ORIGINAL ARTICLE

Thrombocytopenia and leukocytosis are independent predictors of hyperprolactinemia in systemic lupus erythematosus patients

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Available online 17 April 2011

KEYWORDS
Systemic lupus erythematosus; Serum prolactin; Hyperprolactinemia; Disease activity; Thrombocytopenia; Leukocytosis

Abstract
Introduction: Systemic lupus erythematosus (SLE) flares have been linked to reproductive hormones. Prolactin hormone is involved in a number of rheumatic and autoimmune disease. It was implicated in the pathogenesis of SLE.

Aim of the work: This study was conducted to evaluate serum prolactin level in a group of Saudi SLE patients and to explore its correlation to clinical and laboratorial markers of disease activity.

Patients and methods: Thirty-three Saudi female patients who fulfilled the American College of Rheumatology criteria for SLE were investigated. Disease activity was assessed using the published SLEDAI. Fasting and resting basal serum prolactin and the serological and laboratory profiles of the studied patients were assessed.

Results: Hyperprolactinemia was detected in 10 (30.3%) patients with a mean serum prolactin of 680.7 ± 1021 mIU/L. There were no significant correlation between SLEDAI score and serum prolactin levels. Linear regression analysis selected low platelet count and raised total leukocytic count as the best predictors of serum prolactin level in the investigated Saudi SLE patients ($R^2 = 0.4$, $P = 0.002$).
1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that commonly affects women during childbearing period. SLE flares have been linked to reproductive hormones [1,2].

Prolactin (PRL) acts as a hormone due to pituitary secretion; and as a cytokine due to extrapituitary production [3]. Most of the immune cells secrete PRL which stimulate proliferation, differentiation and maturation of T and B lymphocytes. It amplifies interleukin-2 (IL-2) action and inhibits lymphocytes apoptosis [4]. PRL, as an important immunomodulator, is linked with a number of rheumatic and autoimmune diseases [5]. It was implicated in the pathogenesis of SLE [6–9]. Hyperprolactinemia (hPRL) was observed in SLE patients of both genders and was associated with disease activity [10–13]. However, some studies did not support this association [14–16]. The role of prolactin in the pathogenesis of SLE is not yet conclusive. There is scarcity of data on PRL and its relation to SLE from Arab countries. The Saudi community is a unique, closed community that has special social, environmental and genetic characteristics, and this is the first study attempting to evaluate serum PRL level in a group of Saudi SLE patients and to explore its relation to disease activity and various clinical, laboratory and serological features and comparing results with reports from other parts of the world.

2. Patients and methods

2.1. Patients

2.1.1. Inclusion criteria

Thirty-seven consecutive patients fulfilled the American College of Rheumatology (ACR) criteria for SLE [17] were studied. Patients were either inpatients or outpatients of the Rheumatology and Immunology unit-Internal Medicine Department, King Khalid University and Asser Central Hospital (ACH), Abha, Saudi Arabia. The protocol was approved by the local ethics committee of KKU and all patients gave informed consent prior to entering the study.

This study was conducted between January 2008 and June 2009 as an observational cross-sectional survey. Demographic characteristics, clinical features and serological profiles were recorded. Disease activity was classified according to the published SLE Disease Activity Index (SLEDAI) [18]. Patient’s score > 4 was considered as an active disease.

2.1.2. Exclusion criteria

Patients with renal and/or hepatic failure, pregnancy, hypothyroidism or taking medications known to affect PRL level were excluded from the study.

2.2. Measurement of serum PRL

All blood samples were drawn between 8:30–10:30 am. The subjects under investigation were fasting and resting for at least 30 min, then a canula was introduced with minimal trauma into the Cubital pit vein. The blood samples were drawn after another 30 min. Intervals of 30 min were chosen because PRL is a stress hormone that is released in repeated pulses and the biological half life of PRL is 20–30 min [19]. Basal PRL was determined by immuno-radiometric assay (IRMA). Normal levels of serum PRL in ACH laboratory were (72–511 mIU/L) for females and (86–390 mIU/L) for males.

