Journal of Internal Medicine 1989; **226**: 241–44

Serum sex hormone and gonadotropin concentrations in premenopausal women with multiple sclerosis

L. GRINSTED*, A. HELTBERG†, C. HAGEN‡ & H. DJURSING*

*From the * Department of Obstetrics and Gynaecology, University Hospital of Copenhagen, Hvidovre, † Department of Neurology Amtssygehuset, DK 4000 Roskilde and MS Rehabilitation Center, DK 4690 Haslev, and ‡ Department of Internal Medicine and Endocrinology, University Hospital of Odense, 5000 Odense, Denmark*

Abstract. Grinsted L, Heltberg A, Hagen C, Djursing H (Department of Obstetrics and Gynecology, University Hospital of Copenhagen, Hvidovre, Department of Neurology Amtssygehuset, DK 4000 Roskilde and MS Rehabilitation Center, DK 4690 Haslev, and Department of Internal Medicine and Endocrinology, University Hospital of Odense, 5000 Odense, Denmark). Serum sex hormone and gonadotropin concentrations in premenopausal women with multiple sclerosis. *Journal of Internal Medicine* 1989; **226**: 241–44.

Dysfunctions within the hypothalamic–pituitary–gonadal axis occur frequently among women with multiple sclerosis (MS) and may induce menstrual disturbances and subsequent infertility. We have measured serum concentrations of prolactin, gonadotropins and sex hormone binding globulin (SHBG) as well as free and bound oestrogen and androgen levels in 14 women of fertile age with MS. These women all displayed regular cycles without having experienced fertility problems. As controls 14 normal women with regular periods and ideal body weight of 91% (range 80–101) were included. Serum from both groups was sampled during the early follicular phase. The MS-patients had significantly ($P < 0.05$) higher concentrations of prolactin, LH, FSH, total and free testosterone ($P < 0.01$) and a significantly lower serum concentration of oestrone sulphate ($P < 0.01$). The abnormal hormone concentrations were not related to clinical status of the disease. We propose that the increased androgen levels are of ovarian origin as adrenal androgens were normal.

The reason for the slight increase of prolactin and the marked increase of gonadotropins in women with MS is speculative. As oestradiol levels, however, were within normal range, we assume that a peripheral resistance to gonadotropins combined with an abnormal central regulation causes the increased pituitary secretion.

Keywords: multiple sclerosis, sex hormones.

Introduction

The lesion in multiple sclerosis (MS) is a perivenular demyelination in the central nervous system, possibly on an immunological basis, although the aetiology of this disease remains unknown.

The central regulation of ovarian function is located within the hypothalamus and the pituitary gland. Therefore diseases in these areas may lead to irregular menstrual cycles and infertility. Recently Hansen *et al.* [1] and Møller *et al.* [2] reported that a proportion of patients with MS has circulating IgG autoantibodies reacting against cytoplasmic components in the somatotropic cells of the anterior pituitary lobe. The presence of these autoantibodies may lead to disturbances in the hypothalamic–pituitary function. In addition Sørensen *et al.* [3] found altered somatostatin concentrations in MS-patients connected with relapses of the disease. Somatostatin is known to affect the secretion of various neurotransmitters and hormones that

Abbreviations: CNS, central nervous system. DHEAS, dehydroepiandrosterone sulphate. DHT, dehydrotestosterone. FSH, follicle stimulating hormone. LH, luteinizing hormone. MS, multiple sclerosis. SHBG, sex hormone binding globulin. SEM, standard error of the mean.

influence the pituitary–gonadal axis [4] and a relationship between somatostatin and dopamine is also known.

Therefore changes in somatostatin release may influence dopaminergic neurone activity and thus lead to altered pituitary–gonadal function [5]. Dougados *et al.* [6] examined the plasma androgen status of several autoimmune diseases and did not show any difference between MS-patients and controls. Poser *et al.* [7] found decreased values of gonadotropins and oestrogen in the urine of MS-patients.

In the present study, we have evaluated the menstrual pattern and the basal hormonal profile of the pituitary–gonadal axis in women with MS of fertile age.

