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Hypothalamic endocrinopathy in multiple sclerosis and neuromyelitis optica syndrome

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) are two inflammatory disorders of the central nervous system with different pathogenesis. The aim of this study is to evaluate endocrinopathy in these patients. *Methods:* By convenient sampling method, 20 MS, 20 NMOSD and 20 normal age and sex matched as control were enrolled in this study. Hormonal assay including TSH, free T3, free T4, , FSH, prolactin, cortisol, IGFI, thyroid-stimulating hormone (TSH), free T3, free T4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, cortisol, insulin-like growth factor I (IGF-I), urine specific gravity and anti-aquaporin immunoglobulin G (AQP4-IgG) level was measured. Also adrenocorticotropic hormone (ACTH) stimulation test was done for MS and NMOSD patients. *Results:* Hypothyroidism was prevalent and found in 30% of MS, 40% of NMO patients, and only 9.5% of the controls. We detected greater rate of hypothyroidism in NMO patients compared to control (p=0.027). Mean level of anti-thyroglobulin antibody in MS and NMOSD patients was higher than control (p=0.037). One patient in MS group, 6 in NMOSD and 11 control had IGFI level lower than lower limit of their age groups (p=0.001).
Conclusions: Although the result of this study did not support significant hypothalamic-pituitary axis endocrinopathy in NMOSD compared to MS and controls, there is a higher prevalence of some hormonal abnormalities, especially thyroid dysfunction in NMOSD cases, that needs more clinicians' attention.

Keywords: Neuromyelitis optica, multiple sclerosis, aquaporin 4 receptor, hormone

INTRODUCTION

Neuromyelitis Optica Spectrum Disorder (NMOSD) and multiple sclerosis (MS) are two inflammatory CNS disorders with different pathological and clinical manifestations. While Infiltration of immune cells and progressive myelin and axonal loss is common pathologic finding of both disorders,[1] the main pathologic finding of NMOSD is related to the production of serum immunoglobulin against aquaporin 4 receptors (AQP4-IgG).[2] Although the definite etiology of NMOSD remains unknown, interaction between multiple genetic and environmental factors such as infectious, autoimmune, toxic, metabolic and vascular events had been proposed.[3] This disorder is frequently associated with other autoimmune disorders, and sometimes with paraneoplastic disorders.[4]

Some NMO patients experienced bilateral optic neuritis and spinal myelitis but according to international consensus diagnostic criteria, the core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings in the optic nerve, spinal cord, area postrema, other brainstem regions, diencephalic, or cerebral involvement.[5] NMO patients with anti AQP4 antibody frequently have hypothalamic lesions with different clinical and paraclinical manifestations.[6] High levels of AQP4 mRNA are found at the ependymal lining of the aqueduct system, supraoptic region, Purkinje cells of the cerebellum and paraventricular nuclei of the hypothalamus.[7] Paraventricular hypothalamic areas are prone to complement induced injury and some of these lesions had been associated with endocrinopathy.[8]

About two decades ago, eight Antillean women from Martinique and Guadeloupe presented with symptoms of NMO and endocrinopathies including amenorrhea, galactorrhea, diabetes

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insipidus (DI), hypothyroidism, or hyperphagia.[9] Some years later, a patient with Devic's disease and positive AQP4-Ab presented with recurrent hypersomnia, reduced orexin and symmetrical hypothalamic lesions.[10] Other patients of NMO disorder were reported to have amenorrhea, galactorrhea, DI, hypothyroidism, and syndrome of inappropriate secretion of anti diuretic hormone (SIADH).[11–13]

To the best of our knowledge, we identified no case control study on endocrinopathy in MS and NMO patients compared to normal subjects. The aim of this study is to evaluate hypothalamic-pituitary axis hormones in MS, NMOSD, and control groups.

METHODS

Case Selection

By a convenient sampling method, 60 cases were enrolled in this study. The subjects were divided into 3 groups: 20 patients with diagnosis of MS according to 2010 Revised McDonald Diagnostic Criteria, 20 patients with diagnosis of NMO according to Wingerchuk diagnostic criteria[14] and 20 age and sex matched healthy control subjects. The inclusion criteria were: female gender, and at least one year disease duration for patients in the first two groups. The Exclusion criteria were: concurrent history of any endocrine problem, any other autoimmune disorder such as vasculitis, treatment with methylprednisolone at previous six months, concurrent use of tricyclic antidepressant drugs and/or bromocriptine, fever or any infectious state during testing and pregnancy. After explaining the objectives and methods of the study, a written informed consent form was obtained from all participants. This study was approved by the Medical Research Ethics Committee of Shiraz University of Medical Sciences with approval number 91-3068.

