CASE REPORT

Autoimmune autonomic ganglionopathy manifesting as acute-onset orthostatic hypotension in a patient undergoing peritoneal dialysis

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Abstract Orthostatic hypotension is an important complication in the management of patients receiving dialysis therapy. As for the orthostatic hypotension caused by decreased peripheral artery resistance, diabetic neuropathy and amyloidosis are the two main causes of hypotension in dialysis patients. However, some patients develop orthostatic hypotension that is caused by dysfunction of the autonomic nervous system, not by diabetic or amyloidosis-related neuropathy. We herein present a case of a 56-year-old man with a 17-year history of peritoneal dialysis therapy, who developed acute-onset orthostatic hypotension accompanied by hypohidrosis and erectile dysfunction. Because serum autoantibodies to ganglionic nicotinic acetylcholine receptor were detected, he was diagnosed with autoimmune autonomic ganglionopathy (AAG). He was treated with high-dose immunoglobulin therapy (0.6 g per kg of body weight per day) for 5 consecutive days, which resulted in a gradual improvement in dizziness. Two months after the onset of AAG,

he could discontinue vasopressors (fludrocortisone acetate and midodrine hydrochloride) and continued maintenance dialysis therapy without the use of vasopressors. This case indicates that physicians should consider autonomic neuropathy including AAG as a differential diagnosis when they encounter dialysis patients with orthostatic hypotension.

Keywords Autoimmune autonomic ganglionopathy · End-stage kidney disease · Immunoglobulin · Orthostatic hypotension · Peritoneal dialysis

Introduction

Hypotension is an important complication in patients receiving dialysis therapy. Dialysis-related hypotension is classified into the following three categories: intradialytic hypotension, chronic sustained hypotension, and orthostatic hypotension [1]. In patients undergoing peritoneal dialysis (PD), the last two are clinically important.

Dialysis hypotension has a multifactorial etiology, including disparate causes such as autonomic dysfunction, decreased plasma osmolality, decrease in extracellular fluid volume with inadequate plasma volume, impaired venous compliance, decreased cardiac reserve, changes in serum potassium and calcium concentrations, and, perhaps, an accumulation of nitric oxide [2]. As for hypotension caused by decreased peripheral artery resistance, diabetic neuropathy and amyloidosis are the two main causes in dialysis patients [3]. However, some patients develop orthostatic hypotension that is caused by dysfunction of the autonomic nervous system.

We herein present a Japanese patient with a 17-year history of PD therapy who presented with acute-onset

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orthostatic hypotension, and was finally diagnosed with autoimmune autonomic ganglionopathy (AAG).

Case report

A 56-year-old man was admitted to our hospital with a 3-day history of symptomatic orthostatic hypotension and recurrent falls, which compromised his activities of daily living. He had been receiving regular follow-up for PD at our hospital for 17 years. The cause of end-stage kidney disease was biopsy-proven chronic glomerulonephritis. He had neither diabetes mellitus nor neuropathy. At the last visit, 1 month prior to admission, his blood pressure in the sitting position was 120/80 mmHg. At that time, he had no complaints. He had no history of surgery, epidural anesthesia, or immunization within the 6 months before admission. In addition, he did not show any antecedent viral infection, including upper respiratory tract infection or gastroenteritis.

On admission, the patient was alert. His blood pressure was 81/54 mmHg in supine position, his heart rate was 127 beats/min, and his body temperature was 36.5 °C. Blood pressure levels in the supine, sitting, and standing positions are shown in Fig. 1a. The systolic blood pressure difference between supine and standing positions was 49 mmHg, meeting the criteria of orthostatic hypotension. A physical examination revealed palpebral conjunctiva anemia and findings of a decrease in skin turgor and a dry oral mucosa. A neurological examination showed that the cranial nerves, including pupillary function, were not involved. Superficial sensations in the extremities (legs more than arms) were mildly lost. Muscle strength testing revealed 4+/4+ strength in the proximal part of the lower extremities and 5/5 strength in the distal part of the lower extremities. Deep tendon reflexes were normal in the upper and lower

extremities. A detailed medical interview revealed erectile dysfunction and decreased sweating, suggestive of autonomic dysfunction.

