Functional Hyperprolactinemia and Hypophyseal Microadenoma in Systemic Sclerosis

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ABSTRACT. ***Objective***. Hyperprolactinemia (HPRL) has been identified in more than half of patients with systemic sclerosis (SSc). However, the association with pituitary adenoma and the status of hypothalamic dopaminergic tone using metoclopramide (MTC) test has not been studied. We investigated the prevalence of prolactin (PRL)-secreting pituitary adenoma and evaluated production of PRL by dynamic testing with MTC in SSc.

Methods. We studied 30 patients with SSc (mean age 38 ± 10 yrs) and 20 healthy controls (mean age 37 ± 11 yrs). Serum PRL concentrations were determined by radioimmunoassay in all subjects, and PRL response was measured 30, 60, 90, and 120 min after injection of 10 mg of MTC. Computed tomography (CT) of the sella turcica was performed.

Results. The mean basal serum PRL levels before and after stimulation with MTC in SSc patients versus controls were: basal 18.2 ± 5.4 versus 8.7 ± 1.6 ng/ml, p = NS; 30 min: 175.0 ± 5.4 versus 61.0 ± 42 ng/ml, $p < 0.001$; 60 min: 160 ± 64 versus 52 ± 30 ng/ml, $p < 0.001$; 90 min: 125 ± 57 versus 42 ± 21.0 ng/ml, $p < 0.05$; 120 min: 108.0 ± 57 versus 30.0 ± 10 ng/ml, $p < 0.005$. CT scan showed microadenomas in 24/30 SSc patients and 1/20 controls (p = 0.001).

Conclusion. Our study suggests that a group of patients with SSc have a high prevalence of HPRL with increased central dopaminergic tone, and microadenomas. PRL may have a role in the pathogenesis of SSc. Further studies are necessary to confirm our results. (First Release May 15 2006; J Rheumatol 2006;33:1108–12)

Key Indexing Terms:
SYSTEMIC SCLEROSIS PROLACTIN HYPERPROLACTINEMIA MICROADENOMA

Systemic sclerosis (SSc) is a systemic autoimmune inflammatory connective tissue disorder characterized by excessive production of extracellular matrix by fibroblasts and endothelial damage in small vessels with subsequent intimal hyperplasia, tissue ischemia, and activation of the immune system[1]. Proposed initiating factors include environmental, genetic, and hormonal stimuli[2]. It has been suggested that estrogens[3], dehydroepiandrosterone[4], thyroid hormones[5], prolactin (PRL)[6,7], insulin[8], peptide YY[9], and other factors may be implicated in the pathogenesis and clinical manifestations of SSc.

PRL, the lactotrophic polypeptide hormone produced in the anterior pituitary gland, is a versatile hormone with more than 300 separate functions. It is now recognized that PRL is a hormone-cytokine and is produced in a number of extrapituitary sites, including immune cells[10]. There are diverse causes of hyperprolactinemia (HPRL), but it is most commonly caused by PRL-secreting pituitary adenomas and medication, which affects dopamine secretion[11,12].

The reported prevalence of anterior pituitary microadenomas ranged from 1.5% to 27% in 2 autopsy series[13,14]. The diagnosis of a prolactinoma is confirmed by clinical manifestations, sustained HPRL, neuroradiological findings, and/or histological features of a pituitary tumor[15,16].

The most widely used functional test for PRL secretion is measurement of the PRL response after administration of thyrotropin-stimulating hormone. Metoclopramide (MTC), a dopaminergic-blocking agent, can be used to evaluate the status of the hypothalamic dopaminergic tone[11,17].

HPRL has been reported in 13.6% to 59% of patients with SSc. Different factors may explain the discrepant findings, such as the inclusion of heterogeneous groups of patients and variations related to method used. Elevated serum PRL is due to both a sustained increase over 24 h and a shift in the diurnal rhythm[18-20]. There is an association between HPRL, disease duration, and involvement of certain organs such as skin tethering and diastolic dysfunction in diffuse SSc[7]. However, the origin of HPRL and the association with pituitary adenomas have not been studied, and dynamic hormonal testing has been done only in a small number of patients with SSc[18].

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We investigated the production of PRL, using dynamic hormonal testing with MTC, in patients with diffuse and limited SSc, and the prevalence of prolactin-secreting pituitary adenomas.

