Ganglionic Acetylcholine Receptor Antibodies in Postural Tachycardia Syndrome

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Abstract

Objective

Postural tachycardia syndrome (POTS), the most common form of dysautonomia, may be associated with autoimmunity in some cases. Autoantibodies against the ganglionic acetylcholine receptor (gAChR) have been reported in a minority of patients with POTS, but the prevalence and clinical relevance is unclear.

Methods

Clinical information and serum samples were systematically collected from participants with POTS and healthy control volunteers (n = 294). The level of positive gAChR antibodies was classified as very low (0.02–0.05 nmol/L), low (0.05–0.2 nmol/L), and high (>0.2 nmol/L).

Results

Fifteen of 217 patients with POTS (7%) had gAChR antibodies (8 very low and 7 low). Six of the 77 healthy controls (8%) were positive (3 very low and 3 low). There were no clinical differences between seropositive and seronegative patients with POTS.

Conclusions

Prevalence of gAChR antibody did not differ between POTS and healthy controls, and none had high antibody levels. Patients with POTS were not clinically different based on seropositivity. Low levels of gAChR antibodies are not clinically important in POTS.
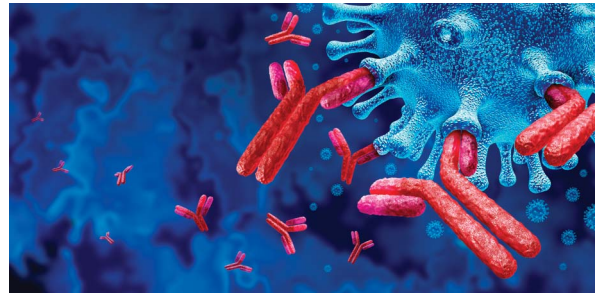
Postural tachycardia syndrome (POTS) is estimated to affect up to 3 million Americans.[1] This syndrome is defined by an excessive increase in heart rate on standing with orthostatic symptoms in the absence of hypotension.[2] Symptoms can include lightheadedness, blurred vision, cognitive difficulty, palpitations, gastrointestinal distress, tremulousness, fatigue, and weakness. The typical patient with POTS is a young woman (female: male ratio 4.5:1). Associated comorbid conditions are common, including migraine headache, gastrointestinal dysmotility, joint hypermobility, and autoimmune disorders.[3] The cause of POTS is likely multifactorial, and autoimmunity is believed to play a role in some patients with subacute onset after infection, physical injury, immunization or surgery, a personal or family history of autoimmune disease, or laboratory evidence of autoimmunity.[4,5]

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The ganglionic nicotinic acetylcholine receptor (gAChR) mediates synaptic transmission in all autonomic ganglia.[6] Antibodies against gAChR are found at high levels in autoimmune autonomic ganglionopathy,[7] a disorder of severe diffuse autonomic failure that may respond to immunomodulatory treatment.[8] These antibodies (at low levels) have also been reported in POTS with prevalence as high as 14% in 1 study.[9] In real-world practice, the prevalence seems to be much lower, and the interpretation of gAChR antibody in POTS remains unclear.[4] In other studies, more than 50% of patients with low levels of gAChR antibody had no evidence of an autoimmune neurologic disorder.[10] This antibody may be found in 3%–4% of healthy controls.[11] Variability in normal values used by commercial laboratories further complicates the interpretation of gAChR antibody results in clinical practice.[12]

Methods

This analysis was part of an observational study to characterize antibody prevalence in community patients with POTS and contemporary healthy controls. Participants were recruited onsite at either the 2014 or the 2016 annual patient and caregiver conference sponsored by Dysautonomia International. Interested participants were informed of the study protocol and provided informed consent (n = 173 in 2014 and n = 152 in 2016). Twenty-four patients participated in both the 2014 and 2016 cohorts; to ensure these participants were only counted once, their data from 2016 were not included in the combined analysis. The POTS group consisted of those who reported being diagnosed with POTS by a physician, and the self-reported healthy controls gave no history of an autoimmune or autonomic disorder. Eight patients reporting an autonomic diagnosis other than POTS were excluded. The final study cohort included 217 patients with POTS and 77 healthy controls. Because of the method of recruitment at a POTS conference, many of the healthy controls were related to patients with POTS.

Participants completed multiple questionnaires that addressed symptoms and medical history and standardized assessments of fatigue, symptom burden, and quality of life. An autonomic specialist measured supine and standing heart rate and blood pressure during supine rest and at intervals during a 10-minute active stand test. Patients reported symptoms that arose during standing using the Vanderbilt Orthostatic Symptom Score near the end of the stand. The Beighton score for joint hypermobility was determined by examination. Antibodies against gAChR were measured using radioimmunoprecipitation assay (as described previously),[8] and antibody levels were categorized as very low (0.02–0.05 nmol/L), low (0.05–0.2 nmol/L), and high (>0.2 nmol/L).

