

Growth Hormone Response to Clonidine Administration for Evaluation of Autonomic Dysfunction in Multiple Sclerosis Patients

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ABSTRACT

Objectives: Our objective was to assess the dynamic serum growth hormone (GH) response to clonidine administration in multiple sclerosis patients, looking for a possible biomarker of degenerative process and to correlate with disability.

Methods: 21 patients with relapsing remitting multiple sclerosis, who were evaluated clinically by expanded disability status scale (EDSS) score and multiple sclerosis functional composite (MSFC) score and for whom we measured the GH before and one hour after oral clonidine administration.

Different cut-off values of EDSS score were chosen for observation of GH serum dynamics after clonidine administration. All patients had normal IGF1 values.

Results: There was a significant positive correlation between EDSS and time to walk 25 feet ($r = 0.5$, $p = 0.002$) and EDSS and nine holes peg tests for dominant and non dominant hands ($r = 0.37$, $p = 0.024$ and $r = 0.53$, $p = 0.001$, respectively).

There was a moderate negative correlation, significant statistically, between EDSS and paced auditory serial additional test (PASAT) ($r = -0.36$, $p = 0.046$).

4 out of 7 patients with EDSS score over 3.0 failed to increase serum GH levels after clonidine administration, as compared to 4 out of 14 patients with EDSS < 3 ($r = 1.6$; $p = 0.02$), revealed by means of the Pearson chi square test.

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Conclusion: *Despite the small number of subjects enrolled in this pilot study, there is a tendency of blunted GH response in patients with more severe physical disability (stated by an increased value of EDSS), suggesting that GH response to clonidine could assess central autonomic dysfunction in MS patients.*

Keywords: autonomic dysfunction, physical disability, multiple sclerosis

BACKGROUND

Multiple sclerosis (MS) is the most frequent chronic neurological disease affecting young people.

Besides an autoimmune etiology, multiple sclerosis also has a degenerative one, both pathologies being able to cause autonomic dysfunctions of central origin (1,2).

Symptoms related to autonomic dysfunctions are quite frequent for patients with MS. Orthostatic intolerance, sleep disorder, impotence, micturition problems, sudomotor and gastrointestinal disturbances are among the most common disorders in multiple sclerosis. All of these disturbances are difficult to assess due to the lack of standard methods (3-5).

Only a few studies regarding autonomic dysfunctions in patients with MS can be found in the medical literature (6).

Clonidine growth hormone test (CGHT) has usually been used to differentiate between central and peripheral autonomic dysfunctions.

Many neurodegenerative diseases of the central nervous system cause autonomic dysfunction. CGHT was recently used to differentiate between two different diseases with central autonomic dysfunction: Parkinson disease and multiple system atrophy (MSA), but results are controversial (7,8).

The secretion of growth hormone is regulated by a complex neuroendocrine control system based on the balance between two hypothalamic neurohormones: growth hormone-releasing hormone (GHRH), exerting a stimulative influence upon growth hormone secretion and, respectively, somatostatin, who has an inhibitory effect.

GHRH and somatostatin release are modulated by neurotransmitters, such as the norepinephrine and acetylcholine (9).

Specifically, the activation of hypothalamic α_2 -adrenoceptors and muscarinic cholinergic receptors induces growth hormone release

through stimulation of GHRH and respectively, by inhibition of somatostatin.

Clonidine release growth hormone effect is based on its action upon α_2 -adrenoceptors. □

OBJECTIVES

To assess growth hormone (GH) serum dynamic response to clonidine administration to multiple sclerosis patients, and to identify by this test a possible serum biomarker of the degenerative process, able to assess autonomic dysfunction. □

METHODS

Study population

21 patients diagnosed with relapsing remitting multiple sclerosis according with 2005 revised Mc Donald criteria, who were under immunomodulatory therapies (interferon-beta or glatiramer acetate) have been included in this study.

The patients have not received methylprednisolone during the previous 30 days prior to the study and were free of central nervous medication.

All signed up the informed consent to participate in the study (approved by the local ethical committee).

They were clinically evaluated by the expanded disability status scale (EDSS) score and multiple sclerosis functional composite (MSFC) score in order to determine their physical and cognitive disabilities.

EDSS and MSFC were performed by neurologists and psychiatrists qualified for these evaluations.

