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Clinical phenotype of postural orthostatic tachycardia associated with anti-adrenergic receptor antibodies

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KEYWORDS

Postural orthostatic tachycardia syndrome (POTS).
Orthostatic intolerance.
Autoimmunity.

Abstract:

Purpose:
Our aim is to describe the clinical and hemodynamic characteristics of autoimmune postural orthostatic tachycardia syndrome (POTS), an entity whose frequency and clinical characteristics are not sufficiently defined yet.

Methods:
We retrospectively analyzed clinical, hemodynamic and serum autoimmunity bi-omarkers

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in 105 POTS patients and 79 age-sex-matched controls. We recorded clinical manifestations and relevant comorbidities. Participants underwent non-invasive quantitative cardiovascular autonomic testing by measuring changes in heart rate (HR) and blood pressure (BP), baroreflex sensitivity (BRS), total periph-eral resistance (TPR), stroke volume (SV) and cardiac index in response to deep breathing, valsalva maneuver, 60º head-up tilt, and quantitative evaluation of electrochemical skin conductance. In 61 POTS patients and 15 controls we quan-tified autoantibodies against adrenergic receptors (AR) alpha1 (anti-a1AR), beta1 (anti-b1AR), and beta2 (anti-b2AR) and antinuclear antibodies.

Results:
Joint hypermobility and chronic fatigue syndrome-fibromyalgia was significantly higher in POTS. We observed significant differences in cardiovascular autonomic tests with higher HR increase, lower TPR at 3 min in the tilt test, and higher BRS. AR antibodies were significantly higher in POTS (62%) than in controls (17%), with anti-a1AR in all antibody-positive POTS, 21.1% POTS had a combination of anti-a1AR with other AR antibodies. The presence of palpitations and orthostatic intolerance was significantly higher in anti-AR positive.

Conclusion:
Our results suggest that the prevalence of anti-AR antibodies is significantly higher in POTS, with the levels of such antibodies being correlated with the presence of symptoms associated with POTS.

Adrenergic receptors autoantibodies.
Autonomic nervous system.

Fenotipo clínico de la taquicardia ortostática postural asociada a anticuerpos anti-receptores adrenérgicos

Objetivo:
Nuestro objetivo es describir las características clínicas y hemodinámicas del síndrome de taquicardia postural ortostática autoinmune (POTS), entidad cuya frecuencia y características clínicas aún no están suficientemente definidas.

Métodos:
Análisis retrospectivo de los biomarcadores clínicos, hemodinámicos y de autoinmunidad sérica en 105 pacientes con POTS y 79 controles emparejados por edad y sexo. Se registran manifestaciones clínicas y comorbilidades relevantes. Los participantes se sometieron a pruebas autonómicas cardiovasculares cuantitativas no invasivas midiendo los cambios en la frecuencia cardíaca (FC) y la presión arterial (PA), la sensibilidad barorrefleja (BRS), la resistencia periférica total (TPR), el volumen sistólico (SV) y el índice cardíaco en respuesta a la respiración profunda, maniobra de valsalva, mesa basculante a 60º y evaluación cuantitativa de la conductancia electroquímica de la piel. En 61 pacientes con POTS y 15 controles, cuantificamos autoanticuerpos contra los receptores adrenérgicos (AR) alfa1 (anti-a1AR), beta1 (anti-b1AR) y beta2 (anti-b2AR) y anticuerpos antinucleares.

Resultados:
La hiperlaxitud articular y el síndrome de fatiga crónica-fibromialgia fueron significativamente más frecuentes en el POTS. Observamos diferencias significativas en las pruebas autonómicas cardiovasculares con mayor aumento de la FC, menor TPR a los 3 min en el test de inclinación y mayor BRS. Los anticuerpos AR fueron significativamente más altos en el POTS (62 %) que en los controles (17 %), con anti-a1AR en todos los POTS con anticuerpos positivos, el 21,1 % de POTS tenían una combinación de anti-a1AR con otros anticuerpos AR. La presencia de palpitaciones e intolerancia ortostática fue significativamente mayor en los casos con anti-AR positivos.

