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Serum prolactin levels and Behçet disease

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PURPOSE. *To evaluate serum prolactin levels in Behçet disease (BD) and correlate with phenotypic expression of the disease.*

METHODS. *This was a prospective, nonrandomized comparative trial. Twenty-two patients fulfilling BD Research Committee criteria and 21 healthy control subjects were included. Patients were classified in complete-type or incomplete-type BD subgroups according to clinical characteristics such as recurrent oral ulcers, genital ulcers, skin lesions, and ocular disease. Age, sex, HLA phenotyping, and therapy were recorded for comparative analysis between groups. Serum prolactin levels were determined by electrochemiluminescence immunoassay on a Modular Analytics E170 analyzer.*

RESULTS. *Prolactinemia was significantly higher (mean=19.34 ng/mL) in BD patients vs controls (mean=9.83 ng/mL) (p=0.009). This value was also statistically higher in complete-type BD subgroup vs controls (p=0.02). Younger patients (<30 y) required corticosteroids plus immunosuppressives more often (75%), suggesting an association between age and disease severity, although not statistically significant.*

CONCLUSIONS. *Results suggest the role of prolactin in BD pathogenesis and its association with disease expression, especially in complete-type BD. (Eur J Ophthalmol 2007; 17: 404-7)*

KEY WORDS. *Behçet disease, Serum prolactin levels, Uveitis*

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INTRODUCTION

Prolactin (PRL) is a circulating hormone usually known by its important role in lactation. It is a polypeptide chain secreted by pituitary gland. Its secretion is hypothalamus controlled by inhibitory factors, like dopamine, and stimulatory factors, such as thyrotropin-releasing-hormone. There is also feedback by numerous circulating factors.

There has been a remarkable development in knowledge of prolactin's physiopathologic role, especially concerning immunology.

There is conclusive scientific evidence of prolactin's functions as a cytokine (1-5). Prolactin is thymogenic and thereby influences immune cells' proliferation and differentiation. Prolactin-specific receptors have been identified on B and T lymphocytes, monocytes, and natural killer cells. There is a structural homology between receptors for PRL and for interleukins 2 and 6. Lymphocytes have also been shown to secrete a prolactin-like substance. It has been proven that hypophysectomized rats are immunocompromised and PRL introduction can restore their immune function (1).

Dopaminergic agonists that suppress serum prolactin have been enrolled in clinical trials for autoimmune disease treatment and organ transplant rejection prevention (1, 2).

Abnormal serum prolactin levels are related to many immunologic diseases, such as systemic lupus erythematosus, autoimmune uveitis, thyroid disease, Reiter syndrome, rheumatoid arthritis, psoriatic arthritis, juvenile chronic arthritis, Sjögren syndrome, scleroderma, dermatomyositis, multiple sclerosis, and Behçet syndrome, among others (1-5).

Prolactin from both pituitary and lymphocyte origin plays

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an essential role in white blood cells' proliferation and function.

Prolactin is a cytokine showing biphasic nature of immunomodulatory effect: hypoprolactinemia and hyperprolactinemia can both lead to immunocompromise (1). Behçet disease (BD) pathogenesis remains obscure, although it has long been postulated that autoimmune responses in genetically susceptible individuals are involved. Based on these data, it seems likely that PRL may play a role in BD pathogenesis. This study was designed to address whether patients with BD had abnormal serum prolactin levels and its potential association with phenotypic expression of the disease.

METHODS

In this prospective, nonrandomized, comparative single-center trial, 22 patients fulfilling BD Research Committee criteria and followed as outpatients in our uveitis department were included.

Patients were classified in the subgroups of complete and incomplete type and analyzed according to age, clinical manifestations (recurrent oral ulceration, ocular inflammatory disease, skin lesions, and recurrent genital ulceration), HLA phenotyping, and therapy (corticosteroids vs corticosteroids plus immunosuppressives).

A group of 21 age- and sex-matched healthy subjects was used as control.

Exclusion criteria for both the patient and control groups included pregnancy, nursing, endocrinologic disease such as neoplasia (namely breast cancer or pituitary tumors), hypothalamic and pituitary stalk disease, primary hypothyroidism, chronic renal failure, cirrhosis, immunologic disease except BD, seizures, and medications or drugs (estrogens, neuroleptics [especially phenothiazines], cimetidine, antidepressants, sulpiride, verapamil, metoclopramide, opiates, amphetamines, cocaine).

Serum prolactin levels were determined by electrochemiluminescence immunoassay on a Modular Analytics E170 Elecsys (Roche, Indianapolis, IN) analyzer.

Elecsys Prolactin used two monoclonal antibodies specifically directed against human prolactin. The biotinylated antibody in reagent R1 recognizes the N-terminal end of the prolactin molecule, whereas the antibody marked with the ruthenium complex in reagent R2 reacts with a region in the middle of the prolactin molecule.

The test used the sandwich principle and had a total duration of 18 minutes. Results are determined via a calibration curve which is instrument-specifically generated by two-point calibration and a master curve provided via the reagent barcode.

Blood sampling was performed between 8:00 and 10:00 AM, after fasting. Blood was collected using 20-Gauge needles and 5 mL syringe to standard sampling tubes and kept at ambient temperature (20–25 °C) until measurement, performed within 2 hours.