2.3. Measurement of autoantibodies and other markers of disease activity

Anti ds DNA, complement (C3–C4) and anticardiolipin antibodies were measured by enzyme-linked immuno-sorbent assay (ELISA). Erythrocyte sedimentation rate (ESR), Complete blood count (CBC) and 24 h urinary protein were recorded.

Statistics. Data were analyzed using the statistical package SPSS version 17.0. Data were expressed as means ± standard deviation (SD), median and frequencies. Group differences were compared by using t-test, one way ANOVA, X², Mann-Whitney and Fisher’s exact test when applicable. Pearson’s correlation coefficient (r) between variables was calculated. Linear regression analysis was performed. Serum PRL level was used as the dependent variable. Probability levels < 0.05 were considered significant.

3. Results

3.1. General findings

Thirty-seven Saudi female patients were encountered during the study period. Of these, 4 patients were excluded; 3 were pregnant and one had hypothyroidism. Therefore, 33 SLE female patients were enrolled in the study. The mean age was 29.3 ± 9.5 years, ranged from 13 to 45 years. The mean disease duration was 29.8 ± 18.4 months. Twenty-nine (88%) out of the 33 studied SLE patients were classified as active disease (SLEDAI > 4). hPRL was detected in 10 patients (30.3%) with a mean serum PRL of 680.7 ± 1021.5 mIU/L (range 198–4500 mIU/L, median 318 mIU/L) (Table 1).

3.2. Comparison between normoprolactinemic and hyperprolactinemic patients

Table 2 illustrates the demographic, clinical, laboratory and serological profiles of the normoprolactinemic (normoPRL)
and hyperprolactinemic (hyperPRL) groups of patients. The mean serum PRL in hyperPRL patients was significantly higher than in normoPRL group, which were 1559 ± 1568 and 299 ± 95 mIU/L, respectively (P < 0.0001). Likewise, the antiphospholipid antibody syndrome (APLs) was significantly prevalent in the hyperPRL group, P = 0.03. Although the present study showed more frequent organ involvement and higher trend to active disease in hyperPRL patients compared to normoPRL group, this difference was not statistically significant.

3.3. Association of defined disease manifestations with raised serum PRL

Patients in the age group of 20 to < 30 year exhibited higher mean serum PRL compared to the other age groups; however, this was not statistically significant (r = 1.8, P = 0.18) (Fig. 1). Significant high mean serum PRL was observed among SLE patients presented with fatigue or raised temperature (P = 0.038), articular manifestations (P = 0.035), vasculitis (P = 0.004), encephalopathy (P = 0.024), as well as patients with APLs (P = 0.014). Similarly, thrombocytopenic patients expressed higher mean serum PRL compared with non thrombocytopenic patients (1790 ± 1870.7 vs 381.9 ± 240.7). This was statistically significant, P < 0.0001 (Table 3).

3.4. Correlation of serum PRL levels with SLEDAI score, clinical and laboratorial findings

Pearson’s correlation revealed no significant correlation between the age of the patients, disease duration, SLEDAI score and their serum PRL levels, P = 0.6, 0.7 and 0.09, respectively. Correlation was also tested between PRL level and anti ds DNA titer and complement levels and 24 h urinary protein, again no significant correlation could be demonstrated. However, on the other hand, a statistically significant negative correlation between serum PRL and the platelet count was observed (r = −0.5, P = 0.006); and a significant positive correlation was detected between serum PRL and the total leukocytic count (r = 0.4, P = 0.035) and the body temperature (r = 0.4, P = 0.01) on the other hand.

### Table 1 Demographic data of the studied SLE patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normoprolactinemic</th>
<th>Hyperprolactinemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>33/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Mean age (years) (range)</td>
<td>29.3 ± 9.5 (13–45)</td>
<td>30.3 ± 9.7 (13–45)</td>
</tr>
<tr>
<td>Age category n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>6 (18.2%)</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>20 to &lt; 30</td>
<td>10 (30.3%)</td>
<td>12 (36.4%)</td>
</tr>
<tr>
<td>30 to &lt; 40</td>
<td>5 (15.2%)</td>
<td>5 (15.2%)</td>
</tr>
<tr>
<td>Mean disease duration (ms) (range)</td>
<td>29.8 ± 18.4 (2–72)</td>
<td>31.3 ± 20 (2–72)</td>
</tr>
<tr>
<td>Impatien n (%)</td>
<td>17 (51.5%)</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>SLEDAI (median) (range)</td>
<td>20 (0–30)</td>
<td>29 (88%)</td>
</tr>
<tr>
<td>Active disease n (%)</td>
<td>29 (88%)</td>
<td>30 (90%)</td>
</tr>
<tr>
<td>Serum PRL mIU/L (median) (range)</td>
<td>318 (198–4500)</td>
<td>299 ± 95 (198–4500)</td>
</tr>
</tbody>
</table>