Conclusión:
Nuestros resultados sugieren que la prevalencia de anticuerpos anti-AR es significativamente mayor en POTS, y los niveles de dichos anticuerpos se correlacionan con la presencia de síntomas asociados.

PALABRAS CLAVE

Síndrome de taquicardia ortostática postural (POTS).
Intolerancia ortostática.
Autoinmunidad.
Autoanticuerpos contra receptores adrenérgicos.
Sistema nervioso autónomo.

GILTZA-HITZAK

Takikardia ortostatiko posturalaren sindromea (POT).
Intolerantzia ortostatikoa.
Autoinmunitatea.
Hartzaile adrenergikoen aurkako autoantigorputzak.
Nerbio-sistema autonomoa.

Takikardia ortostatiko posturalaren fenotipo klinikoa, hartzaile adrenergikoen aurkako antigorputzei lotua

Helburua:
Gure helburua takikardia postural ortostatiko autoinmune (POTS) sindromearen ezaugarri klinikoak eta hemodinamikoak deskribatzea da; entitate horren maiztasuna eta ezaugarri klinikoak oraindik ez daude behar bezala zehaztuta.

Metodoak:
Biomarkatzaile klinikoen, hemodinamikoen eta autoinmunitate serikoko biomarkatzaileen atzera begirako analisia POTak eta 79 kontrol parekatu dituzten 105 pazienterengan, adinaren eta sexuaren arabera. Adierazpen klinikoak eta komorbilitate garrantzitsuak erregistratzen dira. Parte-hartzaileek proba autonomiko kardiobaskular kuantitatibo ez-inbaditzaileak egin zituzten, honako hauek neurtuz: bihotz-maiztasunaren aldaketak (FC) eta presio arteriala (PA), sentikortasun barorrefleja (BRS), erresistentzia periferiko totala (TPR), bolumen sistolikoa (BS) eta bihotz-indizea arnasketa sakonari erantzuteko, baltsa-maniobra, 60º-ko mahai baskulatzailea eta larruazalaren eroankortasun elektrokimikoaren ebaluazio kuantitatiboa. POTak eta 15 kontrol dituzten 61 pazientetan, hartzaile adrenergikoen (AR) aurkako autoantigorputzak alfa1 (anti-a1AR), beta1 (anti-b1AR) eta beta2 (anti-b2AR) eta antigorputz antinuklearrak kuantifikatzen ditugu.

Emaitzak:
Artikulazioen hiperlaxotasuna eta neke kroniko-fibromialgiaren sindromea nabarmen ohikoagoak izan ziren POTSean. Alde esanguratsuak ikusten ditu-gu proba autonomiko kardiobaskularretan, EParen igoera handiagoarekin, inklinazio-testean 3 minutura TPR txikiagoa eta BRS handiagoa. AR anti-gorputzak nabarmen altuagoak izan ziren POTean (% 62) kontroletan baino (% 17), antigorputz positibodun POT guztietan anti-a1ARekin alderatuta; POTen % 21,1ek anti-a1AR konbinazioa zuen beste AR antigorputz batzue-kin. Palpitazioen eta intolerantzia ortostatikoaren presentzia nabarmen han-diagoa izan zen anti-AR positiboak izan zituzten kasuetan.

Ondorioa:
Gure emaitzek iradokitzen dute anti-AR antigorputzen prebalentzia nabarmen handiagoa dela POTSen, eta antigorputz horien mailak lotutako sintomen presentziarekin lotzen dira.

Introduction

Postural tachycardia syndrome (POTS) is the main cause of orthostatic intolerance in young people. It was first described in 1871 by Jacob Mendes Da Costa but it was not until 1990 that it was defined as the syndrome we know nowadays[1].

POTS is defined as symptoms of orthostatic intolerance accompanied by a heart rate (HR) increment of 30 bpm (or more than 40 bpm in adolescents), or greater than 120 bpm within 10 min of standing in the absence of orthostatic hypotension[2].