Measurements

Weight and height were measured by a physician. Weight was measured with a standard scale to the nearest 0.1 kg (Seca, Germany), with the participant wearing light clothing and no shoes. Height was measured to the nearest 0.5 cm with a wall-mounted meter with the participant standing without shoes. Neurologic examination and MRI findings was evaluated by one neurologist and according to clinical course MS patients and divided into 4 groups: progressive relapsing (PR) MS, secondary progressive (SP) MS, primary progressive (PP) MS, and relapsing remitting (RR) MS.

All subjects were referred to Shiraz Endocrine and Metabolism Research Center. Blood samples for biochemical analysis was drawn between 8:00 and 10:00 am after an overnight fast by experienced technician and one urine sample was taken. All blood samples were taken in women at the follicular phase of menstrual cycle.

Level of anti AQ4 IgG level was measured by indirect immunofluorescence assay (Institut für Medizinische Diagnostik, Germany). Ratio of less than 10 was considered negative and less than 15 borderline.

Anti-thyroid peroxidase (Anti-TPO) antibody and anti-thyroglobulin (Anti-Tg) antibody was measured by ELISA method (Monobind Inc. Lake Forest, CA 92630, USA) with levels greater than 40 IU/ml and 125 IU/ml respectively being considered positive.

Hormonal assay including LH, FSH, prolactin, cortisol, IGFI, free T3, and free T4 was done by RIA method. LH (normal range of 0.8-27.1 IU/L), FSH (normal range of 2.2-15 IU/L), prolactin (normal range of 1-27 µg/L), TSH (normal range of 0.17-4.05mU/L) by TSH IRMA KITs (Beckman Coulter company), IGFI by Human IGF-1 ELISA kit, normal range of 219-644 ng/ml for 20-30 years old, 140-405 ng/ml for 30-40 years old and 64-336 ng/ml for 40-50 years old), free T3 and free T4 by ELISA DRG Instruments GmbH, Germany (normal range of 1.4-4.2 pg/ml, 9-30 pmol/L).

Rapid ACTH stimulation test was done for all participants. First sample was drawn at 8.00 am, then 1 µg tetracosactin (Synacthen) injected intramuscular and after 30 and 60 minutes second and third blood samples was drawn for plasma cortisol level. A normal response is defined by increment of at least 7µg/dl above the basal level after 30 minutes and peak plasma cortisol level greater than 550 nmol/L (>20 µg/dL).[15]

Urine specific gravity was checked by Digital Densitometry on 1 cm^3 centrifuged urine with normal range of 1.002-1.025.

Statistical analysis

Statistical analysis was done by SPSS Software version 22. Biochemical characteristics reported as mean ± SD. We used independent t-test and Mann-Whitney test to compare mean levels of hormone between control group and patients. We evaluated between group variations of biochemical markers using ANOVA and Kruskal-Wallis. We compared frequency of hormonal abnormalities

by chi-square and Fisher exact test between three groups of subjects. P value less than 0.05 was considered significant.

RESULTS

This study included 20 patients of MS, 20 NMOSD cases, and 20 normal subjects as control with mean ages of 34.4±5.5, 33.7±6.1 and 32.5±5.2 years old respectively (p=0.6).

Patients

All MS patients were diagnosed by 2010 Revised McDonald Diagnostic Criteria and had EDSS ≤ 6 (2.1±1.3). Disease duration in 65% was less than 5 years and the other had disease duration of 5-11 years. Eighty percent of patients had relapsing remitting form of MS (RRMS). Other MS patients included 10% SPMS, 5% PPMS, and 5% PRMS. All of them were treated with one of the interferons. Table 1 shows demographic and disease characteristics of MS patients.

Diagnosis of NMOSD was based on the Wingerchuk criteria. All of them had extended spinal cord lesions more than three vertebral segment without significant or specific brain stem or cerebral lesions. From these patients 30% had AQP4-IgG level <5 IU/ml, 5% had AQP4-IgG level <10 IU/ml, and 65% had AQP4-IgG level >15 IU/ml. Range of duration of disease was 1-5 years, three patients were wheelchair dependent and one patient bedridden. Table 2 shows demographic and disease characteristics of NMO patients.

Hormone profile

Table 3 shows Mean ± SD level for hormonal profile in the patients and control individuals.