MATERIALS AND METHODS

Patients and controls. We studied 30 consecutive female patients with SSc (mean age 38 ± 10 yrs) who met the American College of Rheumatology classification criteria for SSc[21]. Twenty had limited SSc and 10 had diffuse SSc. Included were outpatients over 16 years of age with limited or diffuse SSc from the SSc clinic at the Hospital de Especialidades Centro Médico La Raza, Instituto Mexicano del Seguro Social. All patients had positive antinuclear antibody detected by indirect immunofluorescence using the HEp-2 cell line as substrate. The majority of patients with diffuse SSc (90%) had positive antinucleolar antibodies and 20% had anticentromere antibodies (ACA). In limited SSc, 80% of patients had ACA and 20% had antinucleolar antibodies. All patients were taking D-penicillamine (300–600 mg/day). The Ethics Committee of the Hospital de Especialidades Centro Médico La Raza approved the study.

Patients were excluded from study if they were taking drugs that modify PRL levels (bromocriptine, chloroquine, MTC, sulpiride, domperidone, amitriptyline, verapamil, cimetidine, methyldopa, estrogens, etc.); if they had clinical or subclinical evidence of hypothyroidism or other endocrinologic disorder, hepatic insufficiency, or chronic renal failure; or if they were pregnant. The control group consisted of 20 healthy women (mean age 37 ± 11 yrs). They were mainly recruited from hospital employees, and all were healthy as established by their history based on an interview. Controls were matched according to the ages of the SSc patients.

Determination of basal serum PRL levels. Basal serum PRL levels were determined by immunoradiometric assay (ELSA-PROL; CIS-Bio International, Gif sur Yvette, France) in patients and controls. This method identifies the monomeric PRL form (23 kDa). All baseline serum samples were taken during the morning (8:00 AM to 10:00 AM) in the fasting state. Intra- and interassay variance coefficients were 3.5–5.5% and 4.5–6.1%, respectively. The normal serum values were 2–20 ng/ml. HPRL was defined as > 20 ng/ml and mild HPRL as > 20–40 ng/ml[22].

Metoclopramide test. After serum was collected for basal PRL levels, we injected 10 mg of MTC intravenously (diluted in 20 ml of 0.9% saline solution). The PRL response was measured at 30, 60, 90, and 120 min. After centrifugation, serum samples were stored at –20°C. The normal PRL response after stimulation with MTC is < 100 ng/ml. An increased PRL response to MTC is considered suggestive of an augmented functional dopaminergic tone[23].

Computed tomography (CT) of the sella turcica (ST). High resolution axial CT scans were performed in all patients and controls with sagittal and coronal reconstruction technique with fine cuts of 1 mm, and ioversol 320 mg/ml as a contrast medium. Tumors < 10 mm in diameter are termed microadenomas, whereas those > 10 mm are termed macroadenomas[12]. Results were interpreted by an expert neuroradiologist.

Statistical analysis. All analyses were performed with SPSS/ Windows statistical software (version 10.0).

Differences between SSc patients and controls in basal serum PRL levels and after injection of MCT were determined using t test independent samples. Fisher's exact test was used to compare patients with microadenoma with the control group. Differences were considered statistically significant at alpha level ≤ 0.05.

RESULTS

Demographic and clinical characteristics. The mean age, gender, SSc duration, type of SSc, and treatment of the experimental subjects and controls are shown in Table 1, and clinical manifestations of limited and diffuse SSc are shown in Table 2. Age and gender were similar in both groups. Six patients with SSc (20%) had clinical findings that were attributed to microadenomas: 3 had menstrual disorders, 2 had headaches probably associated with microadenoma, and one had galactorrhea and menstrual disorder.

Table 1. Demographic data on study patients with systemic sclerosis and controls.

	Patients with SSc, n = 30	Controls, n = 20
Age, mean ± SD, yrs	37.8 ± 10	37.5 ± 11
Female/male	30/0	20/0
Disease duration, mean ± SD, yrs	8.5 ± 5.5	
Limited/diffuse SSc	20/10	
D-penicillamine	30/30	
Nifedipine	20/30	
Pentoxiphyline	5/30	

PRL levels in patients and controls. The mean basal PRL levels were higher in the 30 patients with SSc versus the 20 healthy controls: 18.2 ± 5.4 ng/ml versus 8.7 ± 1.6 ng/ml, respectively (p = NS). Mild HPRL (> 20 ng/ml) was found in 12/30 SSc patients (40%) (Figure 1).