In some series, up to 50% of patients describe a precipitant (previous viral illness, pregnancy, surgery). Many patients also have non-orthostatic chronic symptoms due to frequent overlapping conditions. The principal comorbidities are chronic fatigue syndrome (CFS/ME), fibromyalgia, Ehlers-Danlos syndrome, headache, abdominal symptoms, and sleep disorders. Current treatments for POTS are only symptomatic, including nonpharmacological measures and if needed, drug therapy. POTS is a heterogeneous syndrome rather than a unique disease. Its etiology remains unknown but it seems to be the result of a number of heterogeneous, overlapping pathophysiological processes. Based on different aspects from clinical features and ancillary testing and taking into account the associated pathophysiological mechanism, POTS has been classified into neuropathic and hyperadrenergic POTS. Recently an autoimmune subtype is gaining importance, with a growing number of cases reported in the medical literature[3].

The presence of autoantibodies against the adrenergic receptors a1 (A1AR), b1 (B1AR) and b2 (B2AR) has been demonstrated in the serum of patients with POTS[4,5].

The inoculation of serum from patients into laboratory rabbits reproduces clinical findings and when these antibodies are eliminated from the blood of rabbits, the symptoms remit, all pointing to a possible pathogenic effect of the referred autoantibodies[6].

Although the studies dedicated to antibody-mediated POTS are small (<20 cases), clinical improvement has been observed after intravenous immunoglobulin, rituximab and plasmapheresis in highly selected cases with autoimmune comorbidities[7,8], and controlled trials are underway to determine the efficiency of immunomodulatory therapies[9]. Therefore, to be able to identify this potentially treatable POTS subtype, it is essential to improve our knowledge of the phenotype and specific comorbidities of antibody-mediated POTS.

The aim of the present study is to improve the clinical characterization of patients with antibody mediated POTS, comparing them with patients with seronegative POTS and with controls.

Methods

Patient Selection.
We performed a cross-sectional study of 105 patients with POTS and 79 age and sex-matched controls. POTS patients fulfilled standard diagnostic criteria for this syndrome[2], including detection of an increase in heart rate (HR) ≥ 30 beats per minute or a HR> 120 beats per minute after 10 min of standing without any evi-dence of orthostatic hypotension. Participants were recruited in the Autonomic Unit of Cruces University Hospital (Barakaldo, Spain) between the years 2012 and 2020. Controls were selected based on their age and sex match with POTS pa-tients from among all patients who had been evaluated in the Autonomic Unit for clinical purposes, and included healthy participants, patients with neurally medi-ated syncope or chronic pain. The study protocol was approved by the local Clini-cal Research Ethics Committee. All participants gave written informed consent prior to their participation in the study, in accordance with the tenets of the Decla-ration of Helsinki.

Demographic data, clinical manifestations and comorbidities for POTS.
We recorded in all participants age, sex, the presence of clinical manifestations typically associated to POTS (dizziness, palpitations, headache, fatigue, orthostatic intolerance, abdominal symptoms, pain, excessive sweating and history of syncope) and history in clinical records of relevant comorbidities for POTS including fulfillment of diagnostic criteria for joint hypermobility (JH)[10] or chronic fatigue syndrome-fibromyalgia (CFS/FM)[11] or history of autoimmune disease. In POTS patients, we additionally obtained age at the onset of symptoms, age at diagnosis and total duration of symptoms.

Quantitative autonomic function testing.
All participants underwent continuous non-invasive measurement of heart rate and blood pressure changes in response to standard cardiovascular autonomic tasks (deep breathing, Valsalva maneuver and 60º head-up tilt test)[12] with a Task Force Monitor (TFM) (CNSystems, Graz, Austria). Such TFM data was used to calculate baroreflex sensitivity (BRS), Valsalva ratio and changes in stroke volume (SV) and total peripheral resistance (TPR). In addition, in a subgroup of 97 POTS patients and 54 controls sudomotor function was quantified non-invasively in palms and soles with Sudoscan (Impeto Medical; Paris, France) as electro-chemical skin conductance (ESC), which is expressed in microSiemens (μS).

