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Case report

Recurrent autonomic and sensory neuropathy in a patient with anti-ganglionic acetylcholine receptor antibodies

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ABSTRACT

We report a case of recurrent neuropathy with predominant autonomic and sensory involvement whose serum was positive for anti-ganglionic acetylcholine receptor (anti-gAChR) antibodies, a diagnostic marker of autoimmune autonomic ganglionopathy. An 11-year-old girl complained of numbness and limb pain after gastroenteritis. Although hyperalgesia and autonomic dysfunctions, such as orthostatic intolerance and gastrointestinal dysmotility subsequently developed, these symptoms faded after a few days. Similar sensory and autonomic impairments recurred three times within 12 months after the first episode. The sensory and autonomic symptoms were rapidly ameliorated by the administration of intravenous immunoglobulin (IVIg) at the second and third relapse; however, the symptoms persisted even after the administration of IVIg at the fourth relapse. The residual symptoms disappeared after methylprednisolone pulse therapy. The patient's serum was found to be positive for anti-gAChR antibodies at the second relapse, and was negative after methylprednisolone pulse therapy. Further studies are needed to clarify the efficacy of treatment and the nosological position in the spectrum of neuropathies that are associated with autonomic and sensory impairments.

1. Introduction

The autonomic nervous system is involved in a variety of peripheral neuropathies, including immune-mediated neuropathies [1]. Regarding autonomic neuropathies with a monophasic clinical course and an acute or subacute onset, at least three subgroups have been proposed based on the concomitance or absence of sensory and motor dysfunctions: 1) pure autonomic neuropathy [2,3]; 2) autonomic neuropathy with sensory impairment [4] and 3) autonomic neuropathy with sensory and motor impairment [5]. Since the measurement of anti-ganglionic acetylcholine receptor (anti-gAChR) antibodies has become possible, immune-mediated pure autonomic neuropathies have been referred to as autoimmune autonomic ganglionopathy (AAG). The concept of AAG has significantly expanded because anti-gAChR antibodies have even been detected in slowly progressive cases that mimic neurodegenerative diseases [1].

We herein report a case of recurrent autonomic and sensory neuropathy in a patient whose serum was positive for anti-gAChR antibodies and who responded to intravenous immunoglobulin (IVIg) and subsequent intravenous methylprednisolone (IVMP).

2. Case report

An 11-year-old girl with an unremarkable medical history was diagnosed with a subacute viral illness characterized by vomiting, diarrhea, a fever and joint pain. Although these symptoms disappeared three days later, numbness, pain and weakness of the limbs appeared, and she was hospitalized four days later.

On a neurological examination, the patient was alert and well-oriented. Her cranial nerve signs were normal. She had mild weakness in the bilateral quadriceps muscles but normal strength of other muscles. Moderate hyperalgesia was noted on her palm and plantar regions. Sensations of light touch, vibration and position were normal. Deep tendon reflexes (DTR) were absent on the Achilles tendon, while others were reduced. The plantar responses were flexor on both sides. Routine laboratory examinations of the blood and urine were unremarkable

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Table 1
The results of a blood analysis (first admission).

	Patient	Normal values
Plasma		
Albumin (g/dL)	4.7	3.7–5.0
Natrium (mEq/L)	139	138–145
Chlorine (mEq/L)	100	98–106
Calcium (mEq/L)	10.2	8.88–10.04
C-reactive protein (mg/dL)	0	≦0.06
Thyroid gland hormone (mg/dL)	5.9	0.6–6.3
Free triiodothyronine (pg/mL)	5.3	3.4–5.2
Free thyroxine (ng/dL)	1.8.4	0.87–1.29
Vitamin B1 (ng/mL)	22	52–176
Vitamin B12 (pg/mL)	703	150–400
Magnesium (mg/dL)	2.4	1.9–2.5
Antinuclear antibodies	< 40	< 40
Anti-SSA antibodies (U/mL)	≦7.0	≦7.0
Anti-SSB antibodies (U/mL)	≦7.0	≦7.0
Whole blood		
White blood cell (no/mm^3)	6000	3800–8500
Neutrophil (%)	47.7	
Lymphocyte (%)	43.5	
Red blood cell (no/mm^3)	5.22	3.60–5.00 × 10^6
Hemoglobin (g/dL)	15.3	11–16
Erythrocyte sedimentation rate 1 h (mm)	11	5–10
Prothrombin time International normalized ratio	1.01	0.64–1.17
Activated partial thromboplastin time (second)	24	26.6–40.3
Fibrinogen (mg/dL)	250	156–400

(Table 1). Cerebrospinal fluid (CSF) analyses showed a protein level of 35 mg/d and cell count of 20 μL (Mono 20%, Poly 0%). No conspicuous abnormalities were evident on brain or lumbar magnetic resonance imaging.

On the fifth day, the patient showed lightheadedness upon standing, syncope on upright posture, diarrhea, reduced sweating and paroxysmal bursts of pain in the limbs (Fig. 1). A physiological evaluation revealed that the patient's heart rate increased when she transitioned from the supine position to a standing position (90/min to 131/min) without a fall in blood pressure, which is compatible with postural tachycardia syndrome. The patient's pupils were dilated (6/6 mm), and her light reflexes were delayed. All symptoms faded after a few days.

One and a half month after the onset, she showed lightheadedness, syncope, nausea, diarrhea and distally accentuated hyperalgesia in her hands again. Muscle weakness was not noted in the limbs. In the CSF, the protein was elevated (270 mg/dL). A nerve conduction study (NCS) revealed a low sensory nerve amplitude in the left ulnar nerve (14.9 μV, controls > 18 μV). Lightheadedness and syncope improved after administering midodrine, and diarrhea improved after administering polycarbophil calcium. She did not complain of any symptoms four months later. The serum titer of the anti-gAChR antibodies was mildly elevated (0.06 nmol/L, normal < 0.05 nmol/L) on a radioimmunoprecipitation assay [6].