Table 2. Clinical manifestations of systemic sclerosis.

	Limited SSc (%), N = 20	Diffuse SSc (%), N = 10
Organ involvement		
Skin	20/20 (100)	10/10 (100)
Raynaud's phenomenon	20/20 (100)	9/10 (90)
Lung	6/20 (30)	6/10 (60)
Pulmonary fibrosis	6/20 (30)	6/10 (60)
Pulmonary arterial hypertension	3/20 (15)	1/10 (10)
Esophagus	20/20 (100)	9/10 (90)

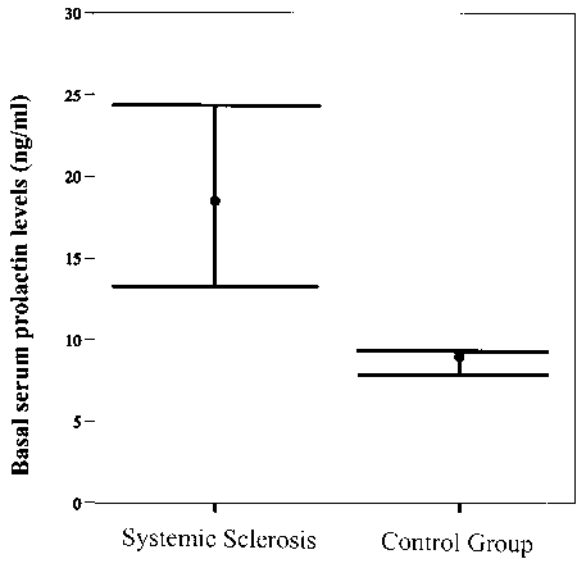

Figure 1. Serum prolactin at baseline in patients with SSc versus controls. Prolactin levels were higher in patients.

PRL levels following MTC injection. The majority of patients with SSc showed a significant increase of PRL at 30, 60, 90, and 120 min in comparison with the control group (Table 3, Figure 2). Higher maximal PRL levels (> 100 ng/ml) were observed in 80% of SSc patients. In contrast, only one control had a higher response. Patients with microadenoma had higher PRL levels, and their response to MTC test was also higher. SSc patients with normal PRL levels also had hyperprolactinemic response to MTC test.

Computed tomography. The frequency of microadenoma (< 10 mm) in patients with SSc was 80% (24 cases). The size of the microadenoma was 5 ± 1.5 mm. Six patients (20%) had no evidence of micro or macroadenomas. In contrast, only one of the controls (5%) had a microadenoma (p = 0.001).

Twenty-four SSc patients had abnormal CT scans of the ST. In 12 instances, the CT scan showed the presence of a microadenoma. In addition, 12 patients had microadenoma plus empty ST (Figure 3), and 6 patients had normal CT scans (Table 4). We did not find differences in PRL levels between diffuse SSc, limited SSc, and CT findings.

DISCUSSION

Our results showed that mean basal PRL levels were not different from healthy controls, but 12 patients (40%) had mild HPRL (> 20 to 40 ng/ml). All controls had normal PRL levels. In addition 83% (25/30) of patients had significantly higher PRL responses to MTC testing in comparison with healthy controls. These results of MTC testing suggest considerable disorders in the dopaminergic regulation of the hypothalamus-hypophyseal system of patients with SSc. Surprisingly, the majority of these patients with increased central dopaminergic tone also had evidence of microadenoma (12 patients) and microadenoma plus partially empty ST (12 patients) demonstrated by CT.

