Hyperprolactinaemia in patients with systemic lupus erythematosus

L. Moszkorzová[1], Z. Lacinová[2], J. Marek[2], L. Musilová[1] , A. Dohnalová[3], C. Dostál[1]

[1]Institute of Rheumatology, Prague; [2]Third Medical Department, First Medical Faculty Charles University, Prague; [3]Institute of Physiology, First Medical Faculty Charles University, Prague, Czech Republic.

Abstract

Objective

To verify the presence of hyper-PRL in SLE patients, its association with high disease activity, specific organ involvement or presence of anti-ds-DNA antibodies.

Methods

The group under study consisted of 80 patients with systemic lupus erythematosus (SLE), 28 patients with rheumatoid arthritis (RA) and 27 healthy controls. PRL serum levels were assayed using standard commercial kits (Immunotech Prague) with the radioimmunometric method for testing three samples of each of the subjects. The samples were taken in the morning hours (9-11 a.m.) of absolute rest 30 minutes after the introduction of the cannula at 30-minute intervals.

Results

A significantly higher rate of elevated PRL levels was found in SLE patients (40.0%) compared with the healthy controls (14.8%, $p < 0.017$). No proof was found of association with the presence of anti-ds-DNA or with specific organ involvement. Similarly, elevated PRL levels were found in RA patients (39.3%). The PRL elevation tended to decline from the 1st to the 3rd sample in the group of patients with SLE and RA but not in healthy controls.

Conclusion

As follows from our measurements of prolactin serum values in SLE patients they are varriable by definition. According to our opinion further investigations are needed

Key words

Systemic lupus erythematosus, elevated serum prolactin values, diseases activity, anti-dsDNA antibodies, specific organ involvement.

This study was supported by the Internal Grant Agency of Ministry of Health of the Czech Republic No NK 5370-3/99.

Please address correspondence to: Ctibor Dostál MD, PhD, Institute of Rheumatology, Na Slupi 4, 128 50 Prague 2, Czech Republic.

Received on February 4, 2002; accepted in revised form on September 4, 2002.

Introduction

Prolactin (PRL) is a polypeptide hormone of 23 kDa molecular weight made up of 199 amino acids, and produced by lactotropes, acidophilic cells of the anterior lobe of the pituitary. PRL is also synthetized in some other parts of the brain and in certain peripheral blood elements (1). Whether this extra-pituitary PRL, also known as PRL-like hormone (2), interferes with serum PRL radioimmunoassay (RIA) and whether it also has a feedback effect on PRL secretion in the pituitary, has yet to be elucidated. There is, however, proof of its apocrine and paracrine function of cellular growth factor, a function enhancing mitogenesis and lymphocyte differentiation at the site of inflammation and thereby their own production of yet other mediators and immunomodulators - including interleukines (IL) and growth factors. PRL also directly interferes with the synthesis of some acute-phase proteins in the liver (stimulating, e.g., alpha-2-macroglobulin synthesis). As a result of these discoveries, PRL was classed among immunomodulators, and the hypothesis was advanced of its part in the pathogenesis of autoimmune diseases (3).

While there are number of studies (4-7) showing a frequent occurrence of serum PRL elevation in SLE, only few also take into account the physiological properties and secretion control of this hormone. PRL assumes the greatest so far known relevance during pregnancy and subsequent lactation marked by a gradual long-term increase in its serum levels. Serum PRL also shows short-term elevation in situations of stress, elevated temperature or as a consequence of some other disease or, last but not least, the intake of some medicaments (8).

PRL secretion is not under the usual feedback control. Instead, it is of the pulse-type, episodic, and influenced by a number of factors of humoral nature, apparently also by nitrogen oxide. Beside this, it is subject to a certain diurnal and, in women, monthly rhythm, reaching peak values in the early morning hours, close before waking up, in the REM phase of sleep. Women show maximum values just before menses (9).

For those reasons,samples of blood for the estimation of basal serum PRL levels are usually taken 1 - 2 hours after awakening, in fertile women on days 12-14 of the menstrual cycle. However, most of the studies (4, 6, 10) concerning PRL relative to SLE as published so far fail to mention the conditions or technique of sample taking, and often even fail to take into account the different physiological norms for men, for women in the child-bearing age, and post-menopausal women. The majority (6,11, 12) operate merely with moderate hyper-PRL ranging from 20 to 30 ng/l (in our laboratory 600-1000 mUI/l). To Batrinos and others (13, 14), higher PRL levels are not subject to the circadian rhythm of secretion; responsible for their secretion appears to be a permanent source, most likely a microadenoma. Nevertheless, values lower than that (20 ng/l) may represent but a transient increase with rapid normalization caused, probably, by the subject´s overall condition at the time of examination rather than by disorders of the neuroendocrine or immune systems.

