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PROLACTIN SECRETION IS INCREASED IN PATIENTS WITH MULTIPLE SCLEROSIS

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ABSTRACT

Before the onset and during experimental allergic encephalomyelitis (EAE), the animal counterpart of multiple sclerosis (MS), prolactin levels were found to be elevated and bromocriptine was found to attenuate the attacks. This study was designed to determine whether patients with MS show evidence of hyperprolactinemia. Twelve patients with MS and twelve healthy controls were studied at baseline and with TRH stimulation, a provocative test for prolactin secretion. Compared to matched controls, patients with MS had slightly but significantly higher prolactin levels at baseline (10.2±1.6 vs 6.4 4±0.57 ng/ml, P=0.042), however, values were within the normal range. The prolactin levels post TRH were significantly higher in patients with MS: peak prolactin level was higher in patients than controls (57.08±6.144 vs 32.94±4.92 ng/ml, P=0.006). The area under the curve of prolactin was also higher in patients than in controls (3421.87±394.53 vs 2317.62±257.22 ng/ml, P=0.030). These findings are compatible with data from studies of experimental animals with MS and suggest that prolactin may play a role in the immunology of MS.

INTRODUCTION

The etiology of multiple sclerosis (MS) and the factors triggering and mediating the immune response in this disease are still unknown. After administration of myelin basic protein, LEW/N rats develop experimental allergic

encephalomyelitis (EAE), an animal model of MS. The disease manifestationsaere accompanied by a rise in serum prolactin levels. Bromocriptine was found to inhibit this rise and attenuate the severity of the attacks (1).

Despite the evidence that prolactin may play a role in the modulation of the immune system, few studies have tried to determine the status of prolactin secretion in patients with MS. One study demonstrated normal prolactin levels in patients with chronic and acute exacerbation of MS (2) while another study showed significant hyperprolactinemia in patients with MS compared to healthy controls (3). Our aim is to determine whether hypersecretion of prolactin may be present in patients with chronic MS. To examine this hypothesis we measured basal and post TRH plasma prolactin levels in patients with MS.

MATERIALS AND METHODS

Subjects

Twelve patients with MS (1 male and 11 premenopausal females; mean age ± SEM, 39.3±3.4yr) were recruited from an MS clinic. Patients were medication free for at least 4 weeks before the study, had not been treated with steroids for more than 2 weeks during the preceding year, and women were not on any estrogen replacement therapy and were randomly seen in regards to the phase of their menstrual cycle. They received a complete medical history, physical and screening laboratory examination to rule out the presence of medical illnesses. All patients were seen by a neurologist (Y.B) to confirm the diagnosis of MS using Poser criteria (4), and severity of illness was rated using the expanded disability status score (EDSS) (5). All the patients had a course characterized as remitting-relapsing. They were recruited during a clinic visit while in the relapsing phase of their illness and prior to starting any medical treatment. The clinical severity of the illness in the group of patients studied was generally mild to moderate by the EDSS (score: 3.7±1.6). Previously, all the patients had MRI or

CT scans of their brain. Reports did not mention any hypothalamic lesion or any pituitary anomaly. However, repeat brain imaging was not done as part of this study. Controls were 12 age (42.2±5.3 years) and sex-matched healthy subjects and were also randomly seen in regards to the phase of their menstrual cycle (Table. I). The institutional research board approved the study, and subjects gave informed consent before beginning the study.

Procedures

All patients and control subjects received 200 mcg of TRH during morning hours (one to two hours after waking up, from 800 till 1000 hr) as an iv bolus. Blood was sampled prior to TRH injection and at 30, 60, 90 and 120 min after the injection. Prolactin and TSH levels were measured in each sample. T4 and T3 uptake were checked on the baseline samples. All patients and subjects were euthyroid according to the results of the thyroid function tests.

Assays

Prolactin assays were performed using a commercially available two-site fluoroimmunometric assay (Delphia) kit. Assays for TSH, T4 and T3 uptake were performed by commercially available kits: RIA from Orin Diagnostic for T4 and T3 uptake and IRMA from Byk-Sangtec Diagnostic GmbH for TSH.

Statistical analysis

The *peak time*, the time at which prolactin peaked following TRH administration, was determined for each subject. Responses to TRH stimulation were compared between groups by comparison of mean peak response, area under the curve (AUC) and mean AUC of the response. Responses to TRH were calculated using the analysis of variance (ANOVA). Values are reported as mean ± SEM.

RESULTS

Baseline prolactin

Baseline plasma prolactin was within the normal range for all subjects, and significantly higher in patients with multiple sclerosis than in controls. (Table II)

TABLE I

Patient Characteristics

	Multiple Sclerosis	Control
n (M/F)	12(1/11)	12(1/11)
Age (yr)	39.3+3.4	42.3±5.3
EDSS score	3.7±1.6	---
TSH (U/ml)	1.4±0.1	1.4±0.1

TABLE II

Baseline, peak and integrated plasma prolactin (±SEM) after TRH administration

Prolactin	Multiple Sclerosis	Control	P
Baseline (ng/ml)	10.20±1.60	6.44±0.57	0.042
Peak (ng/ml)	57.08±6.144	32.94±4.92	0.006
Integrated (ng/ml)	3421.87±394.53	2317.62±257.22	0.030

There was no significant statistical correlation between the baseline prolactin levels and the EDSS scores.