Thyroid function and autoimmunity

Using one way ANOVA we did not detect significant differences in TSH, free T3, and free T4 levels between MS, NMOSD and control subjects. Sixteen participants had TSH level of greater than 4.5 mIU/L: six MS, 8 Devic, and 2 control subjects. Among these patients with TSH greater than 4.5 mIU/L only two patients had low free T4, one MS and one NMOSD patient, and both had normal free T3 levels.

We found significant difference in mean level of anti-Tg antibody among the 3 groups (p=0.037). Although anti-TPO antibody in NMOSD patients was greater than the other two groups, it was not statistically significant (p=0.24).

Of all the subjects, 18% had positive anti-TPO antibody; 3 MS, 5 NMOSD, and 3 controls (p=0.70). Thirty percent had positive anti-Tg antibody; 9 MS, 5 NMOSD, and 4 controls (p=0.10). We found 9 MS, 9 Devic, and 5 controls had at least one positive anti-thyroid antibody (anti-TPO or anti-Tg or both, p=0.25).

In total 30% of MS, 40% NMO, and 9.5% controls had hypothyroidism although only 2 individuals had overt, and the other subclinical, hypothyroidism. We detected greater rate of hypothyroidism in NMO patients compared to control (p=0.027). We found AQP4-IgG level greater than 15 IU/ml in 75% of NMO patients with hypothyroidism and in 58% of those without hypothyroidism (p=0.39).

Prolactin, LH, and FSH

From our subjects, 2 MS and 1 NMOSD patients had prolactin level greater than 25 µg/L but none was symptomatic. This was not statistically significant (p=0.9). One NMOSD patient had FSH above 40 IU/L (73.3 IU/L). She was a 44 years old woman with LH level of 71.2 IU/L. One way ANOVA didn't show significant difference in these hormone levels between groups (p=0.7 for LH and p=0.5 for FSH)

IGF-I

Level of IGF-I was analyzed according to 3 age groups (20-29, 30-39, and 40-49 years old). We detected mean serum IGF-I levels of 206 ± 100, 190 ± 71, and 137 ± 55 ng/ml in these groups respectively; the mean level in the first age group was lower than normal range (219-644 ng/ml). One MS patient, 6 NMOSD and 11 control subjects had IGF-I level lower than the lower limits of their age groups which was statistically significant (p=0.001).

Cortisol and ACTH stimulation test

Table 4 shows mean cortisol levels in basal state in all the subjects and 30 and 60 minutes after synachten injection in MS and NMOSD patients.

Mean basal cortisol level in all three groups was in normal range (p=0.107). Seven MS patients and 13 NMOSD had basal cortisol levels of 5-18 µg/dl. All had peak cortisol level of more than 20 µg/dl other than 4 NMOSD patients who even after 60 minutes had cortisol level less than 20 µg/dl with less than 7 µg/dl increment.

We evaluated urine for specific gravity in all subjects. MS patients had mean level of 1.017 ± 0.0068. The mean level for NMOSD patients

Table1: Demographic and disease characteristics of MS patients

					MRI					
	Age (years)	**BMI (Kg/m²)**	**EDSS**	**Disease duration (years)**	**Peri-ventricular**	**Juxta-cortical**	**Infra-tentorial**	**Spinal**	**Contrast**	**VEP**
1	38	24	3	3	+	+	+	C2'C5'C6	+	↑P100 latency
2	39	21	2	1	+	+	+	C6'C7'T1	-	↑P100 latency
3	30	25	3	3	+	+	+	C5'C6'C7	-	↑P100 latency
4	26	26	4	3	+	+	+	C3'C4'C5	-	↑P100 latency
5	40	26.5	2	2	+	+	-	C4'C5	-	↑P100 latency
6	44	26	3	3	+	+	-	C5'T2	-	↑P100 latency
7	37	23	2	4	+	+	-	C5'C6'C7	+	↑P100 latency
8	32	24	1	5	+	+	+	C4'C5'C6'C7	-	↑P100 latency
9	27	23	4	3	+	+	+	C3'C4'C5	-	↑P100 latency
10	28	23	2	3	+	+	-	C4'C5	-	-
11	34	27	1	3	+	-	+	T7	+	↑P100 latency
12	32	25	4	2	+	+	+	C2'C3'C6'C7	+	↑P100 latency
13	38	21	3	4	+	+	-	C2 cervicomedullary	-	↑P100 latency
14	29	20	2	4	+	-	+	C3'C5'C6	-	↑P100 latency
15	27	22	1	2	+	+	-	C2'C3	-	↑P100 latency
16	32	21	1	4	+	-	+	C3'C4'C5'C6	-	↑P100 latency
17	38	26	1	2	+	+	+	C3'C4'C6	-	↑P100 latency
18	40	27	1	1	+	+	+	C4'C5	-	↑P100 latency
19	38	27.5	1	5	+	+	-	T1'T2	-	↑P100 latency
20	30	24	5	3	+	-	+	C2'C3'C4'C5	+	↑P100 latency

