

Ganglionic nAChR antibody positive autoimmune autonomic ganglionopathy with spontaneous recovery

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ABSTRACT – We present a case of autoimmune autonomic ganglionopathy associated with ganglionic nicotinic acetylcholine receptor antibodies, orthostatic hypotension and small fiber neuropathy, notable for spontaneous recovery.

Key words: ganglionic nicotinic acetylcholine receptor antibodies, autoimmune autonomic ganglionopathy, orthostatic hypotension, hypohidrosis

INTRODUCTION

Since the identification of ganglionic nicotinic acetylcholine receptor (nAChR) antibodies, autoimmune autonomic ganglionopathy (AAG) has been established as a specific nosologic entity (1). Correlation between the antibody titer and the severity of clinical presentation has been determined (2). Its treatment is mainly based on immunotherapy, although spontaneous recovery has been proposed as well (3). We present a patient with ganglionic nAChR antibody mediated AAG associated with spontaneous recovery.

CASE REPORT

A 30-year-old male was referred for neurological examination following a one-year history of repeated falls that were occasionally accompanied by

transient loss of consciousness with rapid and complete recovery. The falls were preceded by dizziness and typically occurred on prolonged standing and walking. He experienced several cuts and bruises but had neither fractures nor other serious injuries. Besides the repeated falls that occurred almost weekly, the patient complained of a tingling sensation in his hands and feet and experienced weight loss, around 40 kg in a one-year period due to the lack of appetite. A cardiologist evaluated him; seven-day ECG monitoring, heart ultrasound and regular treadmill stress test were all normal. The patient was then referred to our department. His neurological examination was normal. A bat-

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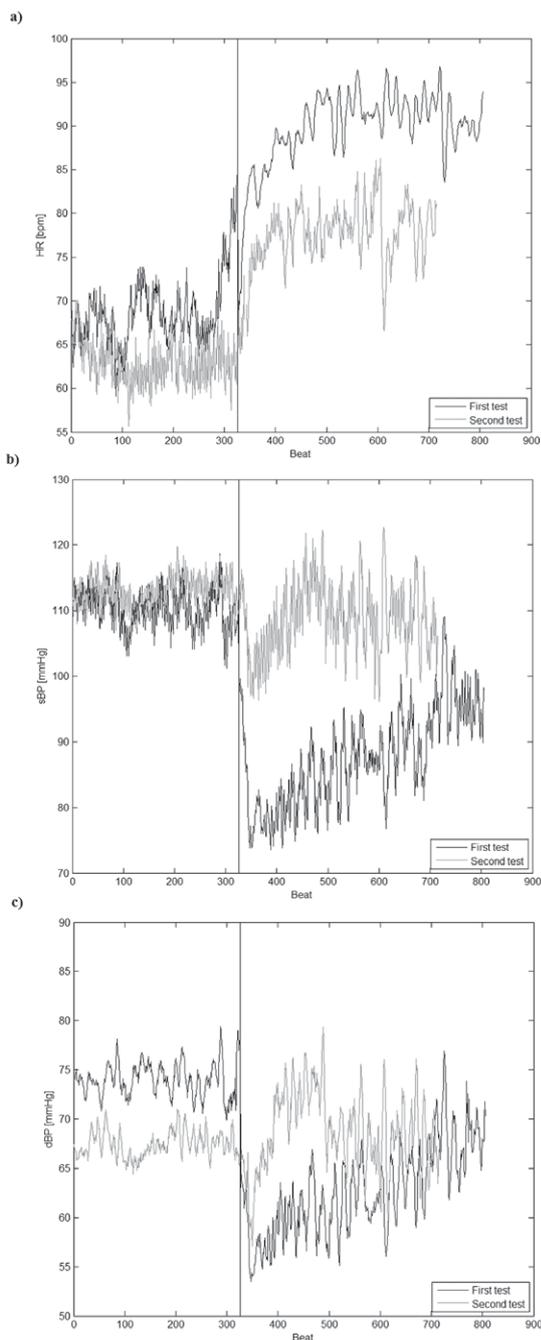


