

Short Communication**Serum prolactin level in multiple sclerosis patients**

Mohammad Ali Shafa\*, Alireza Vakilian\*\*,  
Alireza Poorebrahimi\*\*\*, Jafar Ahmady Kahnali\*\*\*\*

**Abstract**

**BACKGROUND:** Multiple Sclerosis (MS) is the most common demyelinating disease. An autoimmune basis has been confirmed for pathogenesis of MS. Prolactin (PRL) has roles in these mechanisms. Its serum levels change in MS according to some reports. The purpose of this study was to survey these changes in MS patients.

**METHODS:** Sixty MS patients were included in this cross-sectional study. The same number of controls matched for sex and age were studied. Pregnant, lactating women, consumers of specific medications and patients with underlying diseases were excluded from our study. RIA was used for determination of serum levels of PRL.

**RESULTS:** In this study, PRL level in male patients was  $14.23 \pm 11.47$  ng/ml compared to controls with mean level of  $7.21 \pm 4.12$  ng/ml (P value  $<0.001$ ). Mean PRL level in female patients was  $20.18 \pm 11.04$  ng/ml whereas controls had a mean level of  $14.45 \pm 6.93$  ng/ml (one-tailed P value  $<0.05$ ). So there were significant differences in serum PRL level between case and control groups in both men and women

**CONCLUSIONS:** PRL has a positive relation with MS in both sexes. Further studies for determination of causality relation and drug effect in endocrine system on MS pathogenesis are suggested.

**KEY WORDS:** Multiple Sclerosis, prolactin, male, female

JRMS 2006; 11(5): 325-328

Multiple sclerosis (MS) is the most common demyelinating disease in the central nervous system (CNS). It is characterized clinically by episodes of focal disorders of the optic nerves, spinal cord and brain, which remit to a varying extent and recur over a period of many years. A rule that has guided clinicians for many years is that the diagnosis of MS is not secure unless there is a history of remission and relapse with evidence on examination of more than one discrete lesion of the CNS<sup>1</sup>. Pathologically, MS is characterized by multifocal areas of demyelination with relative preservation of axons, loss of oligodendrocytes, and astroglial scarring<sup>2</sup>.

About two-thirds of cases of MS have their onset between 20 and 40 years of age. The incidence of MS is two to three times higher in women than in men<sup>1,3</sup>. All data point to a relationship between MS and some environmental factors. In addition to this initial factor (viral or other infections) there are secondary factors that must be operative in later life to activate neurological disease. The most popular view about pathogenesis of MS is that secondary mechanism is an autoimmune reaction<sup>1</sup>. The endocrine system influences the immune system and vice versa<sup>4</sup>. Dysfunction within the hypothalamic-pituitary-gonadal axis occurs

\*Assistant Professor of Neurology, Kerman University of Medical Sciences, Kerman, Iran.

\*\*Neurologist, Neurology Department, Ali Ebne Abitaleb Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

\*\*\*Neurologist, Emam Reza Hospital, Sirjan, Kerman, Iran.

\*\*\*\*General Practitioner, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Correspondence to: Dr Ali Reza Vakilian, Neurologist, Neurology Department, Ali Ebne Abitaleb Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. e-mail: vakilian\_neu@yahoo.com

frequently in women with MS and induces menstrual disturbances and subsequent infertility <sup>5</sup>. Both the PRL and the PRL receptor genes map to genomic regions that showed linkage with autoimmunity <sup>6</sup>.

Excess prolactin (PRL) augments some immune reaction whereas low serum levels of PRL inhibit immune reaction and prevent experimental allergic encephalomyelitis (EAE), an animal model of MS <sup>7</sup>. Hormonal effect is not evaluated precisely in pathogenesis of MS. In a case-control study done in Iran, authors could not demonstrate a significant difference between PRL level in MS patients and healthy controls <sup>8</sup>. We decided to carry out a study to detect the relation of MS with serum PRL in both sexes in our patients.

## Methods

This cross-sectional study was performed on MS patients from 1999 to 2003. First, a pilot study was performed on 10 male and 10 female patients to determine sample size. Serum PRL was measured. The required sample size was found with respect to variance and mean of patients' hormone levels, mean and standard deviation of hormone levels in normal subjects ( $\alpha$  error = 5%, power=80%). The calculated sample size for PRL was 60 patients. The diagnosis was performed by two neurologists. Past medical history, clinical examination, magnetic resonance imaging (MRI), evoked potentials study and lumbar puncture (LP) were used (Poser criteria for definite MS) <sup>9</sup>. The control group consisted of 60 healthy individuals (40 men and 20 women) selected to match the patients with respect to age and gender. The controls were not pregnant or lactating and did not take any regular medication. The study was approved by the ethics committee of the Kerman University of Medical Sciences and written informed consent was obtained from all subjects before entering the study.

