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Pituitary function in patients with newly diagnosed untreated systemic lupus erythematosus

Concise Report

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Abstract

OBJECTIVES: Several studies provide evidence for a link between hormones and autoimmune diseases. Hormonal dysfunction involving the hypothalamic-pituitary-adrenal (HPA) axis, prolactin (PRL) secretion and sex hormone status has been supposed to contribute to the development of systemic lupus erythematosus (SLE).

METHODS: 11 patients with SLE and 9 healthy controls were tested for their total anterior pituitary gland reserve by simultaneous injection of corticotropin-, growth hormone (GH)-, thyrotropin-, and gonadotropin-releasing hormone. Serum concentrations of adrenocorticotropin (ACTH), cortisol, GH, thyroid stimulating hormone (TSH), PRL, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured at baseline and different time points within 120 min after injection. Additionally, baseline values of estradiol, testosterone and thyroxine were determined.

RESULTS: Basal and stimulated serum concentrations of ACTH, cortisol, GH and PRL were similar in both groups. In contrast, despite similar basal T4 levels the TSH response to TRH was significantly higher in patients than in controls. LH and FSH levels in premenopausal female patients were identical with that in controls. In contrast, 2 of the 3 male patients were clearly hypogonadal without compensatory elevations of basal LH and FSH levels but they retained excessive stimulatory capacity in response to gonadotropin releasing hormone.

CONCLUSION: Our data show no significant alteration of the HPA-axis in SLE patients. But pituitary response can be regarded as inadequate in view of an ongoing inflammatory process. In addition, GH and PRL secretion appeared to be normal. However, the pituitary-thyroid and pituitary-gonadal axes appear to be affected in patients with newly diagnosed untreated SLE.

Key Words: SLE, pituitary gland, endocrine function, hypogonadism

Introduction

Studies show that the neuro-endocrine system influences immunity and vice versa. Inflammation is accompanied by elevated levels of cytokines like interleukin (IL)-6 or tumor necrosis factor (TNF)-α which can activate the hypothalamic-pituitary-adrenal (HPA) axis[1].

Evidence exists showing a link between sex hormones and the development of autoimmune diseases. The prevalence of systemic lupus erythematosus (SLE) is greatest in young women. This is one of the most obvious clinical observations in both, humans and animals suggesting a causal role for sex steroids in the pathogenesis of SLE. Prolactin (PRL) influences lymphocyte function by inducing IL-2 receptor expression. Furthermore, exogenic gonadotropin-releasing hormone (GnRH) increases disease activity in lupus prone mice.

Most studies elucidating the interaction of the endocrine network and autoimmunity in SLE have been performed in patients with long lasting disease and therefore a history of glucocorticoid intake. This may limit the interpretation of those results. Therefore, we investigated the total anterior pituitary reserve in SLE patients before the initiation of glucocorticoid or immunosuppressive therapy.
Methods

Patients and healthy controls

The protocol was approved by the local Ethic Committee. Written consent was obtained from all participants. Eleven patients with SLE according to the revised, updated criteria of the American College of Rheumatology were included: 8 women (2 of them were postmenopausal) and 3 men with a mean age±SEM of 34.1±4.9 yrs. Disease activity was evaluated by European Consensus Lupus Activity Measurement (ECLAM) score and SLE-Disease Activity Index (SLEDAI). None of the patients had ever been treated with corticosteroids or immunosuppressive agents. Ten patients had mild to moderate disease, one patient revealed high activity with lupus-nephritis: mean ECLAM score 3.8±0.6 SEM, mean SLEDAI 9.3±1.8 SEM. Seven women (2 of them postmenopausal) and 2 men with a mean age of 38.3±4.1 yrs served as healthy controls (HC). Demographic data are given in table 1.

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<th>C3</th>
<th>C4</th>
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Sex (female, f; male, m); age (yrs); European Consensus of Lupus Activity Measurement (ECLAM); Systemic Lupus Erythematosus disease activity index (SLEDAI); Antinuclear Antibodies (ANA) titer (tested on Hep-2); antibodies against ds-DNA (measured by RIA; U/ml; normal range <7.0); complement factors (C3, normal range 50-90 mg/ml; C4 normal range 10-40 mg/ml); total hemolytic complement activity (CH50; normal range 50-150%); erythrocyte sedimentation rate (ESR, mm/h); c-reactive protein (CRP, normal range <0.5 mg/dl), thyroxin (T4, normal range 50-120 ng/ml); estradiol (E2, normal range 22-232 pg/ml; not determined in male-n.d.); testosterone (normal range 2.7-10.7 ng/ml; not determined in female-n.d.);