These data have relevance because in earlier studies, the hormonal evaluation of SSc patients included only basal serum PRL levels[24]. Few studies have included a stimulatory test for PRL secretion. Hilty, *et al*[18], studied the diurnal rhythm of PRL and observed a sustained increase over 24 h, with some shift in the rhythm in SSc. Peaks of secretion were detected between 6 and 11 AM, instead of 2–6 AM. We believe that measuring basal serum concentrations of PRL is not sufficient to differentiate an abnormal response from a normal pattern of PRL secretion. Dynamic testing with MTC has been used to diagnose pituitary dysfunction in systemic lupus erythematosus (SLE)[23]. A recent study demonstrated an increase in central dopaminergic tone in SLE and suggested that lymphocyte-derived PRL might contribute to alteration of functional activity of the hypothalamic-dopaminergic system in SLE attempting to maintain serum PRL within a physiological range[25]. In our study, results of the MTC stimulation test suggested a functionally abnormal response in SSc patients. In fact, the majority of our patients had pituitary dys-

Table 3. Basal serum prolactin (PRL, ng/ml) levels and after metoclopramide testing in patients with systemic sclerosis vs healthy controls.

	Basal PRL	30 min PRL	60 min PRL	90 min PRL	120 min PRL
SSc	18.2 ± 5.4	175 ± 5.4	160 ± 64	125 ± 57	108 ± 57
Control	8.7 ± 1.6	61.0 ± 42	52 ± 30	42 ± 21	30 ± 10
p	NS	< 0.001	< 0.001	0.05	0.005

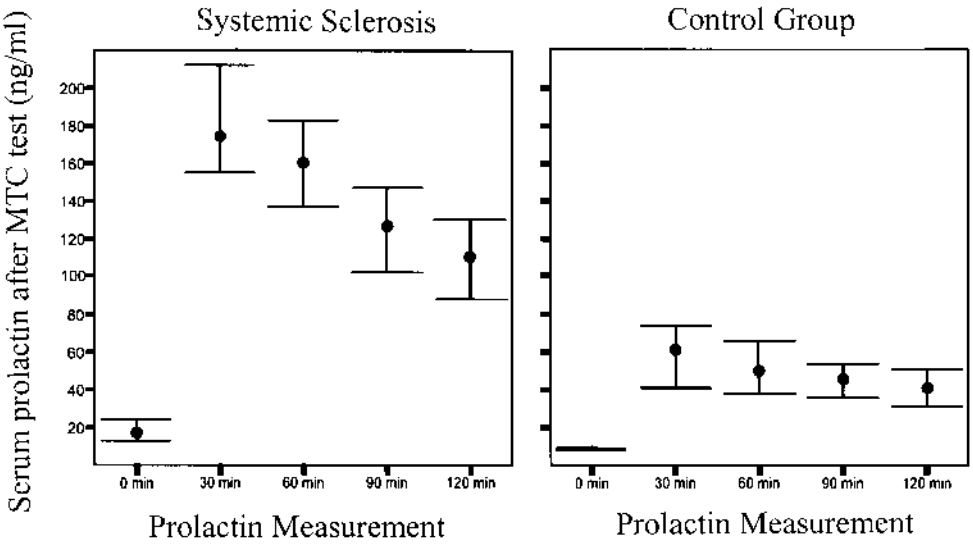

Figure 2. Serum prolactin at baseline and after metoclopramide (MTC) testing in patients with SSc versus controls. After MTC testing, prolactin levels were > 100 ng/ml in patients and < 100 ng/ml in controls.

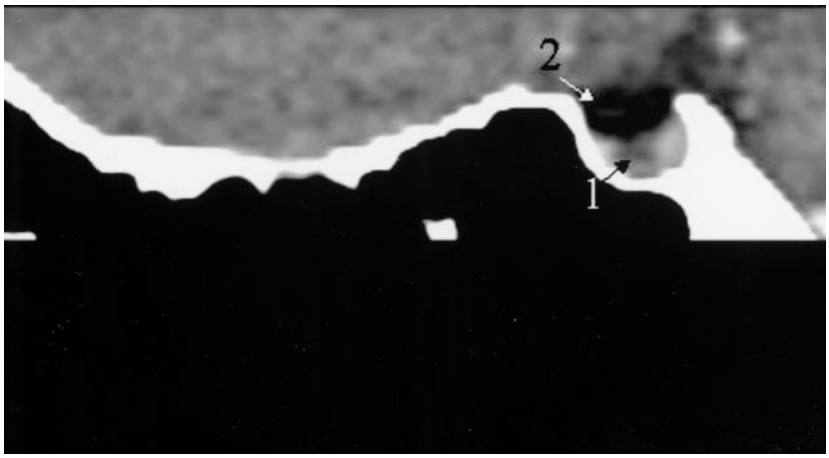

Figure 3. Sagittal CT view of the sella turcica in a patient with SSc. Arrow 1 shows microadenoma with posterior displacement of pituitary gland. Arrow 2 shows partially empty sella turcica.

