Hyperprolactenemia in Women with Systemic Lupus Erythematusus

Meroj A. Jasem*

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Abstract

Recent accumulated evidences suggest that prolactin is an important immunomodulator and may have a role in the pathogenesis of systemic lupus erythematosus (SLE). The aim of this study was to assess the frequency of hyperprolactinemia in women with SLE and to evaluate its correlation with disease flares. Serum prolactin levels were measured in 62 women with SLE and 50 age- and sex-matched healthy controls. In patients and control groups prolactin levels were determined by immunoradiometric assay (IRMA). The prolactin level was found to be higher than normal rang in (40.3%) of SLE patients in active stage versus only (8.06%) of the same SLE patients but in the inactive stage and in (4%) of control group, the elevation was ranging between mild (72%), medium (20%) and high (8%). The study concludes that patients who having a flare - up had a trend to higher mean of prolactin (mild and medium) levels than inactive stage patients.

Introduction:

Prolactin (PRL) is a neuroendocrine pituitary hormone of 23 kDa (peptide in nature consists of 199 amino acids), produced in the anterior pituitary gland and stimulates mammary growth and differentiation (1, 2). The specific prolactin receptors are distributed on the surface of the membranes of immunocompetent T and B cells and monocytes (3, 4). It is recognized that PRL is produced in a number of sites outside the pituitary, including the brain and lymphocytes (5). Evidence indicates that PRL has cytokine-like activities and has important immunoregulatory activities (6). It contributes to the development of lymphoid tissues and the maintenance of physiological immune function and also modulates a variety of T-cell immune responses. It also stimulates production of interferon (IFN) gamma and IFN regulatory factor 1. (6, 7)

Prolactin also one of the stress hormones and the physiological 24 hour curve of its serum concentration are similar to that of the growth hormone, a near relation, but not to those of the hormones along the line connecting the hypothalamus-pituitary-adrenocortex. (8)

There are a gradual increasing in reports that support the hypothesis that mildly or moderately elevated values of serum prolactin have a role in the pathogenesis and clinical activity of autoimmune rheumatic diseases (9,10) especially Systemic Lupus Erythematosus (SLE)(11,12,13,14), which is a chronic, usually life-long, potentially fatal autoimmune disease characterized by unpredictable exacerbations and remission with protean clinical manifestations (15).Women and minorities are more affected and SLE is most common in child bearing age although it has been reported in both extremes of life [e.g. diagnosed in infants and in the tenth decade of life.] (16)

Hyperprolactinemia (HPRL) have been reported in individuals with lupus, and it has been proposed that the non-

*Biology Dep., College of science, Al-Mustansyria University

cycling secretion of abnormally high concentrations of prolactin stimulates autoimmune responses and contributes to the pathogenesis of SLE, and to assess the frequency of hyperprolactinemia in a cohort of Iraqi women with SLE and to evaluate its correlation with disease activity, it was the aim of this study.

Materials & methods:

Subjects: The study included 62 non-pregnant women patients with a definite diagnosis of SLE .These patients attended the immunology dep. in the Central Public Health Laboratories (CPHL) having a flare – up (an active stage of the disease). They were selected and invited into the present study for a period of 10 months in 2004. Mean ±SD age of the 62 SLE patients was 29.4±7.8 years, rang 18 to 45, mean duration of disease, 4.8 ± 3.5 years and mean age at onset, 24.3 ± 5.7 years. Healthy controls consist of 50 sex and age -matched healthy females were also included in the study.

Samples collection: 2 Blood samples were collected from SLE patients, one during the flare – up and another one after 4-6 months of treatment representing the inactive stage of the disease samples. Blood samples were also collected from controls. All the blood samples were allowed to clot at room temperature then were centrifuged at 1000 x g, and supernatants were stored at -20 C until assayed.

PRL measurement: The serum PRL, concentrations were measured in duplicate by immunoradiometric assay (IRMA) using reagents and protocols provided by the producing company. The normal range for PRL was: PRL = 80 - 500 µIU/mL.

Statistics: The results were statistically analyzed using Student – T- test (On 0.05 & 0.01 significant levels) to evaluate the differences between the test groups and control group. The results were given as Mean ± Standard error.

Results & Discussion:

The presence of high prolactin level was rated as mild (500–700 µIU/mL.), moderate (700–1000 µIU/ mL), and high, (>1000 µIU/ mL.).

Serum hyperprolactinemia was found in 25out of 62 (40.3%) patients of SLE in active stage, of whom eighteen (72%) had the mild type, five (20%) had the moderate type, and only two (8%) had the high level type comparing with healthy control's serum hyperprolactinemia which was found only in 2 out of 50 (4 %) subjects all with the mild type.