The patient's biochemical parameters on admission are shown in Table 1. No abnormalities were found on routine blood examination on the day of hospital admission. Blood glucose level was 112 mg/dL, and glycoalbumin was 11.2 % (normal range 11.6–16.4 %). Although the hemoglobin concentration was 10.2 g/dL, upper gastrointestinal endoscopy was performed, because the fecal occult blood test was positive. However, endoscopy did not reveal any signs of hemorrhagic lesions. On echocardiography, heart contraction and intravascular volume were normal, and there were neither local wall asynergy nor granular sparkling that are suggestive of cardiac amyloidosis. The coefficient of variance of R–R interval was elongated on the electrocardiogram. Although level of serum amyloid A protein was higher than the normal range, amyloid fibril was not detected by histological evaluation of a biopsy of the duodenal mucosa obtained at the time of endoscopy.

Oral vasopressors (midodrine hydrochloride, droxidopa, and fludrocortisone) were administered to increase the blood pressure (Fig. 2), because autonomic dysfunction was strongly considered as one of the differential diagnoses. As for the cause of autonomic dysfunction, there were no findings suggestive of autonomic neuropathy caused by paraneoplastic syndrome, and tumor markers and systemic imaging did not detect apparent malignancies. Therefore, the possibility of autoimmune-related autonomic dysfunction, in particular AAG, was considered.

At this point, however, acute autonomic and sensory neuropathy (AASN) and Guillain–Barré syndrome (GBS) could not be ruled out, because AASN can also manifest as dominant autonomic dysfunction with sensory impairment, and GBS can manifest as a combination of autonomic, sensory, and motor neuropathy [4, 5]. To rule out the

Fig. 1 Changes in blood pressure before and after IVIG treatment. Blood pressure levels measured in the supine, sitting, and standing positions before (a) and after (b) IVIG. bpm beat per minute, DBP diastolic blood pressure, SBP systolic blood pressure

Table 1 Results of laboratory tests conducted on admission

<i>Complete blood count</i>			Glucose	112	mg/dL
Hemoglobin	10.2	g/dL	C-reactive protein	1.58	mg/dL
Hematocrit	31.5	%	Vitamin B12 (N; 233–914)	510	pg/mL
White blood cells	12300	/μL	Folic acid (N; 3.6–12.0)	6.5	ng/mL
Platelets	16.0 × 10 ⁴	/μL	Serum amyloid A (N; 0.0–8.0)	11.7	μg/mL
<i>Serum biochemistry</i>			Serum β2-microglobulin (N; <2.2)	40.2	μg/mL
Total protein	6.4	g/dL	Glycoalbumin (N; 11.6–16.4)	11.0	%
Albumin	3.5	g/dL	<i>Immunological studies</i>		
Blood urea nitrogen	55.1	mg/dL	Immunoglobulin G	428	mg/dL
Creatinine	7.31	mg/dL	Immunoglobulin A	209	mg/dL
Uric acid	6.8	mg/dL	Immunoglobulin M	25	mg/dL
Total bilirubin	0.4	mg/dL	C3	64.3	mg/dL
Aspartate aminotransferase	36	U/L	C4	14.8	mg/dL
Alanine aminotransferase	55	U/L	CH50	32.3	U/L
Lactate dehydrogenase	337	U/L	Anti-nuclear antibody	40	×
Alkaline phosphatase	42	U/L	Anti-Sm antibody	(–)	
Creatine kinase	179	U/L	Anti-SS-A antibody	(–)	
Sodium	136	mmol/L	Anti-SS-B antibody	(–)	
Potassium	5.1	mmol/L	MPO-ANCA	(–)	
Chloride	94	mmol/L	PR3-ANCA	(–)	
Calcium	9.8	mg/dL	Anti-AChR antibody	<0.3	nmol/L
Phosphorus	5.2	mg/dL	Anti-gAChR antibody	(+)	
Transferrin saturation	17.0	%	<i>Endocrinology</i>		
Ferritin	107	ng/mL	Brain natriuretic peptide	52.5	pg/mL
Total cholesterol	149	mg/dL			
Triglyceride	132	mg/dL			