Stimulation test and hormone assay

We performed a combined test for total anterior pituitary gland reserve with all hypothalamic releasing hormones [2]. All participants had refrained from food and drinking at least 4 hours prior testing. Baseline blood samples were taken after a 30 min rest at 04:00 p.m. Then releasing hormones were injected simultaneously as bolus: 100 µg corticotropin releasing hormone (CRH, Ferring; Cologne, FRG), 100 µg GH releasing hormone (GHRH, Ferring, Cologne, Germany), 200 µg thyrotropin releasing hormone (TRH, Behring, Vienna, Austria), and 100 µg GnRH (Aventis, Frankfurt, Germany). Peripheral blood levels of ACTH,
cortisol, GH, TSH, PRL as well as LH and FSH were measured at (-15), 0, 15, 30, 60, 90, and 120 min. Additionally, we determined baseline values for estradiol, testosterone and total thyroxine (T4). Commercially available radioimmuno-assays were used to measure estradiol (coefficients of variation (CV) ≤8%), testosterone (CV ≤6%), GH (CV ≤6%; all purchased from Diagnostic Products Corporation Los Angeles, USA), and TSH (CV ≤5%; Behringwerke AG, Marburg, FRG). ACTH was determined by an immunoradiometric assay (CV ≤6%; Cis Bio International, Gif-sur-Yvette Cedex, France), cortisol (CV ≤9%), FSH (CV ≤3%), PRL (CV ≤8%), T4 (CV ≤3%) by enzyme-immunological tests (all from Boehringer Mannheim GmbH, Mannheim, FRG), and LH by time resolved fluoroimmunoassay (CV ≤5%; Wallac, Turku, Finland).

Statistical analysis

Data in figures are expressed as mean ± SEM. After statistical distribution was analyzed by Kolmogorov-Smirnov test values have been compared by using unpaired t-test. A p-value <0.05 was considered statistically significant. All statistics were calculated with GraphPad Prism 3.0.

Results

After injection of CRH a significant increase of ACTH was detected which tended to be higher in SLE patients (peak levels after 30 min SLE: 65.9±25.9 pg/ml vs. HC: 46.3±9.9 pg/ml). However, differences were not statistically significant. Though basal cortisol levels tended to be higher in patients than in HC (10.5±1.6 µg/dl vs. 7.9±1.1 µg/dl), cortisol release was also comparable with maximum concentrations 60 min after stimulation (SLE: 18.1±1.5 µg/dl vs. HC: 18.5±1.2 µg/dl).

Basal T4 levels (88.1±3.5 ng/ml in SLE patients vs. 78.0±4.2 ng/ml in controls, n.s.) were comparable. But following TRH injection significantly higher TSH levels were measured in patients compared to controls (p<0.05; Fig 1). In contrast, basal (SLE: 11.1±1.2 ng/ml vs. HC: 9.8±1.8 ng/ml) and TRH stimulated PRL concentrations (maximum after 15 min-SLE: 100.5±14.8 ng/ml vs. HC: 110.4±19.5 ng/ml) were almost similar.

At baseline and after GHRH injection GH levels were nearly identical in both groups (basal-SLE: 2.1±0.6 ng/ml vs. HC: 2.1±0.9 ng/ml; 30 min-peak-SLE: 20.5±4.2 vs. HC: 24.0±6.3 ng/ml).

Following GnRH injection LH and FSH levels were virtually identical in premenopausal female patients compared to controls (Fig 2a). Interestingly, 2 of the 3 male patients were clearly hypogonadal with low testosterone serum concentrations (Table 1) but (inadequately) normal basal gonadotropin concentrations. However, excessive stimulatory capacity in response to GnRH was retained and even tended to be higher. But due to limited number of individuals tested the difference failed statistical significance (Fig. 2b).

Within the SLE group we found no significant differences between female or male patients in respect to their pituitary response after stimulation.
Discussion

We analyzed the overall pituitary-end organ function in newly diagnosed SLE patients naïve for glucocorticoid or immunosuppressive therapy.

