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BRIEF COMMUNICATION

Autoimmune postural orthostatic tachycardia syndrome

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Abstract

The aim of this study was to evaluate the association between postural orthostatic tachycardia syndrome (POTS) and circulating antiganglionic acetylcholine receptor (gAChR) antibodies. We reviewed clinical assessments of Japanese patients with POTS, and determined the presence of gAChR antibodies in serum samples from those patients. Luciferase immunoprecipitation systems detected anti-gAChRα3 and β4 antibodies in the sera from POTS (29%). Antecedent infections were frequently reported in patients in POTS patients. Moreover, autoimmune markers and comorbid autoimmune diseases were also frequent in seropositive POTS patients. Anti-gAChR antibodies were detectable in significant number of patients with POTS, and POTS entailed the element of autoimmune basis.

Introduction

Orthostasis and fatigue with autonomic dysfunction frequently occur in autoimmune diseases.[1] Postural orthostatic tachycardia syndrome (POTS) is the most common form of orthostatic intolerance characterized by lightheadedness, presyncope and palpitations, and nonorthostatic symptoms, such as fatigue, abnormalities of sleep, myofascial pain, nausea, and migraine headache.[2] Gastrointestinal (GI) disturbances are common and prolonged in patients with POTS, and it remains unknown whether extravascular volume depletion and deconditioning contribute to POTS in patients with other autonomic symptoms.[3,4] The pathophysiology of POTS is heterogeneous and includes impaired sympathetically-mediated vasoconstriction, excessive sympathetic drive, volume dysregulation, and deconditioning.[2]

An autoimmune basis has been suggested as a causal mechanism of POTS, and several autoreactive IgGs have been identified, including ganglionic acetylcholine receptor (gAChR), voltage-gated potassium channel complex, cardiac lipid raft-associated proteins, α1-adrenergic receptor, as well as β1- and β2-adrenergic receptors.[5–7] Moreover, Blitshteyn recently determined the high prevalence of positive ANA and other autoantibodies and the high prevalence of comorbid autoimmune disorders that exist in patients with POTS.[8,9] Sandroni and Low demonstrated occasional positivity to gAChR antibodies in POTS patients.[10] Previously, we reported the relationship among the anti-gAChR antibodies, autonomic

dysfunction, and autoimmune rheumatic diseases.[11–13] We attempted to elucidate the autoimmune pathophysiology of POTS in this study as a part of our comprehensive approach. Therefore, we assessed the frequency of autonomic dysfunction in the patients with two highly prevalent orthostatic intolerances of POTS and neurally mediated syncope (NMS) using objective clinical indicators. And, we examined potential immune-mediation of POTS by evaluating autoantibodies against gAChR, which have been implicated in both POTS and POTS-associated autonomic dysfunction.

Patients and Methods

Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent. The Ethics Committee of Nagasaki Kawatana Medical Center and Kumamoto University Hospital approved the study.

Study design

First analysis (Fig. 1A) tested for the presence of gAChR antibodies in serum samples from 34 patients with POTS, 19 patients with NMS, 34 patients with OND, and 73 healthy controls. The diagnosis of POTS and NMS were confirmed using the consensus statement by the American Autonomic Society, the European Federation of Autonomic Societies, the Autonomic Research Group of the World Federation of Neurology and the Autonomic Disorders section of the American Academy of Neurology, and 2015 heart rhythm society expert consensus statement.[14–16] We compared the frequencies of autoantibodies against gAChR among four groups, and analyzed the clinical features between the POTS group and NMS group.

In second analysis (Fig. 1A), we analyzed the clinical features between the seropositive and seronegative POTS group.