MS, multiple sclerosis; BMI, body mass index; EDSS, Kurtzke Expanded Disability Status Scale

Table2: Demographic and disease characteristics of NMO patients

				MRI				
	Age (years)	**BMI (Kg/ m^2)**	**Disease duration (years)**	**Spinal**	**Contrast**	**Brain**	**VEP**	**Anti NMO Antibody**
1	42	24	3	C6-T2	-	Clear	Rt eye+	>15
2	28	19	1	C3-C5	-	Clear	Both eyes+	<5
3	38	26	3	C4-C7	+	Non-specific	Both eyes+	>15
4	36	25	3	C7-T1	+	Clear	Both eyes+	>15
5	26	20	2	Medulla to C7	-	CLEAR	Rt eye+	<5
6	44	23	3	C1-T2	-	Clear	Rt eye+	>15
7	30	20	4	Medulla to T2	-	Clear	Both eyes+	<5
8	27	21	5	C7-T5	-	Non-specific	Both eyes+	>15
9	43	25	3	C7-T2	-	Clear	Lt eye+	>15
10	29	27	3	C2-C7	_	Non-specific	Both eyes+	<10
11	37	26	3	C4-C6	_	Clear	Rt eye+	>15
12	33	25	2	C5-T2	-	Clear	Rt eye+	<5
13	34	23	4	C2-C6	+	Clear	Both eyes+	>15
14	39	25	4	C7-T2	-	Clear	Both eyes+	>15
15	40	26	2	T2-T4	-	Clear	Both eyes+	>15
16	26	27	4	Medulla to C7	-	Clear	Both eyes+	>15
17	26	25	2	C2-C5	-	Clear	Both eyes+	<5
18	28	24	1	C3-C5	-	Clear	Rt eye+	<5
19	43	18	5	C2-C4	-	Non-specific	Both eyes+	>15
20	39	21	3	C7-T1	-	Clear	Both eyes	>15

NMO, neuromyelitis optica; BMI, body mass index; VEP, visual evoked potential

Table 3: Hormonal profile of MS, NMOSD and control groups (mean ± SD)

	TSH (mU/L)	**Free T3 (ng/dl)**	**Free T4 (pmol/L)**	**Anti TPO Antibody (IU/ml)**	**Anti Tg Antibody (IU/ml)**	**LH (IU/L)**	**FSH (IU/L)**	**Prolactin (µg/L)**	**IGFI (ng/ml)**
MS	3.6±2.4	3.6±0.7	16.2±2.2	64.7±130.6	246.6±313.1	12.8±11.7	5.9±6.9	13.4±6.8	204±57
NMOSD	4.6±4.7	3.6±0.7	17.0±2.8	97.4±170.8	200.5±382.2	17.3±22.3	9.2±15.4	12.7±9.4	197±113
Control	2.9±1.8	3.6±0.5	16.8±1.5	62.0±137.3	156.5±325.0	13.8±17.8	6.5±3.9	12.3±5.1	154±57
P value	NS*	NS	NS	NS	0.037	NS	NS	NS	0.001

MS, multiple sclerosis; NMO, neuromyelitis optica
*NS: Not significant

and controls were 1.014 ± 0.0059 and 1.016 ± 0.0069, respectively (p=0.29).

DISCUSSION

In this cross sectional study we evaluated endocrine parameters of hypothalamic pituitary axis in MS and patients with NMOSD and compared them with control subjects.

The pathophysiology of NMOSD with involvement of aquaporin 4 channel by anti-NMO antibody, and strong AQP4 expression in the periventricular regions and hypothalamus, it appeared that they were more likely to have endocrinopathy than MS patients, especially affecting the hypothalamic-pituitary axis hormones.[2] Although T1 brain lesions (representative of persistent axonal loss in MS) are not found in NMO, a minority of cases have been reported with periventricular, and hypothalamic–diencephalic lesions. These lesions are favorable with hypothalamic localization of AQP4 and may explain the clinical manifestations of hypothalamic dysfunction in these patients.[16]

Vernant *et al*. in 1997 reported 8 Antillean women from Martinique and Guadeloupe with recurrent optic neuromyelitis and endocrinopathies. All the patients had either monocular or binocular involvement, whereas their myelopathy was acute or sub-acute. All 8 patients had endocrinopathies consisting of amenorrhea, galactorrhea, DI, hypothyroidism, or hyperphagia.[9]