Serum anti-adrenergic antibody testing.
The presence and levels of serum alpha 1 adrenergic receptor (A1AR), beta 1 AR (B1AR) and beta 2 AR (B2AR) auto-antibodies was determined in the 61 POTS patients and 15 controls that were included since 2019, date from which AR auto-antibodies identification was commercially available. The AR antibody determinations were performed by enzyme-linked immunosorbent assay (ELISA) in the laboratory of Cell-Trend GmbH © (Luckenwalde, Germany). In addition, the presence of antinuclear antibodies (ANAs) was determined with ELISA in the local laboratory of our hospital.

Statistical analyses.
Demographical, clinical and autonomic tests data for POTS patients and controls were described using mean ± standard deviation (quantitative variables) or frequencies (categorical variables). For group comparisons, Student's t-test (quantitative data) or Pearson chi-square test (categorical data) were used for variables with a normal distribution and Mann-Whitney U test for variables with a non-parametric distribution. Statistical significance was set at $p<0.05$. All the statistical analyses were performed using the SPSS Statistics for Windows version 18.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics and POTS clinical features and comorbidities.
The main demographic characteristics, clinical features and comorbidities of POTS for study participants are shown in Table 01. The 105 POTS patients included had a mean age of 36 years and 78% were women and did not have statistically significant age-sex differences with the control group. The mean age at diagnosis of POTS was 35.86 +/- 14 years. The proportion of participants meeting diagnostic criteria for JH or CFS / FM was significantly higher in the POTS group than in the controls group (JH: POTS 21%, controls 2.7%, $p = 0.02$; CFS / FM: POTS 13.3%, controls 2.7%, $p <0.001$), while we did not observe significant group differences in the prevalence of autoimmune diseases. As expected, the frequency of the cardinal manifestations of POTS (orthostatic intolerance, palpitations, and dizziness) was significantly higher in the POTS group than in controls, and also that of the symptoms typically associated with POTS (Table I).

Tabla I
Demographics and POTS comorbidities and clinical manifestations.

	POTS	Controls	p value
n	**105**	**79**	**NA**
Age, years	35.9 (14.0)	39.1 (13.5)	0.1
Females, n (%)	82 (78.0)	61 (77.0)	0.88
POTS comorbidities			
Autoimmune disease, n (%)	17.0 (16.2)	10.0 (12.7)	0.5
Joint hypermobility, n (%)	22 (21.0)	2 (2.7)	0.02
CFS/FM, n (%)	14 (13.3)	2 (2.7)	<0.001
POTS clinical manifestations			
Dizziness, n (%)	90 (86.5)	32 (40.5)	<0.001
Palpitations, n (%)	47 (45.2)	7 (8.8)	<0.001
Orthostatic intolerance, n (%)	105 (100)	5 (6.3)	<0.001
Fatigue, n (%)	33 (31.4)	6 (7.6)	<0.001
Headache, n (%)	48 (46.0)	16 (20.3)	<0.001
Abdominal symptoms, n (%)	26 (25.7)	5 (3.8)	<0.001
Pain, n (%)	18 (18.8)	8 (6.3)	<0.001

All variables are represented as frequency (percentage) except for age, which is shown as mean (standard deviation). Abbreviations: CFS/FM: chronic fatigue syndrome/fibromyalgia; NA: not applicable SD: standard deviation.

Although the studies dedicated to antibody-mediated POTS are small (<20 cases), clinical improvement has been observed after intravenous immunoglobulin, rituximab and plasmapheresis in highly selected cases with autoimmune comorbidities[7,8], and controlled trials are underway to determine the efficiency of immunomodulatory therapies[9]. Therefore, to be able to identify this potentially treatable POTS subtype, it is essential to improve our knowledge of the phenotype and specific comorbidities of antibody-mediated POTS.