Study population

Serum samples from 53 patients with orthostatic intolerance were obtained from general and teaching hospitals throughout Japan between January 2012 and August 2016. The diagnosis of POTS and NMS were confirmed using the consensus statement on the definition of orthostatic hypotension, NMS, and POTS in 2011. Exclusion criteria are provided as Supplementary Information. The demographic data of 34 patients with POTS were as follows: median age, 22.2 ± 10.8 years old; male/female ratio, 10/24; onset age, 19.8 ± 10.8 years old. In addition, the demographic data of patients with 19 NMS were as follows: median age, 40.9 ± 23.9 years old; male/female ratio, 12/7; onset age, 38.4 ± 22.9 years old. Control groups included 34 patients with other neurological diseases (OND) with any autonomic symptoms (15 women, 19 men, mean age 56.3 years), and 73 healthy controls (HC) who donated blood for this study (42 women, 31 men, mean age 38.3 years).

Luciferase immunoprecipitation system assay for autoantibodies against gAChR

Serum gAChRα3 and β4 antibodies were detected using Luciferase immunoprecipitation system (LIPS) assays, as described previously.[11] Antibody levels were expressed as the antibody index (A.I.). We established a normalized value for HC as <1.000 A.I. To evaluate the diagnostic accuracy of this assay, we verified the cut-off points for all data collected in the previous study.[12,13]

Clinical assessment of autonomic function

Comprehensive clinical, neurological, and serologic assessments were performed for all patients. We queried the presence or absence of each of the following functions that are controlled by the autonomic system as reported in our previous study: syncope or orthostatic hypotension (OH) for orthostatic intolerance (OI); arrhythmia; pupillary dysfunction; sicca complex; coughing episodes; skin dryness or hypohidrosis/anhidrosis for heat intolerance; upper GI system problems; diarrhea or constipation indicating dysfunction of the lower GI system; dysuria or urinary retention needing catheterization for bladder dysfunction; and sexual dysfunction.[11] For the all patients, questionnaires were sent to the referring neurologists.