In our study, 5 MS and 6 NMOSD patients had subclinical hypothyroidism and mean level of anti-Tg antibody significantly higher than control subjects. Munteis *et al*. in Spanish Multiple Sclerosis Cohort study detected anti-thyroid antibodies in 11 MS patients which was five times more prevalent than the control population.[17]

NMOSD is an autoimmune disorder associated with autoantibodies against cellular antigens and autoimmune disorders.[18] Wang *et al*. reported that thyroid autoimmune disorders were frequently associated with this disorder and showed that these patients were seropositive for anti-thyroid antibodies.[19,20]

A recent case study by Watanabe *et al*. reported symptom of galactorrhea without concomitant amenorrhea in a Japanese woman with NMOSD; the authors believed that amenorrhea and galactorrhea were the two commonest endocrinopathy associated with NMOSD and opticospinal variant of MS.[21]

Among our subjects, 2 MS and 1 NMOSD patients had prolactin level greater than 25 µg/L without any symptom of hyperprolactinomia. Prolactin may have an immunomodulatory action and may be related to neuro-protection or remyelination after brain injury.[22]

Cortisol is a key regulator of the immune system, energy metabolism, and stress. The hypothalamus-pituitary-adrenal axis is activated in the majority of MS patients and is correlated to disease progression and comorbid mood disorders.[23] Powell *et al*. mentioned the possible role of cortisol in fatigue experienced in relapsing-remitting MS.[24] Kern *et al*. showed that relapsing-remitting but not secondary-progressive MS patients differed in circadian cortisol release from healthy control subjects. Circadian cortisol release and especially cortisol awakening response was pronounced in relapsing-remitting MS.[25]

We did not find any biochemical abnormality in cortisol response to synacthen test in MS. Four NMOSD patients had subnormal response to tetracosectide even after 60 minutes. We detected slightly greater cortisol response to synacthen in MS patients compared to NMOSD. This was in agreement with Kern *et al*.'s study.[25]

Neuro-hormones such as GH and IGF-I may be involved in the regulation of brain growth, development, and metabolism and their dysfunction causes some neurodegenerative disorders such as multiple sclerosis.[26,27] IGF-1 directly participates in astrocyte neuroprotection

Table 4: basal and peak level of cortisol after injection of tetracosectide (mean ± SD)

	Basal cortisol (µg/dl)	**Cortisol (30 minute)** (µg/dl)	**Cortisol (60 minute)** (µg/dl)
MS	19.04±4.36	27.48±7.07	22.99±6.22
NMOSD	16.89±4.99	23.66±9.37	18.68±8.13
Control	15.57±6.00	NE*	NE
P value	NS	NS**	NS

MS, multiple sclerosis; NMO, neuromyelitis optica
*NE: Not evaluated **NS: Not significant

against oxidative stress.[28] Growth hormone and IGF-I may influence myelin maintenance and central nervous system cell survival.[29] IGF-I acts as a powerful enhancer of regenerative responses in multiple tissue types.[30]

Previous studies found lower level of IGF-I or its bioavailability (IGF-I/IGFBP-3) in MS patients and showed that IGF-I bioavailability more than IGF-I level might be relevant to MS susceptibility.[31]

Davies *et al*. reported a 30-year-old female patient with a 7-year history of multiple sclerosis, who presented with an 18-month history of secondary amenorrhea and vague symptoms which included poor sleep and impaired concentration. Endocrine investigations revealed hypogonadotrophic hypogonadism and GH deficiency, a probable consequence of a hypothalamic plaque.[32]

Consistent evidence associated IGFI deficiency with several mineral deficiency, low protein and low caloric intake, and metabolic syndrome.[33,34] Our result showed high frequency of individuals with low level of IGFI in control group, further research is needed to clarify this finding in our population.

SIADH had been reported in NMO patients,[12,35,36] all of whom had anti-aquaporin-4 antibody; one was a Chinese female without any abnormality in brain MRI[36] but the others were a 15 years old girl[35] and a 63 years old man[12] with hypothalamic lesion in the brain MRI. Injury to the tiny connective fibers of the hypothalamus (undetectable by MRI) may cause this syndrome.

In the present study all subjects had normal urine specific gravity without any symptom of hyponatremia.

In conclusion, we found association of subclinical hypothyroidism and NMOSD with high level of anti-Tg antibody. We did not detect other hormonal abnormality in the hypothalamic-pituitary axis. These findings should encourage larger studies with larger sample size to evaluate endocrinopathy in NMOSD.

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DISCLOSURE

Conflict of interest: None

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