was not achieved. To analyze categorical data, we performed the chi-square test or Fisher's exact test when the expected values were less than 5. Correlations were demonstrated by linear regression lines, and significance was tested by the Pearson test or the Spearman test when the assumption of normality was not realized. Statistical significance was defined as a p value < 0.05.

RESULTS

Serum values of ACTH, cortisol, and DHEAS in patients with PMR/GCA and control subjects are summarized in Table 2. As shown, patients with untreated PMR/GCA had normal baseline serum levels of cortisol and ACTH, with no differences compared with controls; in relation to inflammatory status, a lower than expected basal production of cortisol was observed in active untreated PMR/GCA [the ratios of ACTH divided by

Table 1. Main demographic and routine laboratory data in patients with PMR/GCA and controls. Results are expressed as mean ± standard deviation or number of cases with prevalence rates.

	PMR/GCA Before Therapy, n = 25	Controls, n = 25	p
Age, yrs	74.6 ± 7.8	73.7 ± 7.6	NS
Sex, F/M	13/12	13/12	NS
PM/GCA + PMR, no.	19/6	0/0	
ESR, mm/h	70 ± 20	13 ± 4	< 0.05
CRP, mg/l; reference ≤ 5	48 ± 24	2.3 ± 1.5	< 0.05
Hemoglobin, g/dl	11.8 ± 1.4	13.3 ± 0.6	< 0.05
Platelets × 10^3 cells/mm^3	276 ± 69	254 ± 48	NS
Elevated ALT/AST† (%)	1 (4)	0 (0)	NS
Elevated alkaline phosphatase†	10 (40)	0 (0)	< 0.05

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. † ALT/AST and alkaline phosphatase were considered elevated if values at diagnosis were ≥ 1.5 times normal value.

Table 2. Serum values of ACTH, cortisol, and DHEAS in patients with PMR/GCA and controls. Results are expressed as mean ± standard deviation.

	PMR/GCA Patients	Controls	p
ACTH, pmol/l*	4.4 ± 2.3	3.9 ± 0.5	NS
Cortisol, nmol/l*	379 ± 21	402 ± 22	NS
DHEAS, umol/l*			
All patients	0.99 ± 0.44	2.77 ± 0.77	< 0.05
Low serum DHEAS levels, no. (%)	21 (84)	0 (0)	< 0.05
Male, n = 12	1.31 ± 0.34	3.24 ± 0.74	< 0.05
Female, n = 13	0.63 ± 0.17	2.35 ± 0.51	< 0.05
Ratio of serum ACTH (pmol/l)/serum CRP (mg/l)	0.4	4.1	< 0.05
Ratio of serum cortisol (nmol/l)/serum CRP (mg/l)	16	433	< 0.05

* Reference values: ACTH 2–12 pmol/l; cortisol 138–690 nmol/l; DHEAS: males 2.5–14.3 umol/l; postmenopausal women 1.5–6.4 umol/l. CRP: C-reactive protein.

C-reactive protein (CRP) and cortisol divided by CRP clearly reflect that both hormones are inadequately low in relation to the ongoing inflammation]. By contrast, 84% (21/25) of patients with PMR/GCA had serum DHEAS levels at baseline below the normal range, whereas serum DHEAS levels in controls were within the normal range in all cases. Serum DHEAS levels for the entire patient cohort were significantly lower versus controls ($p < 0.05$); in addition, when we compared the hormonal status in patients versus controls separately according to sex, we found that serum DHEAS levels of patients with PMR/GCA were also significantly lower compared to their controls. The molar ratio of serum cortisol/serum DHEAS was also significantly higher in patients as compared to healthy subjects ($p = 0.037$).

When we explored the correlation between baseline DHEAS values and the laboratory characteristics that reflect the acute-phase response in PMR/GCA patients (Figure 1), we found a significant correlation between DHEAS levels and erythrocyte sedimentation rate (ESR) ($r = –0.461$; $p = 0.041$), hemoglobin values ($r = 0.519$; $p = 0.016$), and platelet count ($r = –0.442$; $p = 0.045$); CRP approached statistical significance ($p = 0.084$).