Serum samples were obtained from controls and patients admitted for therapy and other evaluations or outpatients referred to Shafa Hospital for our study in fasting condition.

In the male group, age was recorded. In the female group, age and date of menstrual cycle were recorded. We decided to perform the female hormonal examination in patients and controls at the end of third week of the menstrual cycle, to exclude biases due to hormonal changes in this period. Primary hypothyroidism, hypothalamic disease, pituitary adenoma, renal failure, seizure, and cirrhosis cases were excluded. Also pregnant, lactating and menopause women were excluded from our study. History of use of drugs such as phenothiazines, butyrophenones, methyl dopa, estrogens, opiates, ranitidine, amitriptyline, nortriptyline, and fluoxetine would also exclude the subject from the study.

Samples were centrifuged and serum was extracted and frozen in laboratory (-15 centigrade). Sixty normal subjects with age and sex characteristics similar to the cases were chosen for PRL study. Samples were extracted from normal controls in fasting condition. Age for both sexes and date of menstrual cycle for females were considered in normal controls in studying hormone level. Radioimmunoassay (RIA) was used to determine serum hormone levels. Data were expressed as mean  $\pm$  standard deviation and one-tailed  $P \leq 0.05$  was considered as statistically significant. Data were analyzed with SPSS using independent t-test.

## Results

In this study serum PRL levels were recorded in 40 male patients and 20 female patients. PRL levels of MS and control group subjects are demonstrated in table 1. PRL level was recorded as ng/ml. The mean age of patients whose PRL was studied was 30.17 years in patients and 30.34 years in controls. 80% of MS patients were aged 20-40 years and 10% were aged over 40.

86% of the patients were of the relapsing-remitting subtypes. 8% of the cases were secondary progressive and the remaining patients were primary progressive or progressive relapsing.

**Table 1.** Comparison between serum prolactin level of MS patients and controls

Sex	Number	Patients Prolactin Level	Controls Prolactin Level	P-value
Males	40	14.23 ± 11.47	7.21 ± 4.12	P<0.001
Females	20	20.18 ± 11.04	14.45 ± 6.93	P<0.05

## Discussion

Multiple sclerosis is a disease of CNS characterized by multiple areas of inflammation and demyelination in the white matter of the brain and spinal cord. Prolactin, which is also produced by activated lymphocytes, has been considered in immunoregulation as a co-factor participating in the immunopathogenic mechanism of MS<sup>10</sup>. PRL belongs to the growth and lactogenic hormone family and has potent immunomodulating properties. Mild hyperprolactinemia has been found to enhance several autoimmune diseases and increased PRL plasma level has been described in the experimental MS model while the PRL antagonist, bromocriptine (BMC) was able to suppress the disease<sup>11</sup>. The use of clones allowed the detection of direct effect of PRL on T-cells, even when these have few or no detectable PRL receptors, confirming that human T-lymphocytes are targets for PRL<sup>12</sup>.

Hypoprolactinemia was marked by the impairment of the ratio of active to total rosette where as hyperprolactinemia was discovered to be altered by a decline in T lymphocyte count. BMC was established to attenuate the MS attacks<sup>13</sup>. In a study, the post-TRH test PRL level was significantly higher in patients with MS<sup>14</sup>. Heesen et al investigated further, the question of PRL alterations in MS. They correlated PRL baseline in 132 MS patients with disease course or activity. According to inhibitory (BMC) and stimulatory (metoclopramide) tests, no correlation of baseline value with disease course or activity was found<sup>11</sup>.

Grinsted et al found that dysfunction within hypothalamic-pituitary-gonadal axis occurs frequently in women with MS. The MS patients had significantly higher concentrations

of PRL, LH, FSH, total and free TES and significantly lower serum concentrations of estrone sulfate<sup>5</sup>. The abnormal hormone concentrations were not related to the clinical status of the disease.

Yamasaki et al clarified the clinical features of MS patients with hyperprolactinemia.