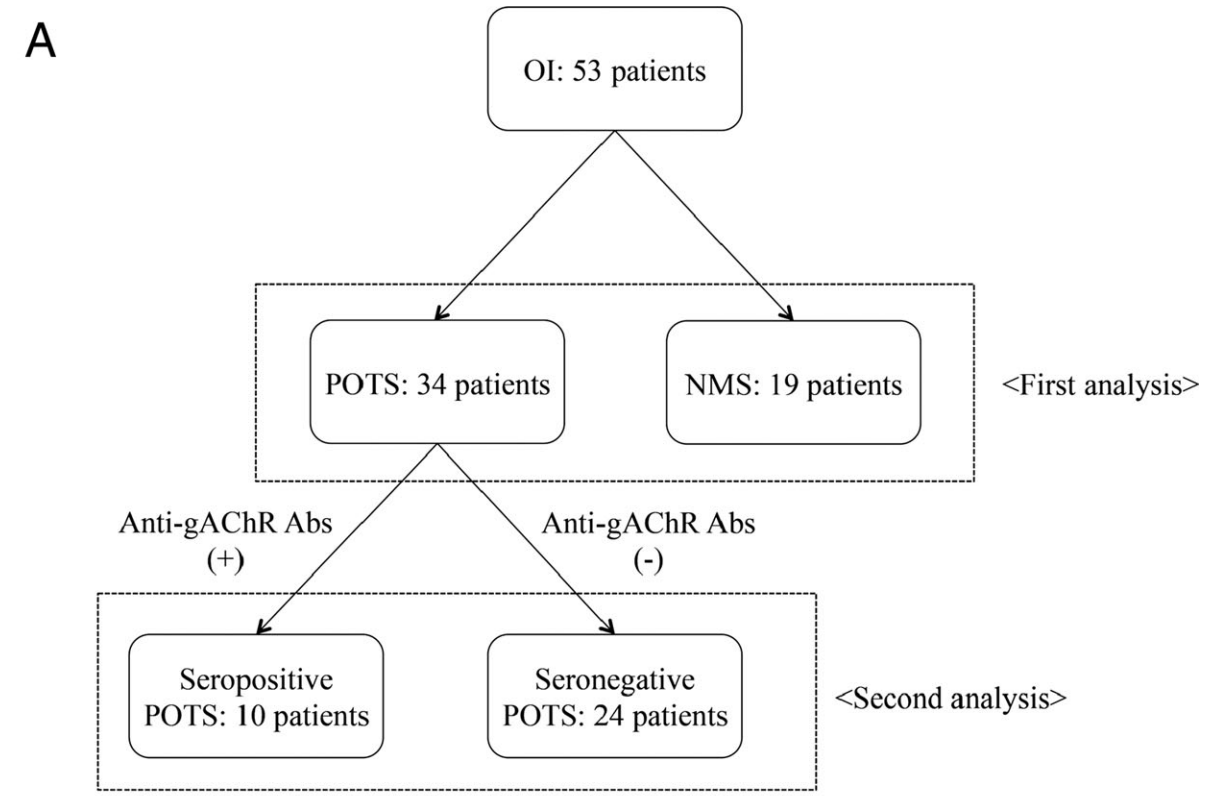
Statistical analyses

SigmaPlot® was used for data analyses. The normally distributed A.I. data were analyzed by one-way analysis of variance between HC, POTS, NMS, and OND groups. Frequencies of autoantibodies and non-normally distributed data were analyzed by one-way analyses of variance of ranks. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Frequencies of autoantibodies against gAChR in first analysis

Using the LIPS assay, we found that 29% (10 of 34) of patients with POTS were positive for autoantibodies. Specifically, anti-gAChRα3 antibodies were detected in 8



