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Review

Autoimmunity in postural orthostatic tachycardia syndrome: Current understanding

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ABSTRACT

There is growing interest in the role of autoimmunity in postural orthostatic tachycardia syndrome (POTS). In recent years, investigators have described an increased rate of co-morbid autoimmune disease, and the presence of several neural receptor autoantibodies and non-specific autoimmune markers in POTS. Case reports on the efficacy of immunotherapy in highly selected POTS patients continue to appear in the literature, while no prospective clinical trials have occurred to date. This article summarizes the current state of knowledge on the role of autoimmunity in POTS, the clinical implications of these findings, and prospects for future research.

1. Introduction

Postural orthostatic tachycardia syndrome (POTS) is a common form of dysautonomia, characterized by an exaggerated increase in heart rate while standing associated with symptoms of lightheadedness and fatigue (Sheldon et al., 2015). Numerous other symptoms have been associated with this condition including gastrointestinal dysmotility, cognitive impairment ("brain fog"), allergic symptoms (suggestive of mast cell dysfunction), and distal changes in sensation (suggestive of small fiber neuropathy). POTS likely has a heterogeneous pathophysiology. Contributing factors include hypovolemia and cardiovascular deconditioning, while a number of clinical features suggest that chronic immune system dysfunction may co-exist or contribute to the pathophysiology of POTS. This review addresses our current understanding and evidence for autoimmunity in POTS.

2. Clinical features

An autoimmune basis for POTS has been suggested based on some of the clinical associations, including acute or subacute onset in the setting of physical stress or infection, and the occasional association of POTS with a personal or family history of systemic autoimmune disorders. Many patients can identify a specific event preceding the onset of their POTS symptoms, including viral illness, vaccination, physical trauma, concussion, pregnancy or surgery. These are events that might be expected to activate the immune system.

In addition to orthostatic intolerance, other symptoms associated with POTS include myalgias, fatigue, nausea, headache, sleep disruption, gastrointestinal complaints (including irritable bowel syndrome or gastroparesis) and interstitial cystitis. Many of these symptoms cannot be easily explained on the basis of orthostatic tachycardia. Together, these symptoms are reminiscent of symptoms seen in chronic viral syndromes or chronic autoimmune disorders. The chronic fatigue and exercise intolerance associated with EBV infection (mononucleosis), for example, shares some clinical features with POTS. Post-viral fatigue has been associated with many other viral infections including human herpes virus 6 (HHV-6) and coxsackie B and with chronic bacterial infections such as Lyme and mycoplasma. A specific infectious cause or trigger of POTS, however, has not been established. On the contrary, a variety of infections have been reported prior to the onset of POTS, most often respiratory, gastrointestinal and skin infections. It may be that a variety of infections can non-specifically trigger a persistent immune system activation in susceptible patients which contributes to the spectrum of symptoms.

There is some data supporting the presence of chronic immune activation in POTS. Increased IL-6 levels are found in POTS patients and are associated with the presence of increased sympathetic activity (Okamoto et al., 2015). IL-6, like many of the proinflammatory cytokines, such as interleukin-1 (IL-1), and tumor necrosis factor (TNF), are associated with symptoms of malaise, nausea, changes in body temperature, and tachycardia. Along with chemokines and other inflammatory molecules, these signals can also mediate vasodilation and increased vascular permeability (Pavlov and Tracey, 2012). Chronic immune activation and inflammatory mediators may also contribute to volume dysregulation, cardiovascular deconditioning and a hyperadrenergic state.

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There is a complex bi-directional relationship between the autonomic nervous system and the immune system. The vagus nerve controls heart rate, gastrointestinal motility and many other visceral functions, but also mediates a neuro-inflammatory reflex that controls immune responses and inflammation during infection or tissue injury. Specifically, efferent vagus nerve activity suppresses proinflammatory cytokine levels in animal models through cholinergic innervation of spleen and other immune organs (Pavlov and Tracey, 2012). Conversely, adrenergic (sympathetic) signaling can increase production of proinflammatory cytokines like IL-6. Patients with POTS are often characterized as having a shift in autonomic activity toward excessive sympathetic activity, which would be expected to be associated with a chronic inflammatory or autoimmune state.