Stress, both psychic and physical, induced , e.g., by mere intake of food or needle entry into the vein, is another significant, often ignored, factor likely to influence PRL synthesis and secretion (15).

We also aimed at finding out to what extent the stress factor can affect the serum levels of PRL. In essence, the point was to see if an increased PRL serum level is in any way associated with SLE activity (rated in terms of SLEDAI), with the presence of anti-ds-DNA antibodies, or with the defined organ involvement as lupus nephritis (LN) and neuropsychiatric lupus (NPSLE) as part of the underlying disease; diagnosed on the basis of 1999 ACR criteria (16).

Materials and methods

A total of 80 patients with definite SLE were examined diagnosed on the basis of ACR criteria. The results were compared with 28 patients suffering from rheumatoid arthritis in different stages of diseases, and with 27 healthy controls (Table I).

After 6 months, 34 SLE patients were re-investigated. All the SLE patients had their disease activity rated with the SLEDAI score (regarded as “inactive”

Table I. Demographic characteristics of the investigated SLE, RA patients and healthy controls.

	SLE	Mean age	RA	Mean age	Healthy controls	Mean age
Total	80	40.8 ± 11.34	28	54.64 ± 14.45	27	39.57 ± 19.75
Women in fertile age	49	34.4 ± 8.20	8	37.13 ± 11.84	11	29.72 ± 10.37
Women in menopause	24	54.04 ± 3.07	15	62.2 ± 7.25	5	63.40 ± 13.61
Men	7	40.43 ± 9.14	5	60.0 ± 10.79	11	38.55 ± 20.99
Lupus activity (SLEDAI > 4)	62	-	-	-	-	-
Lupus inactivity (SLEDAI ≤ 4)	18	-	-	-	-	-
Anti-dsDNA positive	42	-	-	-	-	-
Anti-dsDNA negative	38	-	-	-	-	-
Lupus nephritis	27	-	-	-	-	-
NPSLE*	31	-	-	-	-	-

*Neuropsychiatric SLE.

were those with SLEDAI < 4); also under scrutiny were the presence of specific anti-ds-DNA autoantibodies and actual organ involvement. Excluded from the group were patients with other causes of hyper-PRL (severe renal insufficiency, hypothyroidism, prolactinoma, pregnancy, treatment with hyper-PRL-inducing medication). Patients and healthy subjects with highly increased serum PRL (in men > 800 mIU/l, in women: > 1000 mIU/l) underwent clinical examination as well as MR imaging for the purpose of ruling out the presence of pituitary adenoma. All healthy individuals had basic screening performed to rule out the presence of any autoimune or endocrine involvement.

Serum PRL assay

All samples of blood were taken in the morning hours (9-11 a.m.). After 30 minutes of the subjects' perfect relaxation, a cannula was introduced and then, after another 30 minutes, sample No. 1 was taken. Samples 2 and 3 were taken at intervals of the same duration, i.e.,each time after 30 minutes. The concentrations of PRL were measured in duplicate by immunoradiometric assay (IRMA, IMMUNOTECH, Prague). Serum samples (50 µl were incubated with ^{125}I-labelled antibody 150000 cpm/ 500 µl) in tubes precoated with monoclonal anti-prolactin antibody for one hour at room temperature by continuous shaking. The contents of tubes were aspirated. The tubes were washed twice with 2 ml of wash solution, and the radioactivity bound to the tubes was measured in a gamma counter.

The standards supplied with the kits were calibrated using the international standard WHO 84/500 (1 ng/ml = 30.3 mIU/l). The limit of sensitivity of the assay was 30 mIU/l. The intra- and inter-assay coefficients of variation were determined with the use of pooled patients' serum samples 4.5 and 8.8%, respectively.