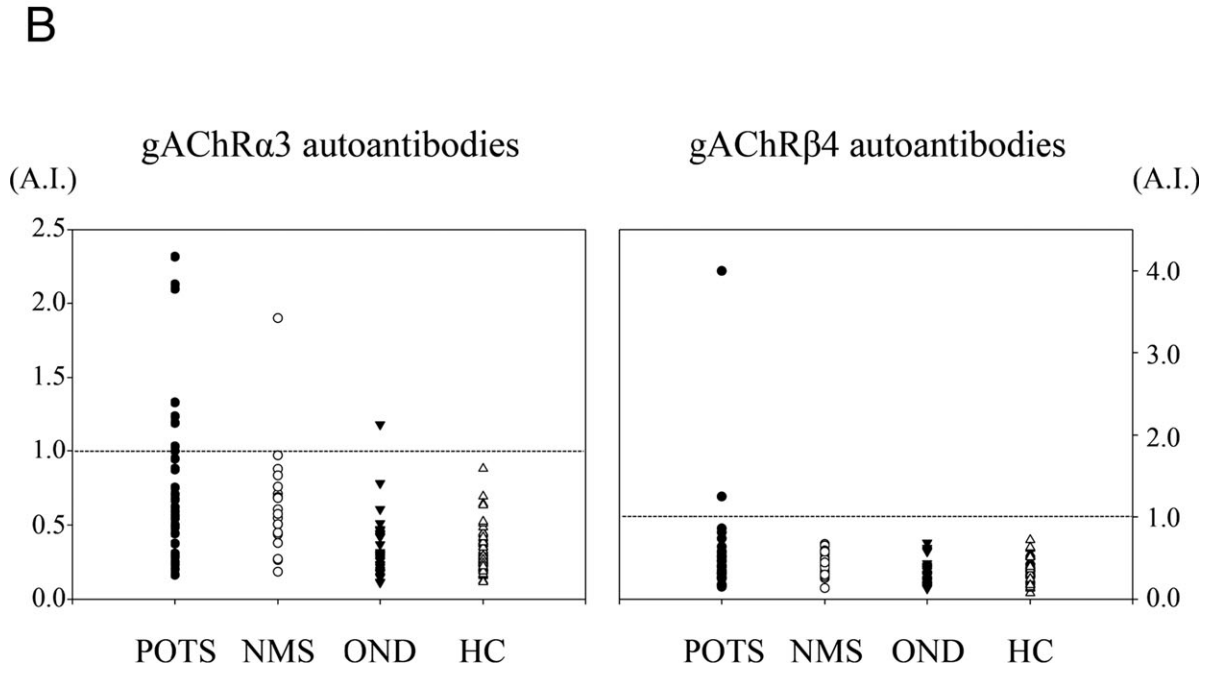


Figure 1. (A) Study design and participant information. Details regarding study design and participant recruitment for each subject group. OI, orthostatic intolerances; POTS, postural orthostatic tachycardia syndrome; NMS, neurally mediated syncope; anti-gAChR Abs, antiganglionic acetylcholine receptor antibodies. (B) Anti-gAChRα3 and *β*4 antibodies in sera from patients with postural orthostatic tachycardia syndrome (POTS). Anti-gAChRα3 and *β*4 antibodies were assessed using luciferase immunoprecipitation system (LIPS) assays. The dotted line indicates the cut-off. We tested sera from healthy controls (HC), as well as from patients with POTS and other neurologic diseases (OND). Autoantibodies against anti-gAChR were detected in 29% (10 of 34) samples from patients with POTS.

samples (24%), and anti-gAChRβ4 antibodies were detected in two samples (6%). Furthermore, no samples from the seropositive patients with POTS were positive for both antibodies. In contrast, we found that only one patient (5%) with NMS was positive for autoantibodies against gAChRα3. The frequencies of gAChRα3 antibodies in patients with POTS were statistically higher than those in patients with NMS ($P = 0.041$). However, no statistically significant difference was detected in between the POTS group and NMS group on the prevalence of anti-gAChR antibodies ($P = 0.479$). In all 73 HC, anti-gAChRα3 and anti-gAChRβ4 antibodies were absent, and anti-gAChRα3 antibodies were detected in the serum of one patient in the OND group, who had suspected amyloid neuropathy (Fig. 1B).

The mean A.I. value for anti-gAChRα3 antibodies in the POTS group was 0.746, which was significantly greater than those obtained for the HC (0.305) or OND (0.336) groups ($P < 0.001$). The mean A.I. for anti-gAChRβ4 antibodies in the POTS group was 0.536, which was also significantly greater than those obtained for the HC (0.367) or OND (0.302) groups ($P = 0.007$) (Fig. 1B). However, the mean A.I. value for anti-gAChRα3 antibodies in the NMS group was 0.638, and the mean A.I. for anti-gAChRβ4 antibodies in the NMS group was 0.421. No statistically significant difference was seen in between the POTS group and NMS group on the mean A.I. for anti-gAChRα3 and gAChRβ4 antibodies ($P = 0.774$ and 0.744, respectively).

Clinical assessment of autonomic function in patients with POTS and NMS in first analysis

Table 1 summarizes the clinical characteristics and autonomic symptoms of patients with POTS and NMS. Age

Table 1. Clinical features of patients with POTS and NMS.

	POTS	NMS	*P* value
Number of patients	34	19	
Age (year)	22.2 ± 10.8	40.9 ± 23.9	0.004*
Age at onset (year)	19.8 ± 10.8	38.4 ± 22.9	0.013*
Sex, female (%)	24 (71)	7 (37)	0.018*
Anti-gAChRα3 abs (A.I.)	0.746 ± 0.549	0.638 ± 0.372	0.774
Anti-gAChRβ4 abs (A.I.)	0.536 ± 0.653	0.421 ± 0.145	0.744
Seropostive for anti-gAChRα3 abs (%)	8 (24)	1 (5)	0.041*
Seropostive for anti-gAChRβ4 abs (%)	2 (6)	0 (0)	0.479
Onset (%)[1]	Acute, subacute: 8 (24) Gradual: 26 (76)	Acute, subacute: 5 (26) Gradual: 14 (74)	0.832
Antecedent infections (%)	10 (29)[2]	0 (0)	0.010*
Orthostatic intolerance (%)[3]	33 (97)	19 (100)	0.479
Arrhythmia (%)	6 (18)	8 (42)	0.901
Pupil abnormalities (%)	2 (6)	0 (0)	0.299
Sicca complex (%)	13 (38)	5 (26)	0.639
Coughing episodes (%)	1 (3)	0 (0)	0.479
Heat intolerance and/or anhidrosis (%)	14 (41)	5 (26)	0.289
Upper gastrointestinal tract symptoms (%)[4]	13 (38)	4 (21)	0.145
Lower gastrointestinal tract symptoms (%)[5]	14 (41)	9 (47)	0.674
Bladder dysfunction (%)	4 (12)	2 (11)	0.906
Endocrine disorder complications (%)	4 (12)[6]	0 (0)	0.129
Autoimmune disease complications (%)	8 (24)[7]	4 (21)[8]	0.979

*P< 0.05

abs, antibodies.