3. Association with autoimmune disorders

Autoimmune disease is estimated to affect 5%–8% of the population with approximately 78% of autoimmune patients being female (Fairweather et al., 2008). POTS is a strongly female predominant condition, with studies reporting up to 94% female predominance (Stiles et al., 2017). Women with POTS have a significantly higher incidence of gynecological disorders associated with elevated estrogen and/or estradiol, including uterine fibroids, dysfunctional uterine bleeding, ovarian cysts, endometriosis, and galactorrhea (Peggs et al., 2012). While the overall role of estrogen and other sex hormones in predisposition to autoimmunity is not entirely clear, numerous studies have identified relationships between estrogen and immune dysfunction (Grimaldi et al., 2002; Cutolo et al., 2012).

Patients with POTS have a higher than expected frequency of defined autoimmune disorders such as multiple sclerosis, lupus, Sjögren syndrome, or celiac disease (Table 1). Researchers at the University at Buffalo identified a confirmed autoimmune disease in 20% of POTS patients in a 100-patient chart retrospective (Blitshteyn, 2015). A 3300 patient POTS registry and comprehensive survey developed by Dysautonomia International, Vanderbilt University and University of Calgary found that 16% of POTS patients have been diagnosed with an autoimmune disease, including but not limited to Hashimoto's thyroiditis, Sjögren syndrome, lupus, rheumatoid arthritis, and celiac disease (Raj et al., 2016). In a UK study, 4% of POTS patients carried a biopsy-confirmed diagnosis of celiac disease, compared to 1% of controls, and 42% self-reported gluten sensitivity, compared to 19% of controls (Penny et al., 2016). In addition to systemic autoimmune diseases, POTS has been associated with autoimmune thyroid disease, and thyroid autoantibodies are found at a significantly higher prevalence than healthy controls (Blitshteyn, 2015; Raj et al., 2016; Singer et al., 2014). POTS has also been reported in association with antiphospholipid antibody syndrome (Schofield et al., 2014), chronic inflammatory demyelinating polyneuropathy (Adamec et al., 2016), multiple sclerosis (Kanjwal et al., 2010; Habek et al., 2017), Bechet's disease (Tellioglu and Robertson, 2001), and a high prevalence of antibodies recognized in autoimmune diseases (Blitshteyn, 2015).

Table 1
Autoimmune disease co-morbidity reported in POTS (Blitshteyn, 2015; Raj et al., 2016; Penny et al., 2016; Schofield et al., 2014; Adamec et al., 2016; Kanjwal et al., 2010; Habek et al., 2017; Tellioglu and Robertson, 2001; Goodman et al., 2017; Goodman, 2017; Barun et al., 2014; Grubb, 2008).

Ankylosing spondylitis
Antiphospholipid syndrome
Behcet's disease
Celiac disease
Chronic immune demyelinating polyneuropathy
Inflammatory bowel disease (Crohn and ulcerative colitis)
Hashimoto's thyroiditis
Multiple sclerosis
Neuromyelitis optica
Rheumatoid arthritis
Sarcoidosis
Sjögren syndrome
Systemic lupus erythematosus
Juvenile rheumatoid arthritis
Adult Still's disease
Undifferentiated connective tissue disease

4. Sjögren syndrome

Sjögren syndrome (SS) is a chronic autoimmune disorder that characteristically presents with dry eyes and dry mouth. Neurological impairment can occur in SS, but prevalence estimates vary widely (Mori et al., 2005). SS syndrome can be associated with autonomic neuropathy or sensory and autonomic ganglionopathy, but even in the absence of a demonstrable autonomic neuropathy, autonomic dysfunction is common in SS. Symptoms of lightheadedness, GI motility dysfunction, dry eyes, dry mouth which are commonly encountered in POTS may be indistinguishable from initial presentation of SS. POTS and SS share many other similar associations including profound fatigue, “brain fog”, small fiber neuropathy, a strong female predominance, and association with co-morbid autoimmune conditions. In a recent case series, Goodman et al. described autonomic dysfunction in 13 patients with confirmed diagnosis of SS (Goodman et al., 2017). Among these, eight met the criteria for diagnosis of POTS. It is likely that undiagnosed SS patients reside within the POTS population. The neurological manifestations of SS often precede sicca symptoms, by over a decade in some cases (Mori et al., 2005; Tobon et al., 2012). Sjögren syndrome patients with neurological involvement may be more likely to have negative SS-A and SS-B blood tests (Tobon et al., 2012). POTS patients with symptoms suggestive of Sjögren syndrome, particularly dry eyes or dry mouth (not caused by medication) and/or small fiber neuropathy, should be carefully screened for Sjögren syndrome using SS-A and SS-B blood tests, and a minor salivary gland biopsy when the blood tests are negative or indeterminate (Shiboski et al., 2017).