Finally, to study sex differences in PMR/GCA patients we also performed a comparison of hormonal values and labora-

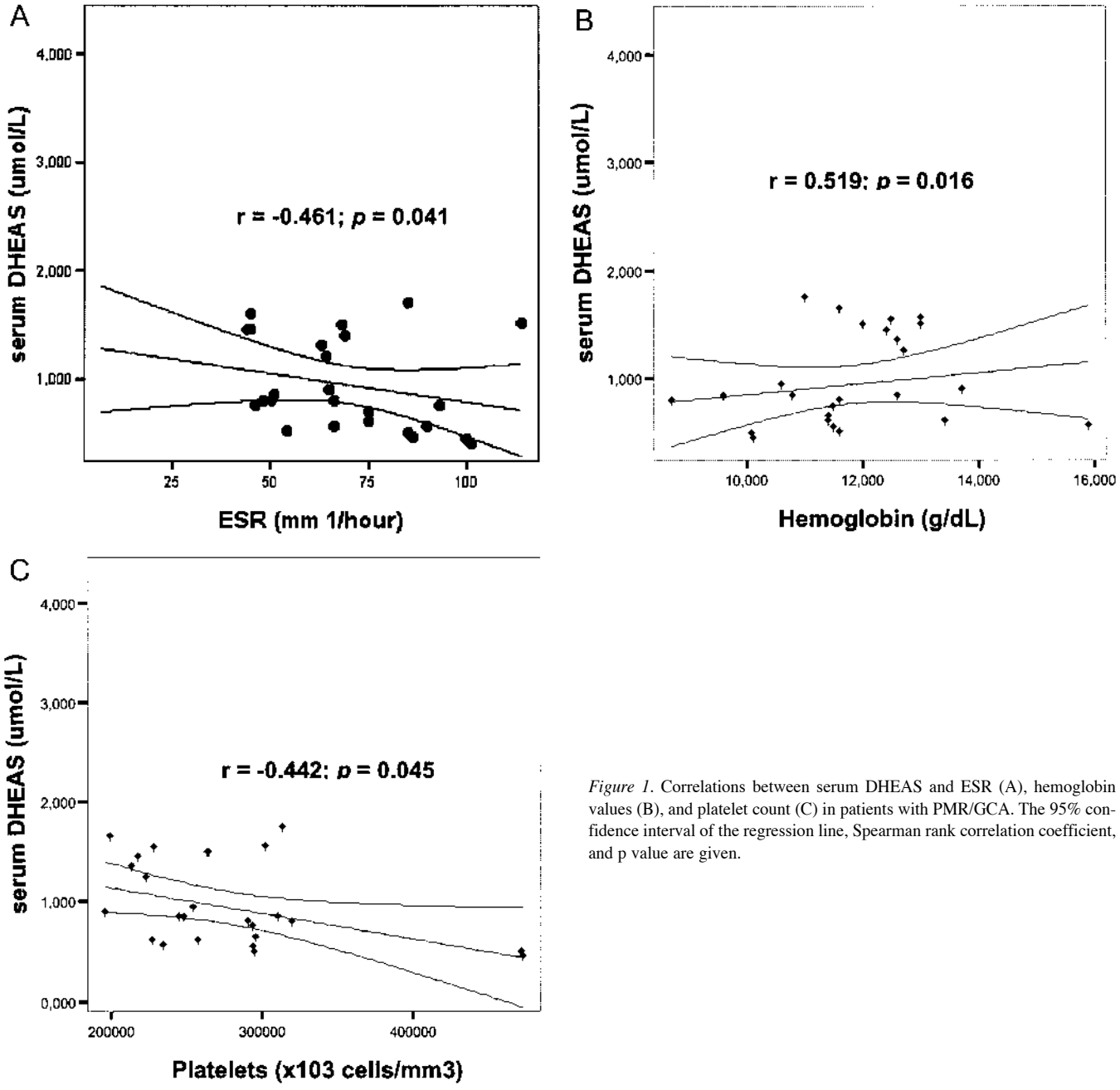

Figure 1. Correlations between serum DHEAS and ESR (A), hemoglobin values (B), and platelet count (C) in patients with PMR/GCA. The 95% confidence interval of the regression line, Spearman rank correlation coefficient, and p value are given.

tory features at presentation between men and women (Table 3). Since the reference values for serum DHEAS levels are different in each sex, we also calculated rate of reduction in DHEAS as a percentage in relation to the lower limit of the normal range. Modest differences were found, suggesting that female patients have a more severe inflammatory response with higher ESR and CRP values, lower hemoglobin levels, higher platelet count, and higher prevalence of hepatic involvement. In addition, the percentage of reduction of serum DHEAS levels at baseline was higher in women than men, although this difference did not reach statistical significance.

DISCUSSION

We found that PMR/GCA patients with new-onset active disease before steroid treatment have normal serum values of ACTH, an inappropriately normal cortisol level in relation to the ongoing inflammation (the stressful situation secondary to the disease process should induce higher than normal levels of cortisol), and significantly lower levels of DHEAS compared to age- and sex-matched control subjects. These results are in accordance with most previous studies on this issue[3-8] and support the existence of relative adrenal hypofunction in both entities.