Materials and methods

Fourteen consecutive patients (Table 1) with multiple sclerosis according to the criteria of Schumacher *et al.* [8], 24 to 45 years old (mean 36.4 ± 2.4 years, SEM 2.3) were included in the study. Age at onset of disease varied from 18 to 35 years, and the duration of the disease ranged from 1 to 27 years. Five of the patients with relapsing-type of MS displayed clinically acute attacks, manifested by an objective progression of the previous symptoms, two patients displayed slowly progressive symptoms and 7 patients were in stationary phase at the time of blood sampling. Four of the patients had disability status score according to Kurtzke [9] between 2 and 4 and ten patients had a score of between 6 and 7 (Table 1). Ten patients had increased IgG concentration in the cerebrospinal fluid. The mean body weight of the MS-patients was 89% (70–113%) of ideal.

Table 1. Clinical data on 14 women with multiple sclerosis

% of ideal body weight	Disability status scale (Kurtzke)	No. of deliveries	Increased IgG in cerebrospinal fluid
113	2	2	+
76	6	2	+
68	7	1	−
97	6	0	−
70	7	1	−
87	7	0	+
100	4	0	+
85	7	0	−
60	6	2	+
82	3	2	+
111	6	2	+
85	7	0	+
97	6	2	+
93	2	1	+

Fourteen regularly menstruating women, age 32.9 ± 3.4, range 28–38 years, 91% body weight, range 80–101%, served as controls. All women were normotensive and had normal serum creatinine concentrations. None received drugs known to influence basal plasma levels of the hormones investigated. All women were free of other diseases known to influence pituitary–gonadal function. All women gave informed consent and the study was approved by the local ethical committee.

Blood samples

Blood samples were obtained from days 1 to 6 of the menstrual cycle, between 10.00 and 12.00 hours and at least 2 h after sleep. After separation of serum the samples were stored at -20 °C.

Sex hormone-binding globulin (SHBG) in serum was measured as previously described by Hertz & Johnsen (1983) [10]. Unconjugated steroids (oestrone, oestradiol-17 beta, testosterone, 5 alpha-dihydrotestosterone (DHT) and delta-4-androstenedione) were determined in serum by radioimmunoassays, after ether-extraction and column chromatography (Emment *et al.* [11]), Parker *et al.* [12]). Dehydroepiandrosterone sulphate (DHEAS) and oestrone sulphate were analysed in the same way as the unconjugated steroids, allowing extraction and subsequent solvolysis/hydrolysis, as described by Frantz *et al.* [13]. Free non-protein-bound oestradiol was measured by centrifugal ultrafiltration-dialysis as descibed by Hammond *et al.* [14]. The interassay coefficients of variation were approximately 10% for steroids and 7% for SHBG. The concentration of free, non-protein-bound testosterone was calculated as described by Bartsch [15]. Serum LH and FSH were determined by RIA as described by McNeilly & Hagen [16]. In the LH and FSH assays LH MRC 68/40 (assuming 77 IU/ampoule) and FSH 69/104 (assuming 10 IU/ampoule) were used as standards, respectively.

Statistics

Specific intergroup comparison was performed using unpaired Student's *t*-test. In addition, linear correlation tests were used in the statistical analysis. The Friedman two-way analysis of variance was used for

evaluating the relationship between hormone levels and activity of MS. As the numbers of women with different degrees of MS were uneven, Kruskal–Wallis one-way analysis of variance was used for evaluating the relationship between hormone levels and degree of MS.

Results

The consecutively included patients with MS showed a regular menstrual pattern and none had experienced fertility problems. Nine of the patients had had 22 pregnancies altogether; seven of these resulted in spontaneous abortion. Five MS-patients had not wished to have any children. The age at MS-onset in these 5 women was from 18 to 24 years. The hormone levels are given in Table 2. Mean serum concentrations of prolactin, FSH, LH, total and free testosterone, DHT and androstenedione were significantly higher and of oestrone sulphate significantly lower in patients than in controls. MS-patients with a disability status score of 6 to 7 had significantly higher testosterone concentration compared with patients having a disability status score of 2–4 (1.4 ± 0.1 nmol/l *vs.* 1.0 ± 0.1 nmol/l). Other hormonal parameters were not related to the age, degree of disability or MS activity.