[1]Subacute onset was defined as the reaching of the peak of autonomic failure within 3 months, and chronic was defined as reaching of the peak after 3 months.

[2]Mycoplasma pneumonia; four patients of flu-like symptom (fever, throat, and joint pain); three patients of upper respiratory tract (URT) infection; gastroenteritis; trauma.

[3]Orthostatic intolerance = orthostatic hypotension and/or palpitation and/or syncope.

[4]Upper gastrointestinal tract symptoms = appetite loss and/or nausea and/or vomiting and/or early satiety and/or postprandial abdominal pain.

[5]Lower gastrointestinal tract symptoms = constipation and/or diarrhea and/or ileus.

[6]Four patients of Amenorrhea.

[7]Three patients of antinuclear antibody positive; two patients of Graves' disease; Sjögren's syndrome; allergic bronchitis; rheumatoid arthritis and fibromyalgia.

[8]Ulcerative colitis; type I diabetes; Hashimoto's disease; IgG4-related disorder.

and age at onset in the patients with POTS were significantly younger than those in the patients with NMS ($P = 0.004$ and 0.013, respectively). Antecedent infections were reported in 10 patients (29%) in POTS group, and there was a difference between POTS group and NMS group ($P = 0.010$). Female was more frequently suffered in POTS group (24 patients, 71%) than in NMS group (7 patients, 37%) ($P = 0.018$).

Clinical assessment of autonomic function in patients with seropositive POTS in second analysis

Table 2 summarizes the clinical characteristics and autonomic symptoms of patients with POTS, according to seroreactivity to anti-gAChR antibodies. The age in seropositive POTS group was significantly higher than those in seronegative POTS group ($P = 0.012$). As for the age at onset, similar trend was observed, but we found no statistical significance ($P = 0.052$). Antecedent infections were reported in five patients (50%) with seropositive POTS, but there were no differences between seropositive and seronegative patients. For autonomic symptoms, pupil abnormality and lower gastrointestinal tract symptoms were most frequently observed ($P = 0.029$ and 0.032, respectively). Other autoimmune diseases were more common in anti-gAChR antibody-positive patients than in those who were antibody-negative ($P < 0.001$). Three of 10 patients in the group of seropositive POTS were treated with intravenous methylprednisolone (IVMP) and resulted in clinical improvements. In the group of seronegative POTS, four of 24 patients were treated with IVMP. Three patients maintained improvements in OI, however, we found no clinical improvement in one patient.

Discussion

In this study, we assessed presence or absence of autoantibodies against gAChR in patients with POTS and NMS. We found that anti-gAChR antibodies were detected more frequently in patients with POTS compared to NMS and controls, suggesting that anti-gAChR antibodies may be associated with POTS and its underlying autonomic dysfunction. POTS and NMS were clearly distinguishable by the prevalence of anti-gAChR antibodies. On the basis of the acknowledgment, we verified widespread autonomic manifestations based on neurological assessments, and identified other autoimmune complications in POTS patients with seropositive for anti-gAChR antibodies.

Table 2. Clinical characteristics of patients with POTS.