The pathophysiological significance of this finding needs to be investigated. The abrupt onset of PMR/GCA, with clinical features similar to the steroid withdrawal syndrome or adrenal insufficiency, the rapid and excellent response to exogenous corticosteroids, and the existence of a relative adrenal hypofunction provide a compellingly attractive basis to postulate that PMR/GCA may be an HPA axis-driven disease. However, similar findings have been documented in rheumatoid arthritis (RA)[8,12,16-19], and a decreased DHEAS serum concentration has been also reported in other autoimmune diseases such as systemic lupus erythematosus[20-22], systemic sclerosis[23,24], inflammatory bowel disease[25], and pemphigus[26]. These data raise the question whether DHEAS deficiency is a constant endocrinologic feature in chronic inflammatory diseases or a crucial factor contributing to their pathogenesis[27]. We did not evaluate the hormonal values after steroid therapy. A recent study demonstrated that serum cortisol and DHEAS levels decrease shortly after the beginning of glucocorticoid treatment: cortisol levels dipped during the first 3 months; thereafter they were restored to baseline levels at the end of the first year of treatment. Serum DHEAS levels decreased shortly after the beginning of glucocorticoid treatment (one month) and remained stable during the followup without returning to baseline levels.

Table 3. Comparison of laboratory features between women and men with untreated PMR/GCA. Results are expressed as mean ± standard deviation or number of cases with prevalence rates.

	Women, N = 13	Men, N = 12	p
Age, yrs	73 ± 8	76 ± 7	NS
ESR, mm/h	75 ± 17	65 ± 21	NS
CRP, mg/l	65 ± 21	34 ± 31	NS
Hemoglobin, g/dl	11.1 ± 1.3	12.5 ± 1.2	< 0.05
Platelets, × 10^3 cells/mm^3	304 ± 82	246 ± 35	< 0.05
Elevated ALT/AST†, no (%)	1 (7.7)	0 (0)	NS
Elevated alkaline phosphatase†, no. (%)	7 (54)	3 (25)	NS
DHEAS, μmol/l	0.63 ± 0.17	1.31 ± 0.34	< 0.05
Reduction in DHEAS, %	57.5 ± 11.7	47.2 ± 13.9	NS

† ALT/AST and alkaline phosphatase were considered elevated if values at diagnosis were ≥ 1.5 times normal value; CRP reference value ≤ 5.

In the group of patients with untreated active PMR/GCA, we also found a significant correlation between baseline DHEAS values and different laboratory measures of disease activity. DHEAS levels determined at baseline showed a significant negative correlation with ESR and platelet count; on the other hand, a significant positive correlation with the hemoglobin values was also found. All in all, these data support a negative correlation between the rate of reduction of DHEAS levels and the severity of the inflammatory response. Similar to our findings, Cutolo, *et* al[6] also found a correlation between DHEAS levels and acute phase reactants (ESR and CRP) in female patients with PMR. Moreover, several studies performed in RA, another disease in which a relative adrenal hypofunction has been well documented, have also found a correlation between baseline DHEAS values and different routine laboratory measures of disease activity[16,28,29]. The observed correlation between DHEAS levels and the severity of the inflammatory response can easily be explained considering the immunomodulatory properties of DHEAS. Serum from patients with untreated PMR/GCA demonstrate evidence of systemic inflammation, with increased levels of circulating immune complexes during active disease and elevated levels of interleukin 6 (IL-6) and IL-1. Indeed, IL-6 is the chief stimulator of the production of most acute-phase proteins and serum IL-6 appears to be closely parallel to inflammatory activity[30]. In this sense, different studies[9-11] have demonstrated that DHEAS has a direct inhibitory effect on IL-6 secretion in monocytes and macrophages, and specifically, in recent studies Straub, *et al*[4] and Cutolo, *et al*[6] proved a correlation between DHEAS levels and IL-6 concentrations in patients with PMR.

Finally, when we compared hormonal values and laboratory features at presentation between men and women with active untreated PMR/GCA, we found modest sex differences, with a greater decrease in DHEAS levels and a more severe inflammatory response in women. Of interest, Cutolo, *et al*[6] also found significantly lower serum DHEAS levels in female patients with active untreated PMR compared to male patients. Several studies have explored sex differences in PMR/GCA; current data support a marked female predominance, women being affected roughly twice as much as men[1], with a slightly more severe inflammatory response[31-34] and longer duration of treatment[35-39], whereas the risk of visual

loss and other cranial ischemic complications is similar in both sexes[30,40]. One can speculate that a greater decrease in DHEAS levels in women may lead to a higher susceptibility to these diseases and perhaps could explain the greater severity of the inflammatory response and the longer duration of treatment observed in this subgroup of patients (in some studies performed in RA, the level of DHEAS inversely correlated with disease duration)[28,29]. More extensive prospective studies are needed to clarify the exact role of DHEAS dysregulation in PMR/GCA.

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