MSFC consists of two physical evaluation scales: first – time to walk 25 foot (TW25F) for the lower limbs disability and second – the nine holes peg test (9HPT) for upper limbs disabilities. The third test, part of MSFC, is passed auditory serial additional test (PASAT) designed to assess cognitive disabilities of MS patients.

Orthostatic intolerance was ruled out for all patients.

Magnetic resonance imaging with gadolinium of brain was available for all patients. The radiologist did not find abnormalities of pituitary gland or pituitary stalk on brain imaging.

Growth hormone (GH) serum levels before and after clonidine administration

We measured the GH before and one hour after oral clonidine administration (dosage used 0.15 mg/ m² body surface of patients). All patients have fasted before the blood test.

Pituitary insufficiency on somatotrophic axis was previously ruled out by normal insulin-like growth factor 1 (IGF1) values. Thyroid deficiency was also ruled out by normal TSH (thyroid stimulating hormone). We didn't measure ACTH (adrenocorticotrophic hormone) level.

Sympathetic skin response

The sympathetic skin response (SSR) measures electrical potentials by electrodes fixed on the foot and hand and indicate sympathetic cholinergic activity on sweat glands. The stimuli used are physiological (inspiratory gasps, loud noise, or touch) or electrical (e.g. median nerve stimulation).

In peripheral autonomic diseases, such as familial autonomic polineuropathy and pure cholinergic dysautonomia, the SSR is absent. In MSA one third of patients have a recordable SSR.

The SSR is absent below the level of lesion in complete spinal cord lesions (10).

All patients were checked for peripheral autonomic dysfunction and for severe myelopathy by sympathetic skin response (SSR), using an electrical stimulus. All tests were performed by the same neuroelectrophysiologist.

Statistical analysis

All statistical analyses were performed using SPSS (version 17.0) statistical software.

Correlation analysis between variables was done using Kendall or Spearman tests for small groups or chi square method when variables considered were non parametric. We used Wilcoxon test for small groups to determine the longitudinal dynamics of variables within the same group.

Different cut-off values for measuring level of physical disability, respectively EDSS score

were chosen for observation of GH serum dynamics after clonidine administration. A 3 points EDSS has been chosen for our study, as it is considered a milestone for the disease disability. □

RESULTS

Patient's characteristics

Average age of the group was 35.41 (22-59) years with an average EDSS of 2.5 (1.0-6.0) and with a predominance of females (17 out of 21).

SSR on all limbs were normal

All patients had normal values (latency and amplitude) of SSR on all limbs (upper and lower).

Physical and cognitive assessments correlate with EDSS score

There was a significant positive correlation between EDSS and time to walk 25 feet ($r = 0.5$, $p = 0.002$) and EDSS and nine holes peg tests for dominant and non dominant hands ($r = 0.37$, $p = 0.024$ and $r = 0.53$, $p = 0.001$, respectively) by Kendall method.

Scatter plot graph with correlation between EDSS and TW25F is shown in Figure1.

Scatter plot graphs with correlations between EDSS and 9HPT for dominant and non

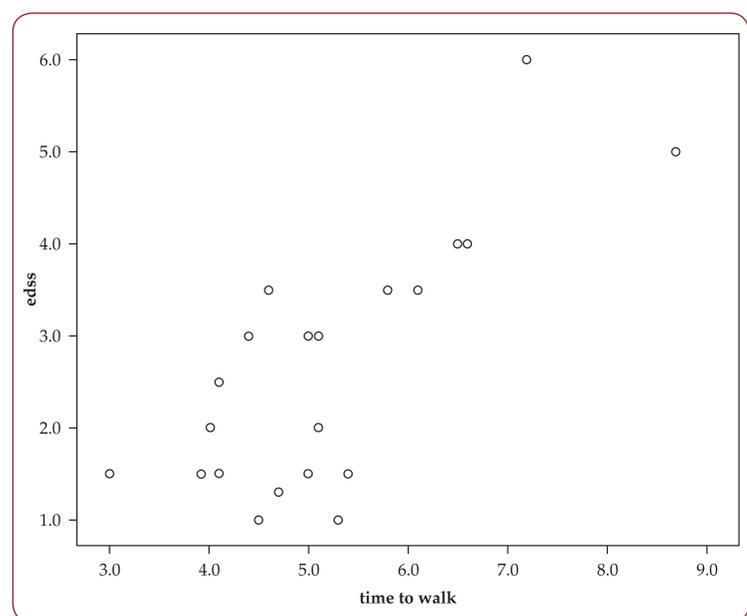


FIGURE 1. Correlation between EDSS and TW25F.