The protocol used for this study was institutionally approved.

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) 12.0 for Windows software (SPSS Inc., 2003) was used. A descriptive analysis of demographic and clinical parameters was performed. Comparisons between groups were performed using Mann-Whitney test, since the sample did not follow a normal distribution. Statistical significance was assumed at $p<0.05$.

RESULTS

A total of 22 patients (45.50% female, mean age 46.00 years, SD=16.79, range 15–70 years) were recruited into this study and underwent the baseline examination. Out of these, 18 (81.80%) had recurrent oral ulcers, 11 (50.00%) had genital ulcers, 20 (90.90%) had ocular disease, and 10 (45.50%) had skin lesions (Tab. I).

According to BD Research Committee criteria, patients were classified into two subgroups: 5 (22.70%) were classified as complete-type BD, fulfilling the four major symptoms simultaneously or at different times, and 17 (77.30%) were classified as incomplete-type BD, presenting with three major symptoms simultaneously or at different times or presenting with typical recurrent ocular disease with one other major criterion (Tab. II).

HLA phenotyping was performed in all patients: 19 (86.40%) were HLA-B51 positive and 3 (13.60%) were positive for HLA other than HLA-B51 (HLA-B8, HLA-B35, and HLA-B40).

Therapy was recorded and patients were classified into two subgroups: 12 (54.50%) requiring corticosteroids alone (topical, periocular, and/or systemic) and 10 (45.50%) requiring corticosteroids plus one or more immunosuppressives (4 [40%] azathioprine, 3 [30%] cy-

TABLE I - PATIENT GROUP CLINICAL FINDINGS

	No.	%
Recurrent oral ulcers	18	81.8
Genital ulcers	11	50.0
Ocular disease	20	90.9
Skin lesions	10	45.5

TABLE II - PATIENT GROUP CLASSIFICATION

	No.	%
Complete type Behçet disease	5	22.7
Incomplete type Behçet disease	17	77.3

TABLE III - SERUM PROLACTIN LEVELS IN PATIENT GROUP AND COMPLETE-TYPE BEHÇET DISEASE SUBGROUP VS CONTROL

	Mean (ng/mL)	p
Patients	19.3	0.009
Control	9.8	
Complete-type Behçet disease subgroup	17.7	0.02
Control	9.8	

TABLE IV - PATIENT GROUP THERAPY ACCORDING TO AGE

	<30 yr	≥30 yr	p
Corticosteroids alone	25.0	61.1	0.3
Corticosteroids plus one or more immunosuppressives	75.0	38.9	

Values are percentages

closporine, 2 [20%] colchicine, 1 [10%] infliximab).

In the control group, 22 subjects were included, 47.60% female, mean age 46.24 years, SD=15.46 (range 15–70 years).

When comparing prolactinemia, mean value was significantly higher in BD patients (mean=19.34 ng/mL) than in controls (mean=9.83 ng/mL) (p=0.009).

This difference was also statistically different when comparing complete-type BD subgroup vs controls (19.34 ng/mL vs 9.38 ng/dL, p=0.02) (Tab. III).

There was no statistically significant association between serum PRL levels and specific clinical features (recurrent oral ulcers, genital ulcers, ocular disease, or skin lesions).

No significant differences were found between HLA-B51 positive patients and HLA-B51 negative patients concerning PRL levels.

Although there was no statistically significant difference in PRL levels comparing patients requiring corticosteroids alone and those requiring corticosteroids plus immunosuppressives, we found that patients under 30 years old required corticosteroids plus immunosuppressives more often (75%) than older patients (Tab. IV).

DISCUSSION

To our knowledge, this is the second report on this subject published in an ophthalmologic journal and the fifth in the general literature.

The mean prolactinemias were within normal range, considering the cut-off 20 ng/mL for men and 30 ng/mL for women. This result corroborates the results found by other investigators (6-8). However, in spite of falling out of the hyperprolactinemia cut-off values, mean PRL levels were statistically higher than controls, in contrast to two previously published articles in which statistical difference was not found (6, 9). The study published on this subject in 2001 found mean PRL levels in BD patients to be higher than normal with p value very near statistical significance (p=0.064) (6). The latest published article on this subject (2006) revealed statistically higher serum prolactin levels in BD patients in comparison to healthy controls (8).

Different study design and patient selection may explain the contradictory results published. Environmental or genetic factors may also play a role.

Mean prolactinemia difference was also statistically significant in complete-type BD subgroup vs controls, with higher mean value in the first group.

We found no statistically significant association between PRL levels and each clinical feature, which is also corroborated by the literature (6).

No significant differences were found comparing prolactinemia in incomplete-type BD subgroup vs controls, suggesting that abnormal PRL levels are only or at least more strongly correlated in the most severe cases. This

result may explain why other authors reported no relation between disease activity and PRL levels, taking into account that BD population was analyzed as a whole (6, 7).
Patients under 30 years old required corticosteroids plus immunosuppressives more often (75%) than older patients, suggesting an association between age and disease severity.
In this study, we found a high frequency of HLA-B51 allele in patients with BD, which is in consonance with the frequencies of occurrence reported from other countries of high prevalence of BD, namely those also bordering the Mediterranean (10-13).
In summary, our results suggest that prolactin can play a role in BD pathogenesis and disease expression, especially in complete-type BD.

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