Table 4. Computed tomography of the sella turcica in patients with systemic sclerosis and in healthy controls.

	Patients with SSc (%)	Controls (%)	p
Microadenomas	12/30 (40)	1/20 (5)	0.001
Microadenomas + empty sella	12/30 (40)	0/20 (0)	0.001
Normal sella turcica	6/30 (20)	19/20 (95)	0.001
Total microadenomas	24/30 (80)	1/20 (5)	0.000

function, with significant increase in dopaminergic tone demonstrated by > 100 ng/ml of PRL serum levels after stimulation with MTC. Of interest, all patients with increased dopaminergic tone also had microadenoma, and only one out of 6 patients without microadenoma had abnormal response to MTC test. Our findings strongly suggest a relationship between increased central dopaminergic tone and microadenomas in patients with Ssc.

The factors responsible for the production of PRL-secreting tumors are obscure. One hypothesis contends that chronic loss of dopamine control from the hypothalamus may be associated with prolactinoma formation. Experimental models suggest that loss of dopamine regulation secondary to prolonged estrogen stimulation leads to adenoma formation[26]. Prolactinomas have been described in adults and pediatric patients with SLE, but the dopaminergic tone with functional test was not analyzed in this subset of SLE patients[27-29].

Screening studies showed that prolactinomas, the most common hormone-secreting tumors of the pituitary gland, have a prevalence of fewer than 5 cases per 10,000 persons[30,31]. These tumors may not be associated with clinical signs or obvious hormonal abnormalities and often remain undiagnosed during the subject's lifetime. According to these studies, only a small number of our patients had clinical manifestations of pituitary tumors.

In a retrospective analysis of 353 individuals with pituitary tumors and other intrasellar masses, 5% had an empty ST[32,33]. In our study, 40% of SSc patients had an empty ST plus microadenoma. The prevalence of a partially empty ST in SSc patients is much higher than expected, probably associated with longterm duration of adenoma.

In our study, all patients were taking D-penicillamine; however, none had gynecomastia. In this regard, there are case reports that show transient gynecomastia occasionally associated with HPRL and D-penicillamine. Kahl, *et al*[34] reported HPRL and massive breast enlargement in a patient that received D-penicillamine for SSc. Serum PRL levels were measured in 4 other patients and were normal in 3. In our study, mean basal PRL levels were not statistically significant in comparison with controls, and HPRL was demonstrated in only 40% of SSc patients. In addition, a recent review did not consider D-penicillamine as a HPRL inducer[35]. Therefore, in our patients, HPRL seemed not to be associated with D-penicillamine.

It is of great interest that many of these patients had abnormal induced levels of PRL without overt clinical manifestations. This condition is a common finding in patients with macroprolactinemia[36]. In our study, the majority of SSc patients (60%) had normal basal PRL levels. Therefore, it is doubtful that HPRL observed in our patients after MTC testing was caused by macroprolactinemia.

There is some information that links HPRL with SSc. La Montagna, *et al*[37] evaluated basal and dynamic levels of pituitary hormone release in female SSc patients using gonadotropin-releasing hormone and thyroid-stimulating hormone stimulation. Basal and stimulated PRL concentrations were associated with skin sclerosis and peripheral vascular and lung involvement. In our study, the majority of patients had the limited form of SSc with visceral involvement.

The role of HPRL in the etiopathogenesis of SSc remains unknown. In SSc there exists a disorder in angiogenesis characterized by insufficient angiogenic response[38]. PRL plays a role as an inhibitor of angiogenesis[39,40], and therefore HPRL in SSc might contribute to angiogenesis abnormalities.

The limitations of our study were that we did not use magnetic resonance imaging (MRI) for diagnosis of microadenomas. Indeed, MRI is better than CT in predicting the presence, position, and size of adenomas in the pituitary fosse[41].

Our study suggests that a subset of patients with SSc have increased dopaminergic tone and microadenomas. The role of hyperprolactinemia in the pathogenesis of SSc remains unknown. Further studies are necessary to confirm our results.

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