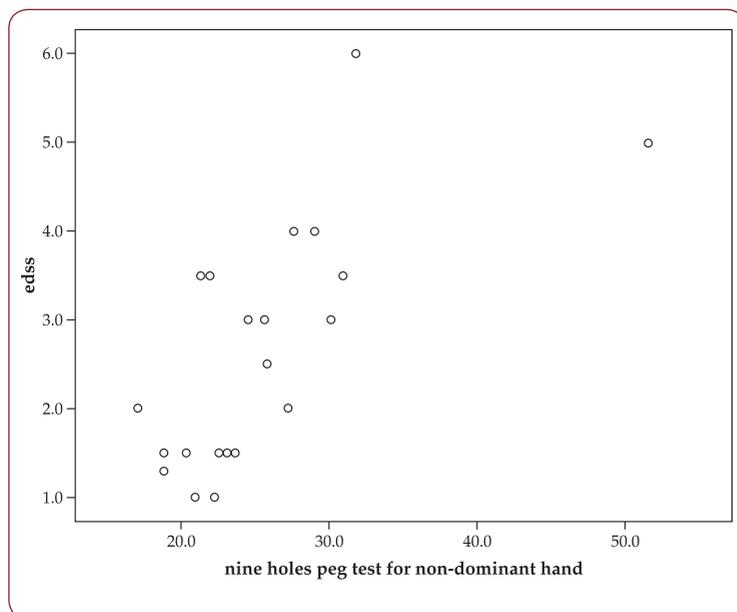


FIGURE 2A. Correlation between EDSS and 9 HPT for non dominant hand.

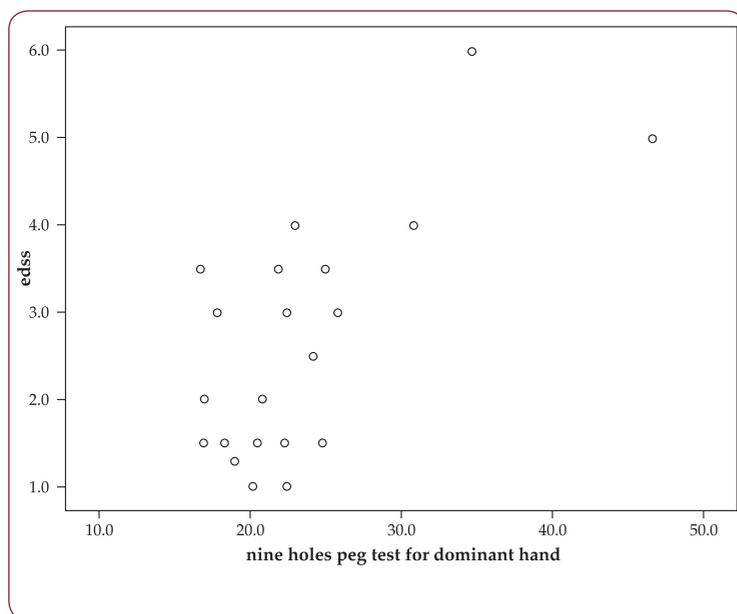


FIGURE 2B. Correlation between EDSS and 9 HPT for dominant hand.

dominant hand are shown in Figures 2a and 2b.

There was a statistically significant negative correlation between EDSS and paced auditory serial additional test (PASAT) $r = -0.36$, $p = 0.046$.

Clonidine growth hormone test (CGHT) is negative for disabled patients

4 out of the 7 patients with more severe disability (EDSS score over 3.0) did not increase

serum GH levels after clonidine administration, as compared to 4 out of the 14 patients with EDSS < 3 ($p=0.2$, chi square method).

Table 1 shows the response of GT to clonidine administration in multiple sclerosis patients when it was chosen a cut off value of EDSS of 3. □

DISCUSSION

The autonomic dysfunction (AD) in multiple sclerosis probably has several etiologies.

There is abundant information about the autonomic dysfunction in neurodegenerative disorders, but in multiple sclerosis it has not been intensively studied. As far as we know this is the first study using CGHT in MS.

Autonomic dysfunction in multiple sclerosis was investigated by cardiovascular functions tests such heart rate response to deep breath, Valsalva maneuver and standing, blood pressure response to standing and sustained hand grip. Statistical analysis indicated that MS patients with a long disease duration rather than high EDSS carried a higher risk of autonomic involvement (11).