MPO-ANCA myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA proteinase 3 anti-neutrophil cytoplasmic antibody, AChR acetylcholine receptor, gAChR ganglionic acetylcholine receptor

Fig. 2 Clinical course before and after IVIG treatment. AAG autoimmune autonomic ganglionopathy, CTR cardiothoracic ratio, DBP diastolic blood pressure, gAChR ganglionic acetylcholine receptor, Hb hemoglobin, IVIG intravenous immunoglobulin, SBP systolic blood pressure

possibility of other autoimmune-related disorders, a variety of autoantibodies were examined, and only anti-ganglionic acetylcholine receptor (gAChR) antibody was positive. Based on these immunological results and the neurological findings, AASN and GBS were excluded. Accordingly, the diagnosis of AAG was made.

The clinical course is shown in Fig. 2. The patient was given high-dose intravenous immunoglobulin (IVIG) therapy (0.6 g per kg of body weight per day) for 5 consecutive days. Although antibodies to gAChR were still present after immunoglobulin therapy, dizziness improved gradually. After IVIG therapy, the patient's blood pressure was 104/64 mmHg (heart rate 95 beats/min) in the supine position and 74/51 mmHg (heart rate 102 beats/min) in the upright position without wobbling. Although orthostatic hypotension remained, the decline in blood pressure with the change in posture became smaller after IVIG treatment (Fig. 1a, b). There were no changes in the hemoglobin level and cardiothoracic ratio before and after IVIG therapy, indicating orthostatic hypotension was not mainly influenced by anemia and volume status. Two months after the onset of AAG, he could discontinue vasopressors (fludrocortisone acetate, midodrine hydrochloride) and was discharged. At 7 months after discharge, he could receive maintenance dialysis therapy without the use of vasopressors.

Discussion

In summary, we described a case of a patient undergoing PD therapy who was hospitalized for the chief complaint of dizziness, and who had orthostatic hypotension, erectile dysfunction and decreased sweating, suggesting the presence of autonomic nervous system disorders. Because anti-gAChR antibodies were present and other causes of autonomic nervous system disorder including diabetic neuropathy, amyloidosis, AASN, and GBS were ruled out, he was diagnosed with AAG.

The following three points were highlighted in this case. First, autonomic dysfunction might be a cause of orthostatic hypotension in dialysis patients. Second, autoimmune autonomic neuropathy was the cause of autonomic dysfunction. Finally, intravenous high-dose IVIG therapy was effective (symptoms improved gradually and the anti-gAChR antibody level became lower).

Neurogenic orthostatic hypotension is the most common, challenging and an often frustrating feature of autonomic dysfunction secondary to diabetes mellitus or amyloidosis in patients on PD. Surprisingly, previous studies have shown that autonomic neuropathy occurs in over 50 % of chronic dialysis patients [6]. Autonomic involvement in dialysis patients has been shown to be

mediated by small-fiber damage including axonal damage. Although the precise pathophysiological mechanism remains unclear, axonal damage is most likely caused by the action of unknown uremic toxins on nerve fibers [7]. Intravascular volume depletion, low cardiac output states, conduction abnormalities, severe anemia, and medications can all lead to a blood pressure drop on standing [8]. Hence, when we evaluate orthostatic hypotension, it is important that we exclude a non-neurogenic cause before attributing it to autonomic neuropathy.

Clinical autonomic disorders can result from diverse causes, including degenerative, inherited, toxic/metabolic, infections and autoimmune/inflammatory conditions. It is particularly important to recognize immune-mediated disorders, since immunomodulatory therapy may lead to recovery of neurological function. Conceptually, autonomic disorders are often categorized as either central or peripheral. In the third category of autonomic disorders, the pathology lies within the autonomic ganglia itself.