Estimation of circulating anti-ds-DNA autoantibodies

Anti-ds-DNA autoantibodies were detected by the indirect immunofluorescence method (SEVATEST, SEVAC, Prague) at the Immunological Laboratory of the Rheumatological Institute in Prague. Trypanosomes were used as substance on the slides containning the kinetoplast consisting of native ds-DNA. After overlaying the substrate with patients' sera, the complex of ds-DNA and specific antibodies was visualized by FITC labelled anti-human globulin conjugate. The slides were examined under a fluorescente microscope and the fluorescence of kinetoplasts was evaluated.

Statistics

The results were expressed in terms of the mean value ± standard deviation in all the subjects investigated. To prove the higher rate of increased hyper-PRL (increase in all three samples) in patients with SLE, with rheumatoid arthritis, as well as in the healthy controls (intercomparison), the χ2-square test was used. The test was also used to show hyper-PRL relative to the disease activity, presence of anti-ds-DNA autoantibodies, or specific organ involvement (kidney and/or central nervous system – CNS). The Friedmanns test was employed for the statistical difference between the mean values in samples No. 1 and 3. Hyper-PRL changes after the given period of time (6 months) were rated by means of the MacNamara test.

Results

A significantly higher rate of increased PRL levels was found in patients with SLE, and with rheumatoid arthritis than in the healthy controls group (Table II). According to the serum PRL readings, the patients found to have the s.c. "idiopathic" hyper-PRL with elevated serum values in all three blood samples, were divided into three groups according to the degree of hyper-PRL into those with mild, moderate and high hyper-PRL (Table II). Simultaneously we observed that the highest mean values of serum PRL were significantly more often found in the first of the three samples taken from all the groups under study - in SLE patients, in patients with rheumatoid arthritis, as well as in healthy individuals (Fig. 1). In patients with SLE and RA, a significant difference was found in the mean PRL values of samples 1 and 3 ($p < 0.001$). This fact was not confirmed for healthy individuals.

Elevated serum PRL levels and lupus disease activity (SLEDAI-rated)

Sixty-two SLE patients were found to be "active" according to our criteria (SLEDAI > 4). 26 of them (i.e.,41.9%) had increased PRL levels (in all three samples). Eighteen were "inactive",

Table II. Distribution of mild, moderate and high serum hyper-PRL estimated in all three blood samples in SLE and RA patients and healthy controls.

	Hyper-PRL	Mild Men > 200 -450 mIU/l Menopausal women > 200 - 450 mIU/l Fertile women > 450 - 600 mIU/l	Moderate Men > 450 - 850 mIU/l Menopausal women > 450 - 850 mIU/l > 450 - 850 mIU/l Fertile women > 600 - 1000 mIU/l	High Men > 850 mIU/l Menopausal women > 850 mIU/l Fertile women > 1000 mIU/l
SLE (n = 80)	32 (40,0%) *	20 (25.5%)	9 (11.3%)	3 (3.8%)
Fertile (n = 49)	12	4	6	2
Memopausal (n = 24)	16	12	3	1
Men (n = 7)	4	4	0	0
RA (n = 28)	11 (39.4%) **	8 (72.7%)	3 (27.3%)	0
Fertile (n = 8)	1	0	0	0
Memopausal (n = 15)	9	8	1	0
Men (n = 5)	1	1	1	0
Controls (n = 27)	4 (14.8%)	4 (100.0%)	0	0
Fertile (n = 11)	0	0	0	0
Menopausal (n = 5)	1	1	0	0
Men (n = 11)	3	3	0	0

χ2-square test: *$p < 0.017$; ** $p < 0.041$

PRL elevation was seen in 6 of them (i.e. 33.3%). No association was found between the disease activity and PRL readings ($p < 0.512$).

Elevated serum PRL levels and the presence of anti-ds-DNA autoantibodies

Forty-two SLE patients were found to have anti-ds-DNA autoantibodies in circulation at the time of blood sample taking for serum PRL assay. Out of these, 42.9% had increased levels of PRL. No evidence was found of an association between the presence of anti-ds-DNA and serum PRL levels in SLE patients ($p < 0.0583$).

Asssociation between serum PRL and specific organ involvement

SLE patients were divided into three groups according to manifest specific organ involvement – lupus nephritis (LN), neuropsychiatric SLE (NPSLE) and other (i.e. with skin disease, pulmonary disease, vasculitis and/or without any specific organ manifestation of the underlying disease). No association was found between increased PRL readings and any specific organ involvement.