Cardiovascular and sudomotor autonomic function.
As expected, in the tilt table test POTS patients had significantly higher absolute HR values at each timepoint and higher increase in HR with respect to baseline than controls, while no significant group differences were found in systolic blood pressure (Table II). In addition, we observed that overall TPR was lower in POTS than in controls during head-up tilt test, being this difference significant for the absolute value of TPR at minute 3 and for the change of TPR from baseline to minute 3. Moreover, we observed a significantly higher BRS at rest in POTS (17.7 +/- 10.8 msec / mmHg) compared to controls (13.2 +/- 10.3 msec / mmHg) (p< 0.01). We did not observe differences between POTS and controls at baseline (supine) position in HR or SV nor in Valsalva ratio. However, we did observe alterations at three minutes of passive tilt at 60º with a significant decrease in SV with respect to decubitus in patients with POTS when compared to controls. Regarding sudomotor function, although POTS patients tended to have lower ESC values than controls, the differences were not significant.

Anti-adrenergic receptor antibodies and their relation with clinical manifestations and comorbidities of POTS.
Serum A1AR, B1AR and B2AR were tested in 61 POTS patients and 15 controls.

Sixty-two percent of POTS patients versus only 17% of controls had one or more types of autoantibodies against AR (p<0.001). In the first place, the A1ARs were present in all the seropositive cases. Second of importance, B1AR antibodies were detected in 16% of POTS patients with positive anti adrenergic antibodies (in 8% with A1AR and in 8% with A1AR and B2AR). Finally, B2AR was detected in 13% of POTS patients with positive anti AR antibodies (in 5% together with A1AR and in 8% together with A1AR and B1AR).

When comparing AR-antibody-positive and -negative POTS patients in terms of their clinical manifestations, the presence of comorbidities and systemic autoimmunity markers (ANAs), we observed several

Tabla II
Cardiovascular and sudomotor autonomic function outcomes.

		POSTS	Control	Value
HR HUTT, bpm	Baseline (supine)	77.14 (12.67)	71.23 (13.05)	<0.02
	3 min	98.6 (17.86)	81.6 (15.75)	<0.001
	10 min	99.43 (18.46)	82.73 (12.91)	<0.001
	Max HR	118.6 (14.9)	96.03 (13.9)	<0.001
SBP HUTT, mmHg	Baseline (supine)	108.0 (14.7)	110.7 (18.6)	0.3
	3 min	129.3 (20.1)	129.80 (21.9)	0.2
	10 min	125.7 (19.1)	121.3 (16.1)	0.1
TPR HUTT, dyne*s/cm^5	Baseline (supine)	1141 (335.1)	1281.7 (335.0)	0.15
	3 min	1417.3 (423.9)	1633.1 (121.1)	0.001
	10 min	1344.6 (425.0)	1485 (384.6)	0.18
ΔSV HUTT, ml	3 min	18.6 (19.6)	12.6 (12.8)	0.2
	10 min	19.86 (16.01)	14.84 (15.81)	0.37
BRS HUTT, msec / mmHg	Baseline (supine)	17.7 (10.8)	13.2 (10.3)	0.008
Valsalva ratio		1.42 (0.39)	1.34 (0.35)	0.2
ESC, ms	Hands	71.1 (14.3)	77.8 (11.4)	0.4
	Feet	73.2 (15.5)	74.6 (14.1)	0.7

Abbreviations: HUTT: Head-up Tilt Test; HR: hearth rate measured in beats per minute (bpm); SBP: systolic blood pressure measured in millimeters of mercury (mmHg); TPR: Total Peripheral Vascular Resistance measured in dyne*s/cm^5 (ratio between dyne per second and centimeter raised to the fifth power); ΔSV: decrease of stroke volume (or volume of blood pumped from the left ventricle per beat) from baseline in milliliters (ml); BRS: baroreflex sensibility measured in milliseconds per mmHg; ESC: electrochemical skin conductance measured in microsiemens (ms).

notable differences. First, 62% of A1AR antibody-positive POTS patients described tachycardia and palpitations while they were referred in only 24% of seronegative POTS patients (p <0.001). Orthostatic intolerance was present in 57% of AR seropositive POTS patients while only 15% of seronegative patients had it (p<0.001).