TRH stimulation

There was no significant difference between the peak time of patients and controls: 32.0±2.5 and 30±0.0 minutes, respectively. The prolactin levels post TRH were significantly higher in patients with MS. Total peak prolactin level was higher in patients than controls (Table II). Total integrated (area under the curve) plasma prolactin was significantly higher in patients with multiple sclerosis than in controls (Table II). The average area under the curve of prolactin was similarly

higher in patients than in controls: 28.51±3.28 vs 19.31±2.14 ng/ml, P=0.030

There was no significant statistical correlation between the peak or the integrated prolactin levels and the EDSS scores.

TSH results:

Baseline and post-TRH TSH values were similar in subjects and controls (Table III).

DISCUSSION

Prolactin abnormalities have been described in a number of immunologic disorders, including systemic lupus erythematosis (6), adjuvant arthritis (7), thyroid disease (8) and autoimmune uveitis (9). This is the first clinical study to evaluate the role of prolactin in patients with MS. However, the interaction between the immune system and prolactin has been the subject of several experimental studies. Hypophysectomized rats were found to be immunocompromised with decreased humoral and hypersensitivity responses. In such animals, immunocompetence could be restored by exogenous prolactin administration (10). Dopaminergic agonists that inhibit prolactin release, induce immunosupression in animals (11) and treatment with prolactin reverses this effect. Prolactin treatment of normal mice results in a dose-dependent increase in splenic cell responses to mitogens such as concanavalin A. Prolactin was also found to induce the expression of IL-2 receptors and promote the secretion of interferon gamma (12). Evidence also exists that both T and B lymphocytes have high affinity receptors for prolactin and the number of receptors per cell is similar for lymphocytes and mammary gland cells. Human studies show that lymphocytes binding to cyclosporine can be reversibly induced by prolactin (13). This may suggest that cyclosporine-induced immunosupression is partly mediated by the interaction with the prolactin receptor. In EAE, the animal counterpart of human MS, initiation of continuous bromocriptine treatment before immunization reduces both the severity and the incidence of clinical signs (1).

TABLE III

Baseline, peak and integrated plasma TSH (±SEM) after TRH administration

TSH	Multiple Sclerosis	Control	P
Baseline (U/ml)	1.45+±0.063	1.41±0.13	ns
Peak (U/ml)	9.83±0.37	12.85±1.24	ns
Integrated (U/ml)	314.69±142.72	430.31±195.45	ns

EAE rats have a three-fold rise in basal prolactin levels on day 4 after immunization and maintain elevated prolactin levels on day 10 before the appearance of clinical signs.

This study does provide preliminary evidence that the changes in regulation of prolactin secretion demonstrated in animals in response to experimentally induced allergic encephalomyelitis also occur in the human disease counterpart. The rise in prolactin levels both in baseline and post TRH does not seem to be related to any pituitary or thyroid abnormalities as evidenced by the thyroid function tests. The patients were clinically stable, without any major stress, and not consuming any drug that may potentially increase their prolactin levels. The role of stress and alterations in the hypothalamic pituitary adrenal axis are not fully understood in patients with MS. Stress may not be very prominent in such patients since, in a previous study of a very similar group of patients, cortisol responses to ACTH stimulation tests and ACTH responses to CRH stimulation tests were normal (14). Another hormonal alteration, namely hypocortisolism, has been implicated in the development of MS. Despite the fact that patients with optic neuritis who were treated with steroids were less likely to develop MS, Michelson et al. (14) did not show any significant hypocortisolism in their patients with MS. On the contrary, they demonstrated mild basal hypercortisolism and blunted ACTH response to AVP suggesting a state of mild chronic immune stress (14). In a similar group of

patients, Wei and Lightman (15) demonstrated a lower response of cortisol to CRH which speaks for a state of relative hypercortisolism.

MS lesions affecting the hypothalamus and interfering with the release of the prolactin inhibitory factor may explain the hyperprolactinemia in these patients. Kira et al (3) studied the presence of hypothalamic lesions in MS patients by MRI. Four out of eight MS patients with hyperprolactinemia had diencephalic hypothalamic lesions contiguous with the third ventricle (3). In our study, each patient has had either an MRI or a CT scan of the brain sometime in the past and prior to enrollment in the study. In the official radiologic reports there was no mention of any hypothalamic lesion or any pituitary anomaly. However, we did not re-read or repeat the brain X-rays in this study to rule out the presence of any missed or new hypothalamic-pituitary pathology.

Finally, this study is limited by the small number of patients and by the lack of detailed sequential imaging of the brain to rule out hypothalamic involvement by MS. However, the results of this study provide evidence that there is a significant rise in prolactin secretion in patients with MS. Determining whether the high prolactin is a factor in the pathogenesis of MS would require a prospective study of patients who have not yet developed MS, so the possibility remains open that hyperprolactinemia contributes to the susceptibility to develop MS. The response to bromocriptine therapy in patients with new onset MS or with optic neuritis may help understand the role of prolactin in this disease.

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