SLEDAI = SLE disease activity index. PRL = prolatin.
studies that reported HPRL in 10-33% of SLE patients [10,12,14,15,20–22]. Higher frequencies were also observed [16,23–25]. Hyperprolactinemia in patients with SLE may be caused by either enhanced secretion of pituitary PRL under the effect of inflammatory cytokines [26] or increased production of PRL by peripheral lymphocytes [9,27]. Furthermore, autoantibodies to PRL might be a potential cause of HPRL in SLE patients [14,28]; owing to the reduced clearance of

Table 3  Mean serum prolactin in SLE patients without and with defined disease manifestations.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean serum prolactin Without n (mean ± SD)</th>
<th>with n (mean ± SD)</th>
<th>$P$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>16 (817.7 ± 1207.9)</td>
<td>17 (1487.5 ± 1824.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Constitutional</td>
<td>24 (456.8 ± 429.5)</td>
<td>9 (1277.9 ± 1758.3)</td>
<td>0.038</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>12 (453.3 ± 539)</td>
<td>21 (810.7 ± 1208.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Articular</td>
<td>4 (227 ± 9.2)</td>
<td>29 (743.2 ± 1076.6)</td>
<td>0.035**</td>
</tr>
<tr>
<td>Nephritis</td>
<td>20 (602.6 ± 953.2)</td>
<td>13 (800.9 ± 1148)</td>
<td>ns</td>
</tr>
<tr>
<td>Serositis</td>
<td>24 (644.8 ± 925)</td>
<td>9 (776.3 ± 1303.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>25 (406.2 ± 381.8)</td>
<td>8 (1538.3 ± 1777.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>CNS</td>
<td>21 (630.9 ± 919.8)</td>
<td>12 (767.9 ± 1218.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>29 (533.7 ± 796.7)</td>
<td>4 (1746.2 ± 1866)</td>
<td>0.024</td>
</tr>
<tr>
<td>APLs</td>
<td>27 (542.9 ± 824.5)</td>
<td>6 (1300.7 ± 1605.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Active disease</td>
<td>4 (331.5 ± 129.9)</td>
<td>29 (728.9 ± 1082)</td>
<td>ns</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (381.9 ± 240.7)</td>
<td>7 (1790.4 ± 1870.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>24 (794.5 ± 1180.3)</td>
<td>9 (377.2 ± 162)</td>
<td>ns</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (438.9 ± 282.6)</td>
<td>17 (908.2 ± 1377.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>20 (602.6 ± 953.2)</td>
<td>13 (800.9 ± 1148)</td>
<td>ns</td>
</tr>
<tr>
<td>Low complement</td>
<td>14 (624.6 ± 1120)</td>
<td>19 (722 ± 972)</td>
<td>ns</td>
</tr>
<tr>
<td>Raised anti ds DNA</td>
<td>20 (600 ± 954.2)</td>
<td>13 (804.5 ± 1146)</td>
<td>ns</td>
</tr>
</tbody>
</table>

CNS = central nervous system, APLs = antiphospholipid antibody syndrome, ds DNA = double stranded DNA, ESR = erythrocyte sedimentation rate, PRL = prolactin.

$P$ significant at <0.05.

ns = non significant.

* t-test.

** Fisher’s exact test.

Figure 1  Mean serum prolactin in different age groups of the studied SLE patients (ANOVA, $P > 0.05$).
The macromolecule IgG–PRL complex from the circulation [29] or its impaired penetration to the hypothalamus and a subsequent disturbance of the hypothalamic pituitary feedback mechanism [30].