Fatigue and sensitive symptoms were also more frequent in patients with AR antibodies (p<0.001). Of note, we observed a significant correlation between the levels of A1AR antibodies and the presence of palpitations (cc=0.25; p<0.001) and orthostatic intolerance (cc=0.29; p<0.001). Regarding POTS comorbidities, CFS/FM was present in 28% of AR seropositive patients while it appeared in 5% of seronegative patients (p<0.04).

Interestingly, although we did not observe differences in the history of autoimmune disease between AR positive and AR negative POTS patients, the presence of ANAs was significantly higher in AR seropositive POTS with 11 cases (18%) compared to no ANA-positive case detected in AR seronegative POTS (p=0.011). Finally, when we compared the results of autonomic cardiovascular tests and sudomotor function between AR seropositive and AR seronegative POTS, we did not observe significant group differences.

Discussion

In this study, we present one of the largest series in the literature on POTS associated to anti-AR antibodies and we compare its clinical characteristics and comorbidities with those of seronegative POTS patients and controls. As the most relevant results, we observed that in comparison with seronegative POTS, the AR antibody-positive POTS patients reported more frequently symptomatic tachycardia, palpitations and orthostatic intolerance, with the presence of these symptoms being significantly correlated with the levels of A1AR antibodies. Moreover, the prevalence of CSF / FM and positive ANAs was significantly higher in AR antibody-positive than in antibody-negative POTS, which supports the possible pathophysiological relationship of

CFS/FM and systemic autoimmunity background with AR antibody-mediated POTS. The presence of autoantibodies against the A1AR and B1/B2AR in the serum of patients with POTS is now well stablished and the pathogenic effect of such antibodies has been shown in rabbits[4].

Our results showed that anti-AR antibodies are present in 62% of patients with POTS (and in only 17% of controls), being anti-A1AR the most frequently detected antibody (100% of anti-AR positive cases), either alone (79%) or associated with anti-B1AR, anti-B2AR or both (21%), and anti-B1AR the second most frequent (16% of anti-AR positive cases), always in combination with anti-A1AR or anti-B2AR. The reason for a higher frequency of cardiovascular symptoms of POTS in anti-AR antibody positive patients and the relationship of these symptoms with higher serum levels of anti-AR antibodies could be related with the varying allosteric effects of AR antibodies, which may cause a positive modulatory effect upon B1AR and a negative modulatory effect on A1AR activity[4].

As previously pointed out, the modulation by the antibodies of the effect of norepinephrine explains why the symptoms appear fundamentally on standing. The evidence in the use of immunomodulatory therapy in POTS associated to anti-AR antibodies is limited to a small number of case reports. Pending further evidence, immunomodulatory therapies are not recommended unless a systemic autoimmune background is confirmed[13].

Our work has some limitations. First, the information has been collected retrospectively which may lead to some loss of information. Second, antibodies were only determined in patients who were studied in the last years in the center, since they were not previously available. We did not perform other autoantibodies that have been described in POTS such as antibodies against ganglionic acetylcholine receptor subunit alpha3[14], muscarinic acetylcholine M4 receptor[15] band angiotensin II type 1 receptor[16]. Finally, specific studies with larger samples of patients will be necessary to confirm our findings.

In conclusion, this paper extends prior knowledge on antibody-mediated POTS showing the idea that these patients have differential phenotypic characteristics with respect to anti-AR antibody negative POTS, with higher prevalence of cardiovascular manifestations (palpitations, orthostatic intolerance), higher frequency of CFS / FM comorbidity and of positive serum ANAs. Future studies specifically dedicated to unveiling the physiopathology, clinical features and immunotherapy response of anti-AR antibody positive POTS are warranted to improve our management of this potentially treatable condition.

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Competing interests.
None of the authors have any conflicts of interest or financial ties to disclose.

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Ethical approval.
The study was approved by the local ethics committee and patients gave written informed consent before inclusion in the study, in accordance with the tenets of the Declaration of Helsinki.

Author contributions.
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Tamara Fernández Valle, Marian Acera and Juan Carlos Gomez-Esteban. The first draft of the manuscript was written by Tamara Fernández Valle and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References.