A follow-up analysis on serum samples of the same SLE patients seen again after 4-6 months of treatment showed that only 5 patients out of 62 (8.06%) still have hyperprolactenemia but they were all in the mild level type. (Table 1)

Table 1: Percentage of Hyperprolactenemia in the study groups

Study Groups	n	Hyperprolactenemia (%)	Normal PRL Con. (%)	Total
Active SLE	62	25/62 (40.3%)	37/62 (59.7%)	100%
Non-Active SLE	62	5/62 (8.06%)	57/62 (91.94%)	100%
Control	50	4/50 (8 %)	46/50 (92%)	100%

A significant difference was found in the concentration of PRL in sera of SLE patients in active stage and control groups [P< 0.01], while there was no important differences in PRL concentrations between both SLE patients (Non - active) and control sera [P< 0.05]. (Figure 1)

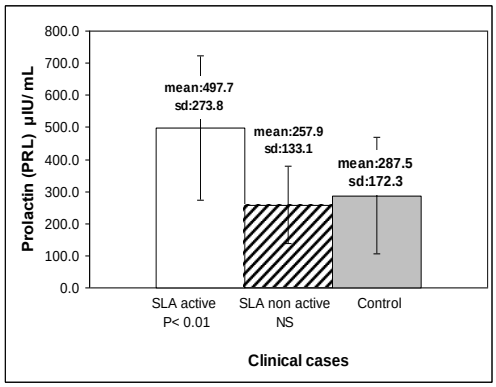

Figure -1- Comparison of concentration of prolactin (PRL) µIU/ mL in SLE active stage patients and SLE non active stage patients with control group

This indicates the presence of a relationship between the SLE activity and hyperprolactenemia. These results came in agreement with the accumulated evidence that support the hypothesis that both mild and moderate elevations of serum prolactin (PRL) participate in the clinical expression and pathogenesis of SLE (17, 18, 19)

Hyperprolactinemia (HPRL) seems to be associated with clinical activity of SLE during pregnancy (20). The relationship between HPRL and active SLE in non-pregnant patients seems to be controversial (21, 22, 23). Mild elevations of serum PRL secondary to microadenoma could trigger the onset of SLE in a subset of patients (24). Moreover, the presence of PRL may reflect an abnormal communication between the immune system and the neuroendocrine system in active SLE. Lymphocytes from patients with active SLE produce increased amounts of PRL (25, 26). This extrapituitary PRL may participate in abnormal immune processes in SLE. There is exciting new evidence that HPRL in SLE may be explained by stimulation of pituitary PRL secretion by cytokines. The interactions between PRL, cytokines, autoantibodies and organ involvement suggest that PRL participates in local and generalized immune and inflammatory processes and acts as a bridge between the neuroendocrine and immune systems in SLE (27). The association between the neuroendocrine and the immune systems has been strengthened and considered increasingly important since the demonstration of PRL-like molecules and PRL-binding sites in human peripheral mononuclear cells (PMNC)(27,28) so the understanding of the interactions between these systems in SLE will help us understand and treat this important autoimmune disease.

A study by Jara *etal.* (29) showed elevated serum PRL levels in a subset of subjects affected with active SLE together with data from the autoimmune female New Zealand Black/New Zealand White F1 (B/W) mouse model (9) strongly suggest that PRL may be associated with disease activity in SLE.

Although the exact mode of action of PRL in autoimmunity is not yet completely explained, experimental hyperprolactinemia has been associated with characteristic Th2 cells cytokine production (30). These data suggest that PRL-driven cytokine production by Th2 cells could stimulate lymphocytes or microenvironmental cells, leading to a deterioration of the autoimmune process. Therefore, additional studies aimed at analyzing the mechanisms and pathways regulating PRL expression on lymphoid cells might provide us with new insights on the role of PRL in both normal and pathological immune conditions.

They note that the exact mechanism for high levels of PRL in SLE patients remains unclear, but Vera-Lastra and associates (31) show that 2 mechanisms involving abnormal secretion of prolactin that were identified in SLE — hypothalamic dysfunction and prolactinomas — can also be operative in scleroderma. Of interest, deregulation of prolactin secretion was linked to pituitary adenomas in scleroderma patients.

Impaired hypothalamic function has been invoked as a contributor to hyperprolactinemia in SLE, and evidence exists that impaired dopamine turnover and altered dopaminergic tone are associated with high prolactin in lupus.

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زيادة هرمون الحليب عند النساء المصابات بداء الذئب الاحمراري

مروج احمد جاسم *

*مدرس مساعد/ قسم علوم الحياة / كلية العلوم / الجامعة المستنصرية

الخلاصة:

تشير الأدلة الحديثة المتزايدة الى كون هرمون الحليب (البرولاكتين) مُعدِّل مناعي مهم وقد يلعب دورا مهما في امراضية داء الذئب الاحمراري. الهدف من هذه الدراسة هو التحري عن تكرار زيادة هرمون الحليب عند نساء مصابات بداء الذئب الاحمراري وتقييم العلاقة بين هذه الزيادة والطور الفعال للمرض. تم قياس تركيز هرمون الحليب في مصول 62 امراة مصابة بداء الذئب الاحمراري في طوريه الفعال والخامل وفي مصول 50 امراة سليمة تمثل مجموعة السيطرة، وقد تم قياس هذه التراكيز المصلية لهرمون الحليب باستخدام تقنية الاختبار المناعي الاشعاعي المتري. لقد لوحظ ارتفاع مستوى هرمون الحليب عند (40.3%) من النساء المصابات بداء الذئب الاحمراري في طوره الفعال مقابل (8.06%) امراة فقط من نفس المرضى ولكن في الطور الخامل من المرض ومقابل (4%) من نساء مجموعة السيطرة ، وقد تراوح الارتفاع ما بين طفيف (72%) ، متوسط (20%) ومرتفع(8%). لقد استنتجت الدراسة ان المرضى بداء الذئب الاحمراري في طوره الفعال يظهرون زيادة طفيفة او متوسطة في التركيز المصلي لهرمون الحليب اكثر منه في الطور الخامل لنفس المرض وعند نفس المرضى.