5. Ganglionic AChR autoantibodies

Antibodies against nicotinic AChR in autonomic ganglia (ganglionic AChR or *g*-AChR) are found in patients with autoimmune autonomic ganglionopathy (AAG), a rare disorder presenting as severe diffuse autonomic failure with prominent features of constipation, gastroparesis, urinary retention, and severe orthostatic hypotension. High levels of *g*-AChR antibodies (typically greater than 1.0 nmol/L using standard radioimmunoprecipitation assay) have been found in approximately 50% of subjects with AAG (Vernino et al., 2000). In the initial reports of *g*-AChR antibodies, positive antibodies were also found in a minority of patients with POTS. Specifically, there was one patient in a control group of 15 POTS patients with a low level of *g*-AChR antibodies (Vernino et al., 2000). In a subsequent retrospective study of 152 POTS patients from Mayo Clinic, Thieben et al., reported a 14.6% prevalence of *g*-AChR antibodies (Thieben et al., 2007). This study had a referral bias for antibody testing and used a lower normal cutoff value than the earlier report. Once *g*-AChR antibody testing became commercially available, it became clear that low positive results (values less than 0.2 nmol/L) are quite non-specific (Y. Li et al., 2015; McKeon et al., 2009). While highly elevated *g*-AChR antibody levels are very specific for AAG (a rare disorder which is distinct from POTS), low positive results can be seen in 4–5% of controls or in patients with unrelated autoimmune disorders (Lang and Pruss, 2017). In a 2015 large-cohort study of unselected POTS patients in the US, using an immunoprecipitation assay previously described (Vernino et al., 1998), the prevalence of *g*-AChR antibodies in POTS patients did not differ from controls (Vernino et al., 2015). A 2018 study from Japan that included individuals with POTS (34), neurally mediated syncope (19), other neurological disorders (34), and healthy controls (73) reported *g*-AChR antibody in 29% of POTS subjects, and none of the healthy

controls (Watari et al., 2018). Specifically, the authors report the presence of antibodies to the *g*-AChR alpha3 subunit in 24% and the *g*-AChR beta4 subunit in 6% of POTS subjects. This study used a luciferase immunoprecipitation system assay (LIPS) to detect antibodies against individually expressed *g*-AChR subunits rather than native *g*-AChR, a very different antibody detection method than the immunoprecipitation assays used in the United States. Further research is needed to compare the sensitivity and specificity of the LIPS assay to existing *g*-AChR assays. At present, low levels of *g*-AChR antibody detected by immunoprecipitation assay appear to have no clinical significance in POTS, but may be considered non-specific evidence of possible autoimmunity. In such patients, a careful consideration of other autoimmune conditions should be undertaken.