Former reports have suggested, that SLE is associated with dysfunction of the HPA axis and PRL secretion. Zietz et al. found an altered function of the HPA axis in moderately active SLE: although baseline and stimulated serum androstenedione, cortisol, and dehydroepiandrosterone (DHEA) were lower in patients with SLE, plasma levels of ACTH were normal. This was not expected in patients receiving prednisolone. Furthermore, in relation to IL-6 or TNF cortisol was clearly low compared to controls [3]. In contrast, we did not find significant alterations of the HPA axis in untreated SLE patients. In face of an active autoimmune disease the failure to activate the HPA axis might be considered as an inadequate response to inflammatory stress. This is in line with data which reveal that levels of ACTH and cortisol are relatively low in relation to levels of IL-6 and TNF in untreated patients with early rheumatoid arthritis (RA) [4].

Prior studies have also reported on abnormal thyroid function tests in SLE patients without known thyroid disease. SLE may be associated with autoimmune thyroiditis and a higher prevalence of hypothyroidism than the normal population [5], though reports are conflicting. SLE patients tested in our study had normal basal T4 and TSH levels. However, compared to controls, stimulated TSH levels were significantly higher, suggesting latent hypothyroidism among patients. Unfortunately, we have not tested auto-antibodies against thyroid antigens.

GH has stimulatory effects on different immune functions. In juvenile RA abnormally low circadian secretion of GH has been measured. Furthermore, we have previously demonstrated a blunted GH response to GHRH in patients with RA [2]. In contrast, no alteration of GH release could be detected here in untreated SLE patients.

In vitro, PRL has been demonstrated to augment lymphocyte proliferation. Moreover, elevated serum PRL concentrations and PRL/cortisol ratio have been reported to be associated with autoimmunity in SLE [6]. However, patients with prolactinomas reveal no signs of lymphocyte activation ex vivo [7]. Here, among SLE patients basal and stimulated PRL levels were comparable to controls.

Mok et al. conclude that ovarian failure with hypoestrogenemia is protective against lupus flares [8]. Furthermore, in lupus prone mice tamoxifen - a estrogen antagonist - had beneficial effects [9], although a clinical trial revealed no benefit using tamoxifen in female SLE patients [10]. Therefore it seems of interest that compared to HC the premenopausal female patients of the present study showed no difference in basal sex hormone levels as well as in gonadotropin response to GnRH.

Findings obtained among male SLE patients appear of particular interest: 2 of the 3 men were clearly hypogonadal. Although the gonadotropin response to a supraphysiological GnRH dose was significantly enhanced the lack of compensatory rise of basal LH concentrations suggests additional pituitary dysfunction. Together these data suggest profound primary hypogonadism but only mild pituitary dysfunction in association with SLE. In another study a small cohort of 4 male patients with normal sexual activity and genital function showed decreased fertility based on sperm abnormalities [11]. But these patients were under therapy with cytotoxic medications. In contrast our patients had not received any...
immunosuppressive therapy before. The finding of low basal and stimulated DHEA levels in female patients with RA [12] as well as in SLE patients [3] and the beneficial effect of DHEA treatment in SLE patients [13][14] support the view that not only estrogens but also androgens might be involved in the pathogenesis of autoimmune diseases. Former studies suggest that testosterone may directly suppress anti-DNA antibody production in PBMC from SLE patients by inhibiting B cell function [15]. The report of significant clinical improvement of SLE symptoms during testosterone therapy provide further evidence for a role of androgens in SLE.

In summary, we found a differential state of pituitary-end organ function in untreated SLE. The HPA axis appeared to be unaffected which seems inadequate in view of an ongoing inflammation. In contrast, the pituitary-thyroid and pituitary-gonadal axes are clearly disturbed. The primary defect appears mainly in the peripheral endocrine organs with an additional mild pituitary dysfunction. Thus, endocrine abnormalities are present among SLE patients at (or before) the onset of disease.

References


Legends

Fig 1:
Thyroid stimulating hormone (TSH) serum concentrations before and after pituitary stimulation by thyrotropin-releasing hormone (TRH) in patients with SLE (■) and healthy controls (□).

Fig 2:
Serum levels of (a) Luteinizing hormone (LH) and (b) follicle stimulating hormone (FSH) before and after pituitary stimulation by gonadotropin-releasing hormone (GnRH) in male patients with SLE (●) and healthy controls (○).
Figure 1

Thyroid Stimulating Hormone

mU/l

0 15 30 45 60 75 90 105 120

time (min)

*
Figure 2

a) LH in response to GnRH (male)

b) FSH in response to GnRH (male)
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