Re-investigated SLE patients

Thirty-four SLE patients were re-investigated after the elapse of six months. A change in serum PRL levels had occurred in 8 patients. Five exhibited spontaneous improvement in their initially diagnosed hyperprolactinaemia, while in four of them hyper-PRL had developed a new by the time of repeated blood sample taking, and that independently of the activity of the disease or the presence of anti-ds-DNA. Hence the overall profile of hyper-PRL in SLE patients showed no particular change after those six months ($p < 0.7398$).

Discussion

As follows from our continual monitoring of PRL secretion, its serum levels are variable by definition. As already pointed out in the Introduction, PRL secretion is subject to a number of regulatory mechanisms. Apart from that, physiological serum PRL levels are different for men and for fertile women. At the time of menopause, the values drop to those typical of men, a fact attributable to decreasing estrogen levels.

Apart from that, there are external influences, e.g., stress; PRL has been included among the so called stress hormones (such as ACTH, cortisol, growth hormone and others) and research clearly demonstrates links bentween the stress system alterations in disease activity, and associaated outcomes in patients with rheumatic disease (17, 18). Some studies indicate that major life events may be implicated in the onset and exacerbation of RA (19, 20). Da Costa *et al*. examined the link between major and minor stressors, disease activity and damage variables, and changes in functional disability in women with SLE over an eight-month period and concluded that various forms of stress may play different roles in SLE-related outcomes (21). Hence, stressor and the components of the stress response seem to be inextricably involved in the disease process of rheumatic autoimmune conditions (22).

According to endocrinologists, samples should be taken repeatedly for any correct estimation of stress hormones. Dostál *et al*. (15) made sure that blood samples were taken repeatedly from SLE patients to assay serum PRL. Thus they were able to prove not only a higher rate of hyper-PRL in SLE patients but also a statistically significant difference between the mean values of samples 1 and 3. Similarly, serum PRL ought to be assayed in the morning hours (9-11 a.m.); however, not even this is always mentioned in the authors' communications (23-25). As in our own study, a number of others are concerned with hyper-PRL in SLE patients, but also with hyper-PRL relative to such factors as disease activity or specific organ involvement. For example Buskila *et al*. failed to prove its

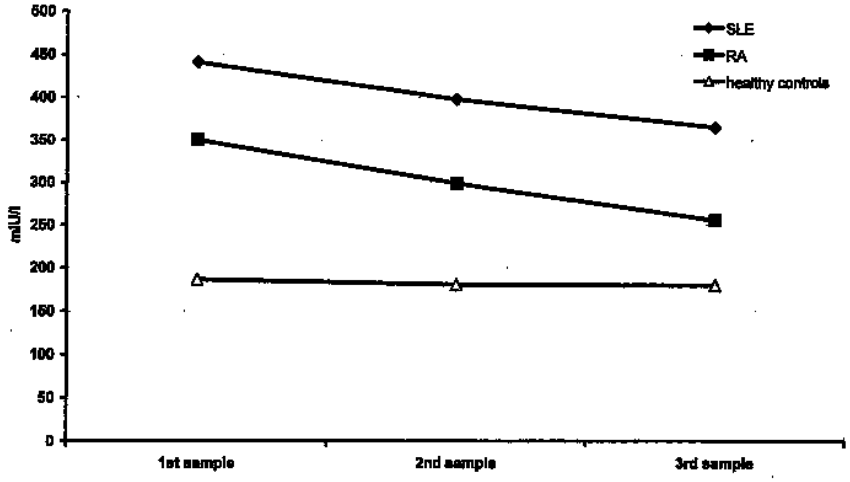

Fig. 1. Mean serum prolactin values in SLE,RA patients and healthy controls taken in three consecutive samples.

Table III. SLE patients-association of serum hyper-PRL with SLEDAI activity score, anti-dsDNA and specific organ involvement (lupus nephritis, NPSLE).

SLE	SLEDAI	Anti-dsDNA	Organ involvement	
			Lupus nephritis	NPSLE
	score > 4	+	+	+
Total (n = 80)	62 (77.5%)	42 (52.5%)	27 (33.75)	31 (38.75)
Hyper-PRL (n = 32)	26 (41.9%)* p < 0.512	18 (42.9%)* p < 0.583	12 (44.4%)* p < 0.563	10 (32.3%)* p < 0.261

*$\chi 2$ test - not significant

relation to disease activity (6), unlike others who did prove this interrelationship in their study. El-Garf *et al*. described hyper-PRL association in SLE patients with CNS involvement, though only in its infantile form (26), Miranda *et al*. again found a hyper-PRL association in SLE patients suffering simultaneously from active lupus nephritis (27).