Nine months after the onset, nausea, diarrhea, headache, lightheadedness, syncope and a painful sensation in her bilateral fingertips had all returned. A neurological examination revealed distally accentuated hyperalgesia in the upper limbs. The motor functions of the four limbs were preserved. DTR were absent on her Achilles and patellar tendons. She was treated with IVIg at 0.4 g/kg/day for 5 days (total 1.5 g), and the spontaneous pain and hyperalgesia rapidly dissipated, and other symptoms disappeared four days later.

Ten months after the onset, pain in the bilateral fingertips and headache returned again. She was treated again with IVIg, and the symptoms disappeared two later.

The patient remained neurologically stable for two months, but the painful sensation in the bilateral finger tips recurred, along with fatigue and hyperalgesia. In addition to the upper and lower limbs, hyperalgesia to pin-pricking was observed at cervical levels 6 to 7, thoracic level 1 and below thoracic level 10. The motor functions of the four limbs were preserved. DTR on her Achilles and patellar tendons was absent. The plantar responses were flexor on both sides. A laboratory examination showed a high level of serum anti-thyroperoxidase (TPO) antibodies antibody (40 U/mL, normal < 16 U/mL), anti-thyroglobulin (Tg) antibody (143 U/mL, normal < 28 U/mL) and anti-Sjögren's syndrome-related antigen A (SSA) antibody (21.9 U/mL, normal ≤ 7.0 U/mL). We administered IVIg for five days, and the symptoms were ameliorated but persisted. After three courses of IVMP (1 g daily, 3 days/week, biweekly), her symptoms rapidly dissipated. Her serum became negative for anti-gAChR antibodies (0.01 nmol/L), anti-TPO, anti-TG, and anti-SSA antibodies. Since then, her neurological findings have been stable for over two years.

3. Discussion

The present patient experienced numbness and weakness in her lower extremities three days after gastroenteritis, followed by a loss of consciousness, diarrhea, hypohidrosis and pain in her extremities. These symptoms spontaneously resolved temporarily but later recurred. Autonomic and sensory impairments were predominant throughout the course of the disease.

Several autoantibodies were detected during the disease course,

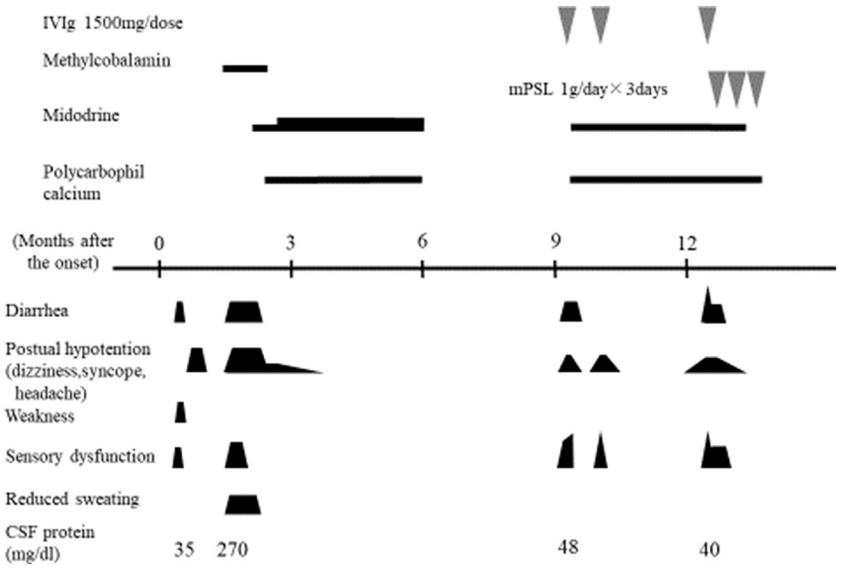

Fig. 1. After at the first attack, all symptoms vanished spontaneously. After the second attack, the symptoms continued, and we administered midodrine and polycarvophil calcium. After this treatment, we detected high levels of a CSF protein. After the third and fourth attacks, IVIg was required. After the fifth attack, although IVIg treatment was unsuccessful, all of the symptoms disappeared after steroid pulse therapy.

suggesting the involvement of some immune mechanisms. Among these, anti-gAChR antibodies have been reported to be detected in patients with AAG [1,7]. As the antigens recognized by anti-gAChR antibodies are mostly located at the autonomic ganglia, patients who are positive for these antibodies usually display autonomic dysfunction without somatic nerve involvement [8]. Anti-SSA antibodies are related to Sjögren's syndrome [9]. Patients with Sjögren's syndrome may report various complaints of chronic neuropathies, including autonomic and sensory neuropathies [9]. Autopsy cases of Sjögren's syndrome-associated neuropathy revealed the loss of neurons in both the autonomic and sensory ganglia [9,10)]. The antibodies that were detected in our patient became negative after the final episode. We therefore suspect that autoimmunity provoked by an antecedent infection widely affected our patient's autonomic and somatic nerves.

In conclusion, we herein reported the case of a patient with recurrent autonomic and sensory neuropathy in whom multiple autoantibodies were detected, including anti-gAChR antibodies. In addition to IVIg, steroids may be effective in such cases. Further studies of such cases are needed to clarify the efficacy of treatment and the nosological position in the spectrum of autonomic neuropathies.

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