	Patients with POTS Anti-gAChR Abs positive	Patients with POTS Anti-gAChR Abs negative	*P* value
Number of patients	10	24	
Age (year)	28.5 ± 12.0	19.5 ± 9.3	0.012*
Age at onset (year)	25.6 ± 12.7	17.4 ± 9.2	0.052
Sex, female (%)	8 (80)	16 (68)	0.458
Onset (%)	Acute, subacute: 3 (30) Gradual: 7 (40)	Acute, subacute: 5 (21) Gradual: 19 (79)	0.589
Antecedent infections (%)	5 (50)[1]	5 (21)[2]	0.099
Orthostatic intolerance (%)	10 (100)	23 (96)	0.561
ΔHeart rate (/min)	39.8 ± 10.4	46.8 ± 13.8	0.084
Arrhythmia (%)	1 (10)	2 (8)	0.917
Pupil abnormalities (%)	2 (20)	0 (0)	0.029*
Sicca complex (%)	5 (50)	8 (33)	0.381
Coughing episodes (%)	1 (10)	0 (0)	0.138
Heat intolerance and/or anhidrosis (%)	2 (20)	12 (50)	0.116
Upper gastrointestinal tract symptoms (%)	6 (60)	7 (29)	0.101
Lower gastrointestinal tract symptoms (%)	7 (70)	7 (29)	0.032*
Bladder dysfunction (%)	1 (10)	3 (13)	0.866
Endocrine disorder complications (%)	2 (20)[3]	2 (8)[4]	0.361
Autoimmune disease complications (%)	6 (60)[5]	2 (8)[6]	0.001*

*P< 0.05

[1]Mycoplasma pneumonia; Three patients of flu-like symptom (fever, throat, and joint pain); URT infection.

[2]Trauma; gastroenteritis; flu-like symptom (fever, throat, and joint pain); Two patients of URT infection.

[3]Amenorrhea.

[4]Amenorrhea.

[5]Three patients of antinuclear antibody positive; Graves' disease; Sjögren's syndrome; rheumatoid arthritis; and fibromyalgia.

[6]Graves' disease; allergic bronchitis.

However, the majority of seropositive samples did not have high levels of autoantibodies for gAChR. Therefore, elevated expression of antibodies to gAChR subunits may contribute to secondary autoimmune responses to ganglionic neuron damage in seropositive patients. The prevalence of anti-gAChR antibodies in this study was higher than that in previous study.[17] Anti-gAChR antibodies may impair autonomic ganglionic synaptic transmission, and antibodies that interfere with ganglionic transmission may contribute to dysautonomia in patients with POTS.[18] Although POTS is pathophysiologically categorized into four subtypes (neuropathic, hyperadrenergic, volume dysregulation, and physical deconditioning), it is not clear which subtype corresponds to gAChR autoimmunity-related POTS, or whether anti-gAChR antibodies have stimulatory functions that produce overactivity of sympathetic ganglia (i.e., type V hypersensitivity).[2] Although POTS is a heterogeneous syndrome with various pathophysiologic mechanisms and complex symptomatology, we demonstrated POTS patients with autoimmune basis were present in significant proportions.[2] In addition, we noted the possibility that anti-gAChR antibodies are associated with autonomic dysfunction (e.g., POTS) in autoimmune rheumatic diseases.[12,13]

This study is limited by an observational design and small sample size. Therefore, a subsequent study will be conducted in order to confirm the potential for immunotherapy to resolve the symptoms of autoimmune POTS and associated autonomic effects. A prospective, multicenter, clinical interventional study is necessary in order to confirm the relationships between levels of anti-gAChR antibodies and the severity of POTS and autonomic symptoms.

In conclusion, we could demonstrate that the anti-gAChR antibodies were detected more frequently in patients with POTS compared to NMS and controls. Seropositive POTS patients demonstrated autoimmune markers and comorbid autoimmune diseases were frequent. The results have important implications for our understanding of the pathophysiology of POTS and for the interpretation of humoral antibody responses in POTS.

Acknowledgments

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Conflict of Interest

All authors have no disclosures to report.

Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Nakane had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MW, SN, AM, HM, and YA conceived and designed the experiments. AM, YM (Yasuhiro Maeda), and OH performed the experiments. MW, SN, AM, MN, YM (Yukiko Mori), TM, KT, YK, and YA collected the samples. MW, SN, AM, MN, and YA analyzed the data. MW, SN, AM, HM, and YA wrote the paper.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Exclusion Criteria

(1) Pregnant or lactating women; (2) the presence of failure of other organ systems affecting the autonomic nervous system or the patient's ability to participate in the study; (3) concomitant therapy that may alter autonomic function; and (4) clinically significant coronary artery disease.