Data were collected and managed using REDCap electronic data capture tools.[13] Statistical comparisons were analyzed using SPSS v26 (IBM, Armonk, NY). Fisher exact tests or χ^2 tests were used for categorical variables, as appropriate. Continuous measures were analyzed using both independent samples t tests and Mann-Whitney U tests. Because the p values were very similar between the parametric and nonparametric analyses, only t test results were reported. For the t test results, if group variances were significantly different, nonpooled t test results were used.

Standard Protocol Approvals, Registrations, and Patient Consents

The project was reviewed and approved by the institutional review boards at UT Southwestern (IRB#042016-036) and Vanderbilt University (IRB#140671). All participants provided written informed consent.

Table 1 Characteristics of Participants (POTS vs Healthy Controls)

	POTS (n = 217)	Controls (n = 77)	p Value
Age, y, mean (SD)	28.5 (±11.8)	48.0 (±12.5)	<0.001
Female sex, n (%)	202 (93)	61 (79)	0.001
Height, cm, mean (SD)	165.6 (±8.1)	167.1 (±8.1)	0.137
BMI, kg/m², mean (SD)	24.7 (±5.6)	28.0 (±5.7)	<0.001
Relative with POTS, n (%)[a]	35 (17)[a]	45 (61)[a]	<0.001
Δ HR at 3 min, bpm, mean (SD)[b]	16.6 (±12.7)[b]	10.3 (±10.1)[b]	<0.001
gAChR Ab ≥0.02 nmol/L, n (%)	15 (7)	6 (8)	0.797
gAChR Ab ≥0.05 nmol/L, n (%)	7 (3)	3 (4)	0.725
gAChR Ab ≥0.2 nmol/L, n (%)	0 (0)	0 (0)	NA

Abbreviations: BMI = body mass index; gAChR = ganglionic acetylcholine receptor; HR = heart rate; NA = not applicable; POTS = postural tachycardia syndrome.
[a] Not all subjects completed the survey, POTS: n = 207 and healthy controls: n = 74.
[b] Not all subjects were able to complete stand test; POTS: n = 209 and healthy controls: n = 70.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Among included participants, 217 reported receiving a formal POTS diagnosis from a physician and 77 were healthy controls. The participant demographics are shown in table 1. Patients with POTS were younger, more often women, and had a lower body mass index.

Fifteen patients with POTS (8 very low and 7 low) and 6 healthy controls (3 very low and 3 low) were positive for gAChR antibodies. The prevalence of gAChR antibody in POTS and controls was not different (table 1). The clinical characteristics of patients with POTS with gAChR antibodies were not different from seronegative patients (table 2). Orthostatic vital signs, symptom severity, symptom duration, and frequency of self-reported coexisting autoimmune diagnosis were not significantly different between seropositive and seronegative POTS groups (table 2 and table e-1, links.lww.com/CPJ/A249).

Discussion

Consistent with previous retrospective reports, low levels of gAChR antibodies are found in a small percentage of patients with POTS. The frequency of gAChR antibodies in patients with POTS (3%–7% depending on the cutoff value) was not different from the frequency of this antibody in healthy controls and not different from the positivity rates in healthy controls reported elsewhere.[11] All seropositive participants in this study (healthy controls or POTS) had low antibody levels (≤0.13 nmol/L). Low gAChR antibody levels may be found in patients with various autoimmune diseases or with cancer[10,12] and in healthy controls.[11] Low gAChR antibody levels (<0.2 nmol/L), therefore, have poor clinical specificity and must be interpreted with caution. Patients with POTS with low-level gAChR antibodies should not have additional extensive diagnostic testing or immunotherapy based on this test result alone.