None of the patients revealed clinical symptoms of hyper-androgenism, hypo-oestrogenism or hyperprolactinaemia.

Table 2. Hormonal parameters in patients with multiple sclerosis (MS) and normal controls

	MS[a]	Normal[a]
Number of subjects	14	14
Prolactin mg/l	12.6 ± 1.6[b] (5–25)	9.3 ± 0.8 (3–20)
LH IU/l	6.2 ± 0.6[b] (2.3–9.0)	4.7 ± 0.4 (2.7–7.3)
FSH IU/L	7.8 ± 1.2[b] (4.5–14)	5.0 ± 0.4 (2.0–7.4)
SHBG nmol/l	73 ± 8 (40–129)	83 ± 8 (41–169)
Oestrone pmol/l	174 ± 10 (130–250)	161 ± 14 (70–265)
Oestradiol pmol/l	154 ± 23 (69–390)	161 ± 18 (80–403)
Free-oestradiol pmol/l	3.7 ± 0.3 (2.3–10.5)	4.1 ± 0.7 (1.0–8.0)
Oestrone-sulphate pmol/l	1686 ± 125[d] (910–2500)	3588 ± 484 (2000–6100)
Testosterone nmol/l	1.3 ± 0.1[c] (0.86–1.8)	0.9–0.1 (0.55–1.8)
Free-testosterone nmol/l	0.018 ± 0.001[d] (0.011–0.027)	0.011 ± 0.001 (0.006–0.034)
DHT nmol/l	0.83 ± 0.05[d] (0.49–1.2)	0.68 ± 0.08 (0.25–1.2)
4-androstendione nmol/l	7.0 ± 0.4[d] (4.1–9.3)	3.8 ± 0.4 (2.4–8.9)
DHEAS nmol/l	4257 ± 616 (1600–8700)	5721 ± 544 (1200–9500)

[a]Indicates mean ± SEM with range in parentheses. [b]Indicates $P < 0.05$ significantly different from normals. [c]Indicates $P < 0.01$ significantly different from normals. [d]Indicates $P < 0.001$ significantly different from normals.

Discussion

In a group of patients with MS we found normal menstrual cycles despite raised serum concentrations of prolactin, LH, FSH, total and free testosterone and androstendione.

The raised gonadotropins did not apparently relate to inadequate ovarian steroid production, as concentrations of oestrone and oestradiol-17 beta were normal. A gradual increase in FSH levels seems to be an effect of reproductive ageing [17]. Increased levels of both FSH and LH prior to the menopause are reported only in subjects over 45 years of age with abnormal menstrual cycles [17, 18]. Premature ageing phenomena within the CNS may, though, be a possibility in MS.

In addition, the hormone concentrations found in patients with MS may in part be explained by a decreased ovarian oestrogen response to gonadotropins leading to raised gonadotropin secretion and thereby augmented ovarian androgen secretion. The raised androgen levels could, however, at least in part be due to a peripheral abnormality that does not influence the secretion of oestrogens and DHEAS. Previously, different sex-hormone profiles in the urine were examined in a study involving 15 women with MS; most of the hormone profiles ranged within the reference interval of normals [7]. Since this study was directed without a control group of normals, the nature of the hormone profiles of women diseased with MS can hardly be concluded from the results.

Dougados *et al.* [6] evaluated different plasma androgen profiles of women with certain autoimmune diseases. No variations were observed of the analysed androgens (testosterone, DHT and delta 4-androstendione) among the 11 patients with MS compared to the normal women.

Whether the high androgen concentration in our present study represents increased adrenal secretion or derives from the ovaries is only speculative. It is, however, most likely that the increased androgen

levels originate from the ovaries, the as DHEAS concentration is within the normal range. However, this hypothesis does not fit well with the fact that the disease is primarily a destructive one within the central nervous system, and it may not explain the raised prolactin levels found in these patients. Alternatively, MS may possess a central hormonal defect or dysfunction of the regulation of gonadotropin as well as prolactin secretion. Dopamine is a central inhibitor of prolactin and gonadotropin secretion. Therefore, a lowered central dopaminergic tone may be a possibility in these patients.