Fig. 1. Results of the first (blue curve) and second (red curve) tilt table test. Black vertical line represents the moment of table tilting to 70 degree angle: (a) curves of heart rate in supine position and in the tilt phase. Note a greater increase of heart rate on table tilting in the first test, a compensatory reaction due to a greater fall of blood pressure; (b) curves of systolic blood pressure in supine position and in the tilt phase. Note blood pressure level falling by more than 20 mm Hg on table tilting in the first test as opposed to a non-significant change in the second test; (c) curves of diastolic blood pressure in supine position and in the tilt phase. Note blood pressure level falling by more than 10 mm Hg on table tilting in the first test as opposed to a non-significant change in the second test.

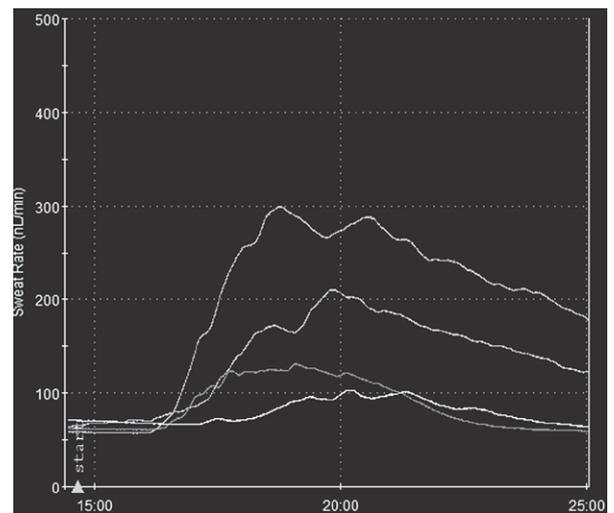


Fig. 2. Results of Quantitative Sudomotor Axon Reflex Test. Red curve represents sweat output recorded at the forearm, blue curve at proximal leg, green curve at distal leg, and yellow curve at the foot. The area under the curve represents total sweat volume, diminished for forearm and foot recordings signifying hypohidrosis.

tery of autonomic tests was performed for quantitative assessment of adrenergic, cardiovagal and sudomotor function, and Composite Autonomic Severity Score (CASS) was applied (4). Tilt table test revealed orthostatic hypotension (OH) (Fig.1). The response of heart frequency and blood pressure values to Valsalva maneuver and deep breathing were normal. Quantitative Sudomotor Axon Reflex Test was notable for hypohidrosis of the forearm and dorsum of his hand (Fig. 2). The values of sweat output measured in microliters were as follows: medial forearm 0.282 (normal value 0.38-2.53), proximal leg 0.746 (normal value 0.58-2.64), distal leg 1.453 (normal value 0.52-2.41), and foot 0.163 (normal value 0.35-1.83). CASS score was 5 (cardiovagal 0, adrenergic 3, sudomotor 2). As the patient's falls and episodes of loss of consciousness were at that time becoming less frequent, no specific therapy was initiated. The patient was referred for electromyoneurography that was normal. Additionally, quantitative sensory testing was performed revealing A δ and C fiber neuropathy. Screening for the potential causes of small fiber neuropathy was normal consisting of the following tests: glycated hemoglobin, vitamin B12, folic acid, paraneoplastic antibody panel (Hu, Yo, Ri), tumor markers (carcinoembryonic antigen, CA19-9, neuron-specific enolase, cyfra 21.1, prostate-specific antigen) and immunological panel (antinuclear antigen, extractable nuclear antigen, SS-A, SS-B, angiotensin-converting enzyme). Testing for antibodies to ganglionic nAChR came

back positive with a titer of 0.333 nmol/L (normal value <0.05). One month later, he presented for follow up and at that time he had no more orthostatic symptoms, did not experience any more falls, and was without further episodes of loss of consciousness. Tilt table test was repeated and was normal (Fig. 1). On the next follow up four months later, the patient was still doing well without any symptoms. His appetite improved and he regained some of his lost weight.

DISCUSSION

We present a case of AAG associated with ganglionic nAChR, OH and small fiber neuropathy, notable for spontaneous recovery.