They found higher levels of PRL only in women with Asian types of MS (optic nerve and spinal cord involvement)<sup>15</sup>. Given these conflicting results, we further investigated the alterations of PRL in MS patients.

In this study we found a positive relation between PRL level and the male sex in MS patients (statistically significant) compared to normal controls. The differences between various studies may suggest that these hormone levels might be secondary to other factors in MS patients. These hormones may not be related primarily to MS. Our experiment had 80% power to detect a difference between means of 0.18 with a significance level of 0.05 (one-tailed). Further studies of other hormones and their regulatory systems may be helpful in this survey. These findings can be due to the effect of MS on hypothalamo-pituitary-gonadal axis. In the Heesen study, PRL does not seem to be relevant as an activity marker in the whole MS population<sup>11</sup>. Another opinion about increased PRL in MS is the effect of plaques in hypothalamus, which cause blockage of PRL suppressor protein secretion. The result of this condition is high PRL serum level and increased immune response<sup>16</sup>. Overall, it seems that hormone changes do not cause MS, but these are systemic changes found in this disease. Further investigations of this relationship and the role of drugs used in endocrinology for PRL changes, on MS are required.

## Acknowledgement

Authors wish to thank the Department of

Neurology and Neural Sciences Research Center (Kerman University of Medical Sciences).

## References

1. Ropper AH, Brown RH. Adams and Victor principles of neurology. 8th ed. New York: McGraw-Hill Professional; 2005. p. 771-96.
2. Micheal J, Dawson O, Dawson D. Multiple sclerosis and other inflammatory demyelinating disease of the CNS. Neurology in clinical practice. Buther Worth Heinemann; 2000. p. 1431-1467.
3. Rowland LP, Miller JR. Multiple Sclerosis. Merritts Neurology. Lippincot Williams & Wilkins, 2005: 941-963.
4. Besedovsky HO, del Rey A. **Immune-neuro-endocrine interactions: facts and hypotheses.** *Endocr Rev* 1996; 17(1):64-102.
5. Grinsted L, Heltberg A, Hagen C, Djursing H. **Serum sex hormone and gonadotropin concentrations in premenopausal women with multiple sclerosis.** *J Intern Med* 1989; 226(4):241-244.
6. Mellai M, Giordano M, D'Alfonso S, Marchini M, Scorza R, Giovanna DM et al. **Prolactin and prolactin receptor gene polymorphisms in multiple sclerosis and systemic lupus erythematosus.** *Hum Immunol* 2003; 64(2):274-284.
7. Reder AT, Lowy MT. **Serum prolactin levels in active multiple sclerosis and during cyclosporin treatment.** *J Neurol Sci* 1993; 117(1-2):192-196.
8. Harirchian MH, Sahraian MA, Shirani A. **Serum prolactin level in patients with multiple sclerosis: a case control study.** *Med Sci Monit* 2006; 12(4):CR177-CR180.
9. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC et al. **New diagnostic criteria for multiple sclerosis: guidelines for research protocols.** *Ann Neurol* 1983; 13(3):227-231.
10. Draca S, Levic Z. **The possible role of prolactin in the immunopathogenesis of multiple sclerosis.** *Med Hypotheses* 1996; 47(2):89-92.
11. Heesen C, Gold SM, Bruhn M, Monch A, Schulz KH. **Prolactin stimulation in multiple sclerosis--an indicator of disease subtypes and activity?** *Endocr Res* 2002; 28(1-2):9-18.
12. Dogusan Z, Martens N, Stinissen P, Hellings N, Demotte N, Hooghe R et al. **Effects of prolactin on cloned human T-lymphocytes.** *Endocrine* 2003; 20(1-2):171-176.
13. Golovkin VI, Mikhailenko AA, Rakov AL. **[Pathogenetic role of prolactinemia in multiple sclerosis].** *Sov Med* 1991; 10:15-17.
14. Azar ST, Yamout B. **Prolactin secretion is increased in patients with multiple sclerosis.** *Endocr Res* 1999; 25(2):207-214.
15. Yamasaki K, Horiuchi I, Minohara M, Osoegawa M, Kawano Y, Ohyagi Y et al. **Hyperprolactinemia in optico-spinal multiple sclerosis.** *Intern Med* 2000; 39(4):296-299.
16. Bernardi S, Grasso MG, Bertollini R, Orzi F, Fieschi C. **The influence of pregnancy on relapses in multiple sclerosis: a cohort study.** *Acta Neurol Scand* 1991; 84(5):403-406.