In conclusion, MS leads to altered hormone secretion within the pituitary–gonadal axis. These altered plasma steroid levels in the MS-patients had only minor, if any, clinical manifestations, as the patients had regular menstrual cycles and no fertility problems. The possible neuromodulators involved, and the exact location of these, need further investigation.

References

1 Hansen BL, Hansen GN, Hagen C, *et al.* Autoantibodies against pituitary peptides in sera from patients with multiple sclerosis. *J Neuroimmunol* 1983; **5**: 171–83.

2 Møller A, Hansen BL, Hansen GN, Hagen C. Autoantibodies in sera from patients with multiple sclerosis directed against antigenic determinants in pituitary growth hormone-secreting cells and in structures containing vasopressin/oxytocin. *J Neuroimmunol* 1985; **8**: 177–84.

3 Sørensen KV, Christensen SE, Dupont E, *et al.* Low somatostatin content in cerebrospinal fluid in multiple sclerosis. An indicator of disease activity? *Acta Neurol Scand* 1980; **61**(3): 186–91.

4 Moreau JP, Defeudis FV. Pharmacological studies of somatostatin analogues: therapeutic advances and perspectives. *Life Sci* 1987; **40**: 419–37.

5 Hagen C, Djursing H, Petersen K, Nyboe AN. The role of dopamine in the modulation of pituitary gonadotrophin secretion. In: *Special Aspects of Psychopharmacology*. Ackenheil Matussek eds. 1983; 295–313.

6 Dougados M, Nahoul K, Benhamou L, *et al.* Etude des androgènes plasmatiques chez les femmes atteintes de maladies auto-immunes. *Revue du Rheumatisme* 1984; **51** (3): 145–9.

7 Poser S, Kreikenbaum K, Kønig A, *et al.* Endokrinologische Befunde bei Patienteninnen mit multiple Sklerose. *Geburtshilfe und Frauenheilkunde* 1981; **41**: 353–8.

8 Schumacher GA, Beebe G, Kibler RF, *et al.* Problems of experimental trials of therapy in multiple sclerosis. *Ann NY Acad Sci* 1965; **22**: 552–68.

9 Kurtzke, JF. Further notes on disability evaluation in multiple sclerosis with scale modifications. *Neurology* 1965; **15**: 654–61.

10 Hertz J, Johnsen SG. Sex-hormone-binding globulin (SHBG) in serum in threatened abortion. *Acta Endocrin (Copenh)* 1983; 104: 381–4.

11 Emment Y, Collins WP, Sommerville JF. Radioimmunoassay of oestrone and oestradiol in human plasma. *Acta Endocrin (Copenh)* 1972: **69**: 567–82.

12 Parker CR, Jr, Ellegood JO, Mahesh VB. Methods of multiple steroid radioimmunoassay. *J Steroid Biochem* 1975; **6**: 1–8.

13 Franz C, Watson D, Longcope C. Estrone sulphate and dehydroepiandrosterone sulphate concentrations in normal subjects and men with cirrhosis. *Steroids* 1979; **34**: 563–74.

14 Hammond GL, Niskar JA, Jones LA *et al.* Estimation of the percentage of free steroid in undiluted serum by centrifugal ultrafiltration-dialysis. *J Biol Chem* 1980; **255**: 5023–6.

15 Bartsch W. Interrelationship between sex-hormone-binding globulin and testosterone, 5-alpha-dihydrotestosterone and estradiol-17 beta in blood of normal men. *Maturitas* 1980; **2**: 109–18.

16 McNeilly AS, Hagen C. Prolactin, TSH, LH and FSH responses to a combined LHRH/TRH test at different stages of the menstrual cycle. *Clin Endocrin* 1974; **3**: 427–35.

17 Reyes FI, Winter JSD, Faiman C. Pituitary–ovarian relationships preceding the menopause. *Am J Obstet Gynecol* 1977; **29**: 557–64.

18 Sherman BM, West JH, Korenman SG. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentration during menstrual cycles of older women. *J Clin Endocrinol Metab* 1976; **42**: 629–36.

Received 30 December 1988, accepted 12 April 1989.

Correspondence: Lotte Grinsted, MD, Department of Gynecology and Obstetrics, University Hospital of Copenhagen, Hvidovre, 2650 Copenhagen, Denmark.