The pathogenicity of ganglionic nAChR antibodies has been established in animal models in which passive transfer of IgG containing ganglionic AChR antibodies induced sympathetic and parasympathetic dysfunction (5). The severity of symptoms is apparently dependent on the antibody titer. Patients with high levels of ganglionic nAChR antibodies tend to have a more pronounced dysautonomia as expressed by CASS (1). As well, the antibody level is dynamic and fall of its titer is correlated with improvement in autonomic function. The presented patient had a titer of 0.333 nmol/L, which is considered to be an intermediate level since the levels >0.5 are considered high and levels from 0.05 to 0.2 in the lower range of positive (1). This is consistent with the clinical picture as the patient's symptoms were already subsiding at the time when serology testing was performed. This particular antibody level could have been a reflection of the dynamic change and probable fall of the antibody titer. However, as the test is not readily available in our institution, we were not able to follow the exact fluctuation of the titer.

Although autonomic symptoms are the most prominent symptoms in patients with AAG, 25% of them experience sensory symptoms without obvious sensory loss (6). The presented patient had positive sensory sensations in his distal extremities and quantitative sensory testing revealed affection of small sensory fibers with normal nerve conduction studies. This is in concordance with previous pathologic studies, which found that patients with ganglionic nAChR antibodies typically had preserved large myelinated nerve fibers with various damage to the thin, unmyelinated ones (7). In this case, the patient also suffered from digestive symptoms, mainly pertaining to the upper gastrointesti-

nal tract, i.e. anorexia. This is also common in patients who are ganglionic nAChR antibody positive, as they are prone to a more widespread autonomic dysfunction than patients negative for the aforementioned antibody (8).

The presented patient initially experienced substantial orthostatic symptoms with frequent falls that considerably affected his quality of life. At that time, immunomodulatory treatment would have been doubtlessly indicated. However, since his specific diagnosis was delayed, this case actually represents a natural evolution of ganglionic nAChR antibody mediated OH. The mainstay of therapy for AAG is immunomodulation, including corticosteroids, intravenous immunoglobulins, plasma exchange for treatment of acute exacerbations, and azathioprine, rituximab and mycophenolate mofetil for maintenance therapy (6). Although this therapeutic approach seems to be efficacious, randomized controlled trials have not been performed to substantiate their effect. Specific side effects of each treatment should also be taken into consideration. The present case is notable for ganglionic nAChR antibody associated AAG with spontaneous recovery that occurred during the work up period. There have been earlier reports of spontaneous recovery of probable AAG (3,9). However, these reports date back to the era before ganglionic AChR antibodies were discovered and therefore these patients cannot be classified as definite, ganglionic AChR antibody positive AAG. To the best of our knowledge, this is the first report of serologically confirmed AAG and spontaneous recovery. This fact bears two meaningful implications. Firstly, if the symptoms in an AAG patient are not as severe and do not greatly impact the quality of life, the wait-and-see approach could be more beneficial than commencement of potentially harmful immunotherapy. Secondly, since the ganglionic nAChR titer has shown significant correlation with symptom severity, repeated antibody testing and monitoring of the titer could help reach a decision on therapy initiation in patients with moderate or fluctuating symptoms. As therapy for ganglionic nAChR autonomic neuropathy is mainly based on immunomodulatory treatment that can be accompanied by potentially serious side effects and given the fact that the titer of ganglionic nAChR antibodies can be dynamic, the question arises whether patients with mild symptoms and intermediate antibody titer should be treated immediately or would benefit from a more conservative approach. This case, presenting an AAG patient with spontaneous recovery, builds an argument for the latter.

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Autoimuna autonomna ganglionopatija pozitivna na ganglionska nAChR protutijela sa spontanom oporavkom

SAŽETAK – Prikazuje se slučaj autoimune autonomne ganglionopatije udružene s protutijelima na ganglionske acetilkolinske nikotinske receptore, ortostatskom hipotenzijom i neuropatijom malih vlakana, s izrazito spontanom oporavkom.

Ključne riječi: ganglionski acetilkolinski nikotinski receptori, autoimuna autonomna ganglionopatija, ortostatska hipotenzija, hipohidroza