Cardiovascular dysfunction in multiple sclerosis is related to involvement of reflex pathway in the brain stem. In some studies cardiovascular dysfunction correlated to brainstem lesions on MRI, and postural blood pressure change was considered a subclinical marker of cardiovascular dysfunction (12-14).

Other study showed that autonomic dysfunction (AD) is related to spinal cord cross-sectional area reduction but not to spinal cord hyperintensities. This observation suggests that AD is more closely related to axonal loss than to demyelinating lesions (15).

There are different endocrine modifications that could accompany the progression of neurodegenerative due to the tight connections between central nervous and endocrine systems. It is known that GH/IGF-1 axis is involved in regulation of brain growth and development, so the dysfunction of GH/IGF-1 axis is checked in neurodegenerative disorders. Until now it isn't established if GH deficiency could be one pathogenic factor of neurodegenerative disorders. In our study all patients had normal insulin-like growth factor 1 (IGF1) values.

A recent study published in 2010 concluded that patients suffering from MS may manifest autonomic dysfunction by developing postural orthostatic tachycardia syndrome (16).

Most of the studies which have looked at autonomic dysfunction in MS patients addressed rather the cardiovascular responses. Finding a marker which can identify and measure the level of autonomic dysfunction in MS is however of high importance (knowing that AD could be an important cause of mortality).

Despite the small number of subjects enrolled in our pilot study, there was a tendency of blunted GH response for patients with more severe physical disability caused by multiple sclerosis.

Therefore we came to the conclusion that autonomic dysfunction measured by CGHT is related with disease severity.

This observation was noticeable in our batch of patients (well defined as physical disability as clinical assessment tests demonstrated), all having mild disability (EDSS average of 2.5) and without severe myelopathy (SSR normal in all limbs).

It is tempting to suggest that GH response to clonidine could be a new biomarker for central autonomic dysfunction in neurodegenerative disorders. But to prove this idea, further studies in larger groups and assessment of GH response to intravenous clonidine are needed.

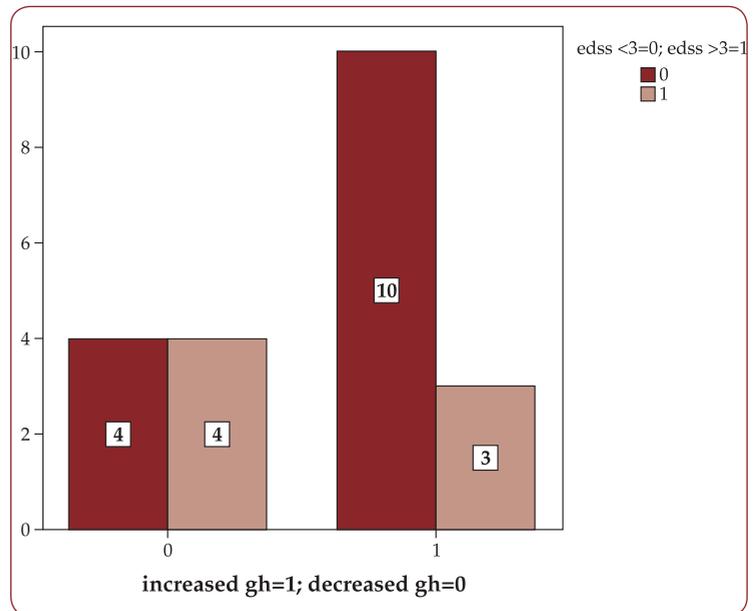


FIGURE 3. CGHT response of MS patients.

Conflict of interest: none declared.

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GH increased=1; GH decreased=0; EDSS<3=0; EDSS>3=1					
			EDSS<3=0; EDSS>3=1		Total
			0	1	
0		Count	4	4	8
		Expected Count	5.3	2.7	8.0
		% within EDSS<3=0; EDSS>3=1	28.6%	57.1%	38.1%
		Adjusted Residual	-1.3	1.3	
1		Count	10	3	13
		Expected Count	8.7	4.3	13.0
		% within EDSS<3=0; EDSS>3=1	71.4%	42.9%	61.9%
		Adjusted Residual	1.3	-1.3	
Total		Count	14	7	21
		Expected Count	14.0	7.0	21.0
		% within EDSS<3=0; EDSS>3=1	100.0%	100.0%	100.0%

TABLE 1. Correlation between GH response and EDSS score.

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