The strength of this study is the examination of a broad cross section of community patients with POTS and controls enrolled in a standardized way. This approach yields a more accurate picture of the serologic profile of POTS in real-world practice compared with previous studies from academic centers

Table 2 Comparison of gAChR Ab Seropositive and Seronegative Patients With POTS

	Ab pos (n = 15)	Ab neg (n = 202)	*p* Value
Age, y, mean (SD)	30.1 (±12.2)	28.4 (±11.8)	0.584
Female, n (%)	13 (87)	189 (94)	0.278
Height, cm, mean (SD)	166.1 (±6.6)	165.6 (±8.4)	0.753
BMI, kg/m², mean (SD)	25.7(±6.4)	24.6 (±5.6)	0.485
VOSS score, mean (SD)[a,b]	28.5 (±15.0)	25.0 (±15.9)	0.422
Beighton score, mean (SD)[a,b]	4.7 (±2.8)	3.6 (±2.6)	0.093
Δ HR at 3 min, bpm, mean (SD)[a]	14.6 (±8.3)	16.6 (±12.9)	0.572
Δ BP at 3 min, mm Hg, mean (SD)[a]	−1.7 (±9.1)	−0.1 (±10.7)	0.592
COMPASS31 total score, mean (SD)[a,b]	45.1 (±13.1)	46.1 (±12.9)	0.796
Coexisting autoimmune disorder, n (%)[c,d]	3 (25)	61 (31)	0.656
Duration of symptoms[c]			0.196
Less than 1 y, n (%)	0 (0)	10 (5)	
Between 1 and 5 y, n (%)	3 (25)	69 (35)	
Between 5 and 10 y, n (%)	4 (33)	51 (26)	
Greater than 10 y, n (%)	5 (42)	66 (34)	

Abbreviations: BMI = body mass index; BP = blood pressure; COMPASS31 = composite autonomic symptom score, 31 question version; gAChR = ganglionic acetylcholine receptor; HR = heart rate; POTS = postural tachycardia syndrome; VOSS = Vanderbilt orthostatic symptoms score.
[a] VOSS, Beighton, orthostatic vitals and COMPASS31 scores were recorded for 12 seropositive and 193 seronegative subjects.
[b] VOSS evaluates the presence of various orthostatic symptoms during stand test with higher score representing more severe symptoms. Beighton Score provides a score of 0–9 with scores of 5 or more indicating joint hypermobility COMPASS31[14] questionnaire provides a total scaled score of 0–100 with higher scores representing more severe autonomic symptom burden.
[c] Coexisting diagnosis of autoimmunity and duration of symptoms data were available for 12 seropositive and 196 seronegative subjects.
[d] Coexisting autoimmune disorder included any of the following: systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, Ankylosing spondylosis, hyperthyroidism, hypothyroidism, diabetes type 1, multiple sclerosis, or other autoimmune disease. Details are provided in table e-1, links.lww.com/CPJ/A249.

where referral bias may affect the study population. Our patients and controls were self-identified at a patient and family conference, which may have introduced a volunteer bias leading to inclusion of some participants who did not have POTS or selecting for patients with POTS who were healthy enough to travel to a patient conference. Indeed, although most continued to have symptomatic orthostatic intolerance, only a minority of patients met the clinical heart rate criteria for POTS at the time of the study enrollment (patients were allowed to continue symptom therapies and medications during the standing test that likely affected the magnitude of the orthostatic tachycardia). Regardless, the use of symptomatic medications for orthostatic or other symptoms would not affect the serologic findings presented in this study.

Low levels of gAChR antibody may be found in a small minority of patients with POTS at a frequency similar to healthy controls indicating that the presence of low levels of gAChR antibody in POTS have no clinical importance.

TAKE-HOME POINTS

→ Patients with POTS may have clinical features suggesting an autoimmune condition.

→ In a community population, the prevalence of low levels of ganglionic AChR antibodies in POTS was similar to that of healthy controls.

→ Low levels of ganglionic AChR antibody (<0.2 nmol/L) in POTS are not associated with any clinical phenotype and seem to have little, if any, clinical importance.

Appendix Authors

Name	Location	Contribution
Meredith Bryarly, MD	Department of Neurology, UT Southwestern Medical Center, Dallas	Drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, study concept or design, and analysis or interpretation of data
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Lauren Phillips, MD	Department of Neurology, UT Southwestern Medical Center, Dallas	Drafting/revision of the manuscript for content, including medical writing for content and major role in the acquisition of data
Linda S. Hynan, PhD	Departments of Population & Data Sciences and Psychiatry, UT Southwestern Medical Center, Dallas	Drafting/revision of the manuscript for content, including medical writing for content and analysis or interpretation of data
Luis E. Okamoto, MD	Autonomic Dysfunction Center, Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN	Drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, and analysis or interpretation of data
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Name	Location	Contribution
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Bonnie K. Black, RN, NP	Autonomic Dysfunction Center, Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN	Drafting/revision of the manuscript for content, including medical writing for content and major role in the acquisition of data
Steven Vernino, MD, PhD	Department of Neurology, UT Southwestern Medical Center, Dallas, TX	Drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, study concept or design, and analysis or interpretation of data

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