Hyperprolactinemic patients in the present study had significantly prevalent APLs. This was supported by Neidhart [31], Jacobi [12], and recently by Jara et al. [13]. They showed the association between hPRL in SLE patients and APL antibodies, namely, anticardiolipin and/or lupus anticoagulant.

There is a controversy about the existence of a correlation between disease activity and the concentration of serum PRL in SLE patients. Some authors reported these two parameters to be positively correlated [10–13,20,21,25,32], whereas, others denied an association [14–16,24,33–36]. In the current study, the observed raised serum concentrations of PRL did not correlate with the SLEDAI score for activity, nor with anti ds-DNA titer; another marker of disease activity in SLE. Furthermore, there was no significant difference in disease activity between hyperPRL and normoPRL patients in the present study.

The conflicting results about the correlation between the disease activity and the concentration of serum PRL might be due to several potential causes such as lack of statistical power [25], heterogeneity of the groups of patients studied, different indices used to measure SLE activity and variable assays used for PRL measurement [7,9,37]. On the other hand, PRL may not be a crucial factor in determining the disease activity [15]. It is believed that SLE is such a polygenic disease, that measurement of one biochemical factor is unlikely to reflect the whole disease process.

In a study by Leaños-Miranda et al. [28], the total serum PRL levels did not correlate with the disease activity. Meanwhile, the free serum PRL correlated with the SLEDAI score in the same study. Current evidences suggested that PRL complexed with anti-PRL antibody or with any other molecule forms big PRL that has attenuated biological activity, and has been postulated to be a cause of HPRL in SLE patients [28–30,38].

Of note, patients in the current study, with general signs of illness, particularly raised temperature, articular manifestations, vasculitis, encephalopathy, APLs or thrombocytopenia had significantly higher mean values of serum PRL compared to patients without these manifestations. In the Jacobi et al. study [12], patients with raised temperature, fatigue, renal involvement or anemia had significantly higher serum PRL. Similarly, participants, in the study of Rezaieyazdi et al. [21], with malar rash and nephritis exhibited higher serum PRL than participants without these manifestations. The PRL-receptor had been identified in a number of cells and tissues of adult mammals, including cells of the immune system, skin, synovial membrane, chondrocytes, cartilage, kidney, central nervous system, endothelial cells and retina [39,40]. Binding to the PRL-receptor is the initial step in the action of PRL [41].

Serum PRL levels in the present study correlated positively with the total leukocytic count and the body temperature. One explanation is that the immune system can synthesize PRL [7]. Another possible explanation is that PRL, itself, is a growth factor for lymphocytes [8]. It is believed that PRL acts locally to stimulate lymphocyte proliferation in an autocrine or paracrine manner. Prolactin is thought to be a cytokine; the PRL-receptor is a member of a novel receptor family that includes...
receptors for interleukin (IL) 2B, IL3, IL4 and IL6 and it shares the intracellular signalization route with the other cytokines [7,42,43].

However, El-Garf et al., [36] reported an inverse correlation of leukocytic and lymphoid count and PRL levels in juvenile SLE patients. Similarly, Haghighi et al. [10] found that leukocytopenia and thrombocytopenia were more frequent in HPRL patients. In line with these results, the platelet count inversely correlated with PRL levels in the current study. Furthermore, thrombocytopenia and leukocytosis were the best independent predictors of raised serum PRL in the studied Saudi SLE patients.

Therefore, bromocriptine, as an anti PRL [5], can be used as a relatively safe adjunctive therapy in the treatment of recalcitrant Saudi SLE patients, having thrombocytopenia and leukocytosis, who are unresponsive to traditional approaches. Additional investigations are needed to verify this hypothesis.

In conclusion hyperprolactinemia occurs in a subset of Saudi SLE patients and can be predicted by the presence of thrombocytopenia and leukocytosis. However, hyperprolactinemia did not correlate with SLEDAI score for disease activity in the studied patients. Studies involving larger cohort of lupus patients are needed to clarify the possible role of PRL in the regulation of immune responses and clinical expression in SLE.

Acknowledgment

Special thanks for Dr. Maha Ahmed Hamouda, laboratory consultant in ACH for her appreciated work.

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