6. G-protein coupled receptor autoantibodies

Studies in the past five years have pointed to the presence of antibodies specific for G-protein coupled receptors (GPCRs) in POTS. In a small study of 14 POTS patients, Li et al. found serum antibodies in all patients which bound and activated alpha 1 and/or beta adrenergic receptors (Li et al., 2014). The same research group subsequently showed antibody-mediated shifts in alpha 1 and beta 1 receptor responsiveness (Fedorowski et al., 2017). By acting as a partial agonist, antibodies against alpha1 adrenergic receptors are hypothesized to reduce the effectiveness of peripheral norepinephrine resulting in increased sympathetic response to posture, resulting in postural tachycardia without hypotension. The same research group recently reported angiotensin II Type I receptor antibody activity in 12 of 17 POTS subjects, while 10 healthy controls and six individuals with vasovagal syncope did not have antibody activity (Yu et al., 2018). All POTS subjects had either the angiotensin II Type 1 antibody or the previously described alpha 1 adrenergic antibody. The angiotensin II antibody appears to cause an inhibitory effect on the angiotensin II type I receptor, and its presence was associated with lower standing blood pressure in POTS subjects. Of note, prior investigators have reported impaired angiotensin II responsiveness in POTS, elevated angiotensin II, and lower aldosterone (Mustafa et al., 2012; Mustafa et al., 2011; Stewart et al., 2006). In another study that included 16 POTS patients and 20 controls, most of whom had other neurological disorders, Dubey et al. reported an increased presence of muscarinic receptor 1 and 2 antibodies in POTS patients compared to controls, and the presence of muscarinic receptor 3 antibody in 2 POTS patients and 2 controls (Dubey et al., 2016). The significance of adrenergic and muscarinic antibodies in vivo in larger cohorts is currently under investigation, and further research exploring the role of the angiotensin receptor antibody is underway. At this time, adrenergic, muscarinic and angiotensin receptor antibodies have not been proven to be causative or useful in confirming a POTS diagnosis.

Autoantibodies against GPCRs are not novel. More than 20 years ago, beta-adrenergic and muscarinic receptor antibodies were described in cardiovascular disorders (Chagas disease and idiopathic dilated cardiomyopathy) (Borda and Sterin-Borda, 1996; Fu, 1996; Magnusson et al., 1994) and thyrotropin receptor antibodies with Grave's disease. Over time, the spectrum of diseases associated with GPCR antibodies has grown significantly. Similar antibodies have been seen in Sjögren syndrome (Nakamura et al., 2008), autoimmune thyroid disease (Rao et al., 2014), peripartum cardiomyopathy (Wallukat et al., 2007), orthostatic hypotension (Yu et al., 2012), malignant hypertension, preeclampsia and primary aldosteronism (H.L. Li et al., 2015). GPCR antibodies have also been found in disorders commonly associated with POTS, including inappropriate sinus tachycardia (Chiale et al., 2006), complex regional pain syndrome (Kohr et al., 2011) and chronic fatigue syndrome (CFS). In one report, nearly 30% of CFS patients had one or more muscarinic or beta adrenergic receptor antibodies (detected using ELISA) (Loebel et al., 2016). The role of GPCR autoantibodies in pathogenesis of these disorders continues to be the subject of debate, particularly since these antibodies are also found in normal controls (Loebel et al., 2016).

Interestingly, these same G-protein coupled receptors are also involved with regulation of immune responses, and GPCR antibodies have been shown to activate transcription factors that may increase inflammatory responses. Additionally, the antibodies may induce activation and degranulation of mast cells (Okruhlicova et al., 2007). Lymphocytes express adrenergic and cholinergic receptors that regulate activation, migration and antibody production (Suzuki et al., 2016) As these antibodies are present in a host of different chronic cardiovascular disorders, they may represent an immune response to tissue injury or some sort of physiological regulatory response to cardiovascular stress. Further research is needed to understand the pathological significance, if any, of GPCR autoantibodies in POTS.

7. Other autoantibodies in POTS

Non-specific serological markers of autoimmunity are prevalent in POTS. A 100-patient chart retrospective identified various autoantibodies in 31% of POTS subjects, including 25% with ANA (Blitshteyn, 2015). A 60-patient chart retrospective found 15% of POTS patients had significant expansion of their double negative T cells, and a decreased HLA-DR to CD69 ratio, features typically associated with autoimmune lymphoproliferative syndrome, which correlated to the presence of serum autoantibodies (Abdallah et al., 2014).

Another study found 45% of POTS subjects had various thyroid and/or neural receptor autoantibodies, with 36% having organ-specific autoantibodies compared to 4.4% of controls. Interestingly, these antibody positive subjects had higher supine and upright heart rate, tended to have higher supine and upright plasma norepinephrine levels, and were more likely to report tremulousness, suggesting a hyperadrenergic phenotype was associated with the antibodies in this study (Singer et al., 2014).