In our own study, we could not demonstrate any association with the disease activity, specific organ involvement or even the presence of anti-ds-DNA antibodies; we found 40% of our SLE group to have serum PRL elevated above the usual norm, but only 11.3% to have moderate hyper-PRL (Table II). This range of values is regarded by the majority of authors as significant in connection with the immune system or its disorders. While this discovery is in the agreement with the conclusions of some recent studies showing hyper-PRL in SLE patients at a rate of 20 - 31%, the differences in the overall number of patients with hyper-PRL and those who exhibit moderate values of elevation may account for the different results obtained in different studies. Another, no less important fact arising from our study is that serum PRL obtained from subsequent samples taken at 30-minute intervals showed a tendency toward decrease or even normalization, and that the mean values of the first and third samples taken showed a significant difference in patients with SLE or RA, but not in the healthy controls (Fig. 1). This may indicate that an immune system disorder responsible for inflammatory processes may result in lower resistance and higher lability vis-à-vis stress.

Differences in the results of the particular studies published so far may, in part, be due also to differences in the techniques of estimation. Similarly, the recently described presence of antibodies against PRL in some SLE patients may have a share in the different readings obtained because on binding with the antibody, prolactin appears to change its biological activity (28,29). Whether those autoantibodies are also found in connective tissue diseases other than SLE is as yet not quite clear. Nor is it clear whether these autoantibodies actually set off hyper-PRL in SLE patients. Another moot question is whether the presence of autoantibodies against PRL has any bearing on the clinical course of the disease and if so, in which sense. Leanos *et al.* found a higher rate of hyper-PRL in SLE patients with autoantibodies against PRL than in patients without such autoantibodies; their patients were also found to have a lower activity of the underlysing disease (30).

Extrapituitary secretion of PRL is another phenomenon requiring elucidation. The conventional techniques of serum PRL assaying fall short of differentiating PRL produced by inflammatory elements and, consequently, fail to take a closer view of its function and effect on the autoimmume process. PRL secretion by polymorphonuclears has already been proved by a number of authors (2,3,31), both in SLE patients and in healthy controls. Gutiérez *et al.* found this secretion to be higher in SLE patients than in the healthy controls group (2). Its share in the pathogenesis and course of the disease still remain unaccounted for; hence, it will be necessary not only to define precisely the actual function of PRL produced in this way, but also to assess its share in the control and secretion of PRL in the adenohypophysis.

Last but not least, there is the question of diagnosing the so-called moderate PRL (ranging from 600 to 1000 ml/IU/l 20-30 ng/l), in which the immunological power of PRL is presumed (32). Is a moderate elevation only a transient factor caused by physiological mechanisms, or is it already a pathological conditions requiring therapeutical intervention? This is still open to discussion. Besides, to take the endocrinological consensus into account, idiopathic hyper-PRL within this range requires monitoring alone rather than suppressive therapy (13). Likewise, it is also unclear whether this applies to patients with idiopathic hyper-PRL and autoimmune disease.

Summarizing the findings of our study, we abided by certain physiological, pathophysiological and endocrinological rules in studying the PRL serum levels, hormones and a potential agent

interconnecting the neurohumoral and immune systems. The blood samples were taken repeatedly after a period of time following the introduction of the cannula, while the subjects were in a perfectly relaxed condition, and in the morning hours. We observed different physiological norms for men, for women in the child-bearing age, and for menopausal women. As positive results were regarded solely increased values in all three samples. However, even these aspects taken into account in our study are far from all the factors that call for closer examination if the PRL-SLE interconnection is to be fully elucidated. Jara *et al*. in their study refer, among other things, to the phenomenon of persisting hyper-PRL (e.g., in microadenoma or under the effect a hereditary disorder of the PRL secretion inhibitory mechanism) as a potential triggering mechanism of the disease as such (33). Another problem to deal with, are PRL receptors and their proliferation in the course of the disease (34). Nobody has as yet studied their connection with the disease activity. In this way, our study has only added to the number of potential factors likely to help expose the PRL relative to the immune system and, consequently, to autoimmune processes and SLE as such.

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