1. Bryarly M, Phillips LT, Fu Q, Vernino S, Levine BD. Postural orthostatic tachycardia syndrome: JACC Focus Seminar. J Am Coll Cardiol. 2019;73:1207-28. doi: 10.1016/j.jacc.2018.11.059.
2. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci. 2011;161:46-8. doi: 10.1016/j.autneu.2011.02.004.
3. Shaw BH, Stiles LE, Bourne K, Green EA, Shibao CA, Okamoto LE, et al. The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. J Intern Med. 2019;286:438-48. doi: 10.1111/joim.12895
4. Fedorowski A, Li H, Yu X, Koelsch KA, Harris VM, Liles C, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace. 2017;19:1211-9. doi: 10.1093/europace/euw154.
5. Li H, Yu X, Liles C, Khan M, Vanderlinde-Wood M, Galloway A, et al. Autoimmune basis for postural tachycardia syndrome. J Am Heart Assoc. 2014;3:e000755. doi: 10.1161/JAHA.113.000755.
6. Li H, Zhang G, Zhou L, Nuss Z, Beel M, Hines B, et al. Adrenergic autoantibody-induced postural tachycardia syndrome in rabbits. J Am Heart Assoc. 2019;8:e013006. doi: 10.1161/JAHA.119.013006.
7. Goodman BP. Immunoresponsive autonomic neuropathy in Sjögren syndrome-case ceries and literature review. Am J Ther. 2019;26:e66-e71. doi: 10.1097/MJT.0000000000000583.
8. Hendrickson JE, Hendrickson ET, Gehrie EA, Sidhu D, Wallukat G, Schimke I, Tormey CA. Complex regional pain syndrome and dysautonomia in a 14-year-old girl responsive to therapeutic plasma exchange. J Clin Apher. 2016;31:368-74. doi: 10.1002/jca.21407.

Tabla III
Adrenergic receptor auto-antibodies in POTS and controls.

	POTS	Controls
n tested	61	15
Negative	23 (38%)	11 (73%)
Positive	38 (62%)	4 (17%)
A1AR	30 (79%)	4 (100%)
A1AR + B1AR	3 (8%)	0
A1AR+B2AR	2 (5%)	0
A1AR + B1AR + B2AR	3 (8%)	0

9. Vernino S, Stiles LE. Autoimmunity in postural orthostatic tachycardia syndrome: Current understanding. Auton Neurosci. 2018;215:78-82. doi: 10.1016/j.autneu.2018.04.005.
10. Remvig L, Jensen DV, Ward RC. Are diagnostic criteria for general joint hypermobility and benign joint hypermobility syndrome based on reproducible and valid tests? A review of the literature. J Rheumatol. 2007;34:798-803.
11. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121:953-9. doi: 10.7326/0003-4819-121-12-199412150-00009.
12. Novak P. Quantitative autonomic testing. J Vis Exp. 2011;19:2502. doi: 10.3791/2502.
13. Cutsforth-Gregory JK, Sandroni P. Clinical neurophysiology of postural tachycardia syndrome. Handb Clin Neurol. 2019;161:429-45. doi: 10.1016/B978-0-444-64142-7.00066-7.
14. Watari M, Nakane S, Mukaino A, Nakajima M, Mori Y, Maeda Y, et al. Autoimmune postural orthostatic tachycardia syndrome. Ann Clin Transl Neurol. 2018;5:486-92. doi: 10.1002/acn3.524.
15. Gunning WT 3rd, Kvale H, Kramer PM, Karabin BL, Grubb BP. Postural orthostatic tachycardia syndrome is associated with elevated G-Protein coupled receptor autoantibodies. J Am Heart Assoc. 2019;8:e013602. doi: 10.1161/JAHA.119.013602.
16. Yu X, Li H, Murphy TA, Nuss Z, Liles J, Liles C, et al. Angiotensin II type 1 receptor autoantibodies in postural tachycardia syndrome. J Am Heart Assoc. 2018;7:e008351. doi: 10.1161/JAHA.117.008351.