In another study on a small cohort of POTS patients, IgGs against a whole host of human cardiac proteins were identified (Wang et al., 2012). Forty unique protein antigens were identified using a proteomics approach. In a follow-up study, this group used sera from a small POTS cohort (10 patients) to identify antibodies binding to cardiac lipid rafts (a membrane subfraction) (Wang et al., 2013). Again a large number of potential antigens were identified (over 70) with no consistent pattern of antibody specificity.

Stanford University researchers recently reported on a series of eight dysautonomia patients that had elevated glutamic acid decarboxylase autoantibodies (GAD-65) (Vlahovic et al., 2017). Five of the eight patients met the criteria for POTS. GAD-65 antibodies are found in many conditions as well as in a significant number of normal healthy controls, so the significance of this finding in POTS is uncertain.

While a whole host of diverse antibodies have been detected in groups of patients with POTS, this finding may simply reflect the immune system dysfunction found in these patients. However, it is attractive to think that autoantibodies directed against components of the autonomic nervous system may have pathological effects that explain the physiological and symptomatic features of POTS. Future research will require the differentiation between antibodies that are pathogenic based on their target antigens and serological markers of autoimmunity without specific pathophysiological effects. Careful standardization of antibody detection techniques is also needed. To date, different laboratories have used different methodologies. The commonly used ELISA method, for example, is notoriously nonspecific, with a frequent rate of false positives. Since ELISA uses soluble peptide antigens rather than intact receptor proteins, antibodies detected this way might not have any meaningful functional effects on intact membrane receptors. More widely accepted antibody detection techniques such as immunoprecipitation or cell-based assay have been difficult to develop for GPCRs.

8. Treatment implications

While autoimmune mechanisms appear to play a role in some POTS cases, this concept requires additional investigation and clarification. Therefore, immunotherapy should not be the first approach for treatment of POTS since immunological therapies have the potential for significant, or even life-threatening, complications. It is reasonable and important to consider the possibility of underlying systemic autoimmune disorders and to evaluate and treat accordingly. At this time, immunomodulatory therapies are not recommended unless a systemic autoimmune disorder is confirmed. The presence of GPCR or low titers of g-AChR autoantibodies alone are insufficient proof of an autoimmune cause for POTS based on current research.

Controlled treatment trials are underway to determine if immunomodulatory therapies may be effective in certain POTS subgroups and related disorders. To date, the published literature is limited to a small number of case reports noting improvement in POTS symptoms after intravenous immunoglobulin, rituximab, autologous adipose stem cell infusions, and plasmapheresis in highly selected cases with comorbid autoimmunity (Adamec et al., 2016; Goodman, 2017; Hendrickson et al., 2016; Numan et al., 2017; Blitshteyn and Brook, 2017).

Alternative therapies such as vagus nerve stimulation that harness the cholinergic anti-inflammatory reflex may also prove to have value. Vagus nerve stimulation has recently shown promise in treating autoimmune diseases such as rheumatoid arthritis, Crohn's and Sjögren syndrome (Koopman et al., 2016; Bonaz et al., 2016; Tarn et al., 2017), and preliminary work is underway exploring the efficacy of vagus nerve stimulation in POTS. There are several non-pharmacological measures already used to treat POTS that have been proven to have a positive impact on vagal tone, including regular exercise, consuming an anti-inflammatory diet rich in omega-3 fatty acids, acupuncture, meditation, music therapy, and biofeedback (Andersson and Tracey, 2012).

9. Summary

POTS is a clinically defined syndrome that is not a homogenous disorder, but rather a set of symptoms that represents the outward manifestation of diverse underlying processes. In many patients with POTS, there is evidence of dysregulation of the immune system, including the presence of autoantibodies directed against targets in the autonomic system. In some cases, an underlying defined autoimmune disorder appears to be the main cause of the symptom complex. In most other cases, the evidence for an autoimmune cause is insufficient at this time and use of immunomodulatory treatment is not supported by currently available research. Additional research is urgently needed to replicate the findings of smaller cohort autoantibody studies in larger cohorts, validate and compare the accuracy of various assay techniques for the GPCR autoantibodies that have been identified to date, and explore the potential for immunotherapy in treating POTS. There is a strong link between the immune system and the autonomic nervous system, and further research into this link promises to yield new insights and novel treatment approaches for POTS and other forms of dysautonomia.

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