For autonomic neuropathy with monophasic, acute or subacute progression, at least three subgroups have been proposed on the basis of the concomitance or absence of sensory or motor dysfunctions: (1) pure autonomic neuropathy; (2) autonomic neuropathy with sensory impairment; and (3) autonomic neuropathy with sensory and motor impairment, although there could be some overlap. Among the three categories, AAG is classified into the pure autonomic neuropathy subgroup.

AAG has been established as an isolated nosological entity since the discovery of anti-gAChR antibodies [4]. The clinical features of AAG reflect impairment in sympathetic (orthostatic hypotension, anhidrosis), parasympathetic (reduced lacrimation, salivation, and pupil constriction), and enteric functions (ileus, abdominal colic, diarrhea, and constipation). The combination of tonic pupils and gastrointestinal dysmotility in the setting of severe orthostatic hypotension is particularly suggestive of AAG [9].

As for the pathogenesis, AAG is classified as an autoimmune disease, although its precise mechanism remains unclear. Up to 50 % of patients with the acute or subacute form of this disorder have high levels of autoantibodies that bind to gAChR [9]. As gAChR is located only in the sympathetic, parasympathetic, and enteric autonomic ganglia, AAG is considered to show autonomic dysfunction without sensory and motor impairment [4]. However, according to a recent review of AAG, 25 % of patients reported minor sensory symptoms [10], although objective sensory impairment was not present. In the present case, the patient had autonomic neuropathy with superficial light sense impairment, although movement impairment was not involved. In this regard, AASN and GBS should be considered in the differential diagnosis because they can both

show autonomic and sensory impairment [9]. Although the presence of an antecedent event, the monophasic nature of the clinical course, and ganglionopathy are shared in AAG and AASN, the presence of obvious sensory involvement and the positive titers of anti-gAChR antibodies strongly indicate AAG, rather than AASN [4]. For these reasons, we ruled out AASN in the present case.

Another important differential diagnosis of AAG is GBS. GBS is a form of neuropathy, of which the immunological targets are the myelin sheath or axon of the peripheral nerves [11]. By contrast, in AAG, anti- α 3AChR antibodies affect transmission of acetylcholine within the synapse of the autonomic ganglia. As autonomic features can occur in GBS, clinical differentiation of AAG from GBS could theoretically be challenging. In AAG, the clinical syndrome only affects the autonomic nervous system, and peripheral strength, reflexes, and motor and sensory nerve conduction studies are normal, unlike GBS. The anti-gAChR antibodies are specific to AAG and should not be present in GBS [12]. In the present case, motor function was intact and the patient was positive for anti-gAChR antibodies, confirming the diagnosis of AAG, instead of GBS.

Anti-gAChR antibodies are an important serological marker of AAG but also cause the characteristic defect in autonomic ganglionic neurotransmission in this disorder [9]. Because nephrologists are not familiar with autonomic neuropathy including AAG, there might be more dialysis patients suffering from AAG who could be treated appropriately.

As yet, there is no standard treatment for AAG. Previous reports have shown that serum levels of anti-gAChR antibody correlate with the severity of autonomic dysfunction. Patients with high antibody levels have the most severe and widespread autonomic failure [13]. Given that AAG appears to be an antibody-mediated autoimmune disorder analogous to myasthenia gravis, immunomodulatory treatments similar to those used in myasthenia gravis should be effective in reducing antibody levels and restoring autonomic function. In fact, several case reports have shown that plasma exchange, either alone or in combination with immunosuppressive drugs, can produce a prompt improvement in autonomic function [14]. In this case, we treated the patient with IVIG, because IVIG was reported to be effective in a number of cases of subacute pandysautonomia prior to the advent of antibody testing [15–17], and more recently in one case of seropositive AAG [18]. After IVIG treatment, serum titer of anti-gAChR antibodies decreased, leading to the amelioration of AAG-related symptoms. In this regard, our case supports the proposed mechanism of AAG and effectiveness of IVIG for patients with AAG.

In conclusion, our case suggests that AAG should be considered in dialysis patients when orthostatic hypotension is present with evidence of autonomic dysfunction. Because measurement of serum levels of anti-gAChR antibodies is not widely available, it is important to develop commercially available detection kits for the prompt diagnosis of AAG in the near future.

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