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Prevalence of Ganglionic AChR Antibodies in Postural Tachycardia Syndrome (POTS)

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Objectives:

- Determine a better estimate of the prevalence of ganglionic AChR antibody in patients with POTS.
- Determine if POTS patients with ganglionic AChR antibody have clinical differences compared to other POTS patients

Postural tachycardia syndrome (POTS)

- POTS is the most common form of dysautonomia. 5-10 times more common than orthostatic hypotension
- Diagnostic criteria include a 30 bpm increment of heart rate when upright in the absence of blood pressure drop.
- Female:male ratio is 5:1. Most patients age 15–40 years.
- Pathophysiology of POTS remains unclear. Several different etiologies may produce the clinical syndrome
- Associations have been reported with joint hypermobility (and Ehlers-Danlos syndrome) and with various immune disorders (e.g. Sjogren syndrome, chronic fatigue syndrome, mast cell activation disorder). Many patients report a subacute onset after viral prodrome

Ganglionic acetylcholine receptor antibodies

- The ganglionic AChR (gAChR) is responsible for synaptic transmission in autonomic ganglia
- Antibodies against gAChR cause autoimmune autonomic ganglionopathy (AAG). Patients with AAG typically have severe autonomic failure with orthostatic hypotension, constipation, urinary retention.
- Patients with AAG typically have gAChR antibody levels greater than 0.2 nmol/L

Previous retrospective studies

- In 2000, in the initial report of gAChR antibodies,**(1)** 1 of 15 POTS patients (7%) was positive (0.11 nmol/L)
- In a 2007 retrospective series of 152 POTS patients,**(2)** 6/42 patients (14%) were positive (0.07 – 0.28 nmol/L)
- In a 2009 review of gAChR antibodies **(3)**,the Mayo autonomic group reported positive antibody in up to 25% of POTS in their clinical practice
- The seropositive rate in these studies may be artificially higher than the prevalence of ganglionic AChR antibody in POTS patients in routine clinical autonomic practice (due to possible retrospective & referral bias at a tertiary referral center, Mayo Clinic)
- In our unpublished recent experience, 3 of 25 (12%) consecutive POTS patients seen at UT Southwestern autonomic clinic. However, 2 of the 3 patients were referred because of positive Ab result elsewhere.

Design/Methods

Prospective study of POTS volunteers

- Participants at 2014 meeting of Dysautonomia International (a patient support and advocacy group) were invited to participate in a serological study
- Demographics and supine/standing vital signs
- All subjects completed VOSS (Vanderbilt Orthostatic Symptoms Score)**(4)**; a rating of 9 common POTS symptoms on a scale of 0-10 (max score is 90)
- Blinded serum samples were sent for antibody testing
- 102 POTS patients (self-reported diagnosis)
  - 5% male, mean age 29.5; range 14-56
  - Mean VOSS – 25.3
- 64 control subjects (healthy family members)
  - 18% male, mean age 50 yrs
  - Mean VOSS – 3.5

Studies were reviewed and approved by IRB at UT Southwestern and Vanderbilt University Medical Centers

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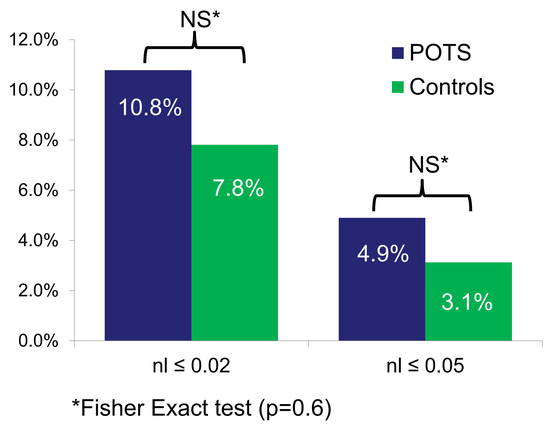
gAChR antibody assay

- Radioimmunoprecipitation assay using solubilized IMR-32 cell tumors complexed to ^{125}I-epibatidine.**(1)**
- Antibody binding capacity measured as nmol gAChR bound per liter of serum (nmol/L)
- Upper limit of normal initially reported at 0.05 nmol/L **(1)**
- Some laboratories now use cutoff of ≤ 0.02 nmol/L

Results



*Fisher Exact test (p=0.6)

Results

- 11 POTS patients had gAChR antibody (> 0.02)
- 5 controls with gAChR antibody (0.02 – 0.10)
- 5 POTS with Ab level > 0.05 (0.06 – 0.13 nmol/L)

- Ab-positive POTS more likely to be male (but the number of male subjects in this study was small)
- The clinical characteristics of POTS with gAChR antibodies were otherwise not different

Clinical characteristics of POTS with & without gAChR antibody (>0.02 nmol/L)

	AChR Ab POS (n=11)	AChR Ab NEG (n=91)	P value
Age (y)	29±11	30±12	NS
Males (%)	22%	3%	0.06
Height (in)	65±3	65±3	NS
Weight (lbs)	168±45	149±35	NS
SUPINE VITALS			
HR (bpm)	69±16	76±13	NS
SBP (mmHg)	111±18	114±13	NS
DBP (mmHg)	75±14	76±9	NS
STAND VITALS			
HR (bpm)	89±18	99±18	NS
SBP (mmHg)	118±22	121±15	NS
DBP (mmHg)	87±15	90±13	NS
VOSS Standing Symptoms Score	32±14	24±15	NS
AChR Ab Titer >0.05 (n)	5	0	
No significant differences using antibody > 0.05 nmol/L			

Anecdotal case

- 17y male - onset of orthostatic intolerance after recovery from a foot injury
- gAChR antibody positive – 0.13 nmol/L
- Autonomic testing normal aside from postural tachycardia (HR increase from 77 to 117 bpm on tilt)
- Plasma NE normal: 284 (supine), 641 (upright)
- Trials of iv and oral steroids and 5 days of IVIG produced no subjective or objective benefit

Specificity of low level gAChR antibodies

- High levels of gAChR Ab (≥ 0.5 nmol/L) are frequently associated with autoimmune autonomic failure **(1)**
- Low Ab levels < 0.1 nmol/L are much less specific. Patients with low Ab have various disorders, including degenerative and non-neurological disorders **(5,6)**
- False positives (in healthy controls) do occur, ranging from 0.6% **(5)** to 3% (this study)
- Low level gAChR antibody may be a useful non-specific marker of autoimmunity but needs to be interpreted critically, according to the clinical context
- Very low gAChR Ab levels ≤ 0.05 nmol/L appear to have questionable significance **(6)**

Summary

- A small minority of unselected patients with POTS and healthy controls were seropositive for gAChR antibodies.
- Prevalence of gAChR antibody in POTS patients (5%; using a cutoff of 0.05 nmol/L) was lower than previous reports.
- All had low antibody levels (≤ 0.13 nmol/L)
- Neither the seroprevalence nor antibody level was significantly different from the healthy control group.
- Seropositive POTS patients were not different in clinical characteristics compared to seronegative POTS, except for a greater number of males.
- Limitations of the study:
  - POTS diagnosis and healthy controls were self-reported
  - All patients were treated at time of symptom assessment However, only one patient (seronegative) on IVIG

- Low level gAChR antibody appears to have little clinical significance in otherwise typical POTS.

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