Regenerative Medicine Options for Postural tachycardia syndrome (POTS)

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I. Overview:

a. Postural tachycardia syndrome (POTS) is defined by a heart rate increment of 30 beats/min or more within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension; the standing heart rate is often 120 beats/min or higher.
b. POTS manifests with symptoms of cerebral hypoperfusion and excessive sympatho-excitation.
c. The pathophysiology of POTS is heterogeneous and includes impaired sympathetically mediated vasoconstriction, excessive sympathetic drive, volume dysregulation, and deconditioning.
d. POTS is frequently included in the differential diagnosis of chronic unexplained symptoms, such as inappropriate sinus tachycardia, chronic fatigue, chronic dizziness, or unexplained spells in otherwise healthy young individuals.
e. Many patients with POTS also report symptoms not attributable to orthostatic intolerance, including those of functional gastrointestinal or bladder disorders, chronic headache, fibromyalgia, and sleep disturbances.
f. In many of cases, cognitive and behavioral factors, somatic hypervigilance associated with anxiety, depression, and behavioral amplification contribute to symptom chronicity.
g.

II. Abstract of article #1:

a. The aims of evaluation in patients with POTS are to exclude cardiac causes of inappropriate tachycardia; elucidate, if possible, the most likely pathophysiologic basis of postural intolerance; assess for the presence of treatable autonomic neuropathies; exclude endocrine causes of a hyperadrenergic state; evaluate for cardiovascular deconditioning; and determine the contribution of emotional and behavioral factors to the patient's symptoms.
b. Management of POTS includes avoidance of precipitating factors, volume expansion, physical countermaneuvers, exercise training, pharmacotherapy (fludrocortisone, midodrine, β-blockers, and/or pyridostigmine), and behavioral-cognitive therapy. A literature search of PubMed for articles published from January 1, 1990, to June 15, 2012, was performed using the following terms (or combination of terms): POTS; postural tachycardia syndrome, orthostatic; orthostatic; syncope; sympathetic; baroreceptors; vestibulosympathetic; hypovolemia; visceral pain; chronic fatigue; deconditioning; headache; Chiari malformation; Ehlers-Danlos; emotion; amygdala;

insula; anterior cingulate; periaqueductal gray; fludrocortisone; midodrine; propranolol; β-adrenergic; and pyridostigmine. Studies were limited to those published in English.

III. **Article #2 (2017):** Case Reports

a. **Abstract**

b. Postural orthostatic tachycardia syndrome and neurocardiogenic syncope are clinical manifestations of autonomic nervous system dysfunction (dysautonomia) that can lead to impaired daily functions. We report two young patients presenting with dysautonomia and autoimmune disease who both received autologous adipose stem cells (ASCs) infusions. This report is the first description of ASCs therapy for patients with combined dysautonomia and autoimmune disease. **Case 1: A 21-year-old female** presented at 12 years of age with escalating severe dysautonomia with weight loss and gastrointestinal symptoms. She had elevated autoantibodies and cytokines and received multiple immune modulation therapies. Her dysautonomia was treated by volume expanders, vasoconstrictors, and beta blockers with mild improvement. She received ASCs about 2 years before this report with dramatic improvement in her dysautonomia and autoimmune symptoms with a 10 kg weight gain**. Case 2: A 7-year-old boy** presented at 2 years of age with polyarthritis. At 5 years of age, he manifested orthostatic intolerance. He received immune modulatory therapies with mild improvement. He received ASCs and showed marked improvement of his dysautonomia and immune symptoms. Dysautonomia symptoms of these two patients improved significantly after modulation of autoimmune components by ASC therapy. Favorable clinical responses of these two cases warrant further case-control studies.

c. Discussion of paper:

d. We have demonstrated both by **improved symptoms and by laboratory tests** the safety and efficacy of autologous ASCs in treating two young patients with autoimmune systemic disease and dysautonomia. Both cases had a severe form of dysautonomia complicated by or secondary to autoimmune processes. Medical therapy initiated in both patients before ASC infusions was intensive, including multiple immune modulatory therapies. We propose that symptoms of dysautonomia improved after modulation of autoimmune components of this syndrome.

e. Human leukoctye antigen-antigen D related (HLA-DR), the major histocompatibility complex II cell surface receptor, interacts with immune cells to cause an immune response. Owing to lack of HLA-DR expression on their surfaces, MSCs have been demonstrated to be immune evasive, and both autologous and allogeneic MSC treatments have achieved promising outcomes in many clinical trials.

f. Autologous MSC therapy is very safe and without causing potential immune rejections after numerous repeated treatments. Numerous secretomes have been detected in MSCs, which are associated with MSC immunomodulation, trophic activities, angiogenesis, and antiapoptosis.

g. High level expression of anti-inflammatory cytokines from MSCs, such as **interleukin-10, interleutin-13**, **macrophage migration inhibitor factor (MMIF)**, and **transforming growth factor β,** plays very important roles in inhibition of inflammation and

immunomodulation by reacting with most of the immune cells, including: T cells, B cells, natural killer cells, and dendritic cells through various mechanisms, such as cell–cell contact and the release of chemokines and cytokines in vivo

IV. **Article #3. William T. Gunning, et al:** Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies.

V. Abstract

VI. The etiology of postural orthostatic tachycardia syndrome (POTS) is yet to be established. The disorder is often misdiagnosed as chronic anxiety or a panic disorder because the autonomic failure in these patients is not severe. A growing body of evidence suggests that POTS may be an autoimmune disorder. Antinuclear antibodies and elevations of ganglionic, adrenergic, and muscarinic acetylcholine receptor antibodies have all been reported.

VII. Article #4: Amy C. Arnold, MD great overview article on POTS 2018. See reference below and full PDF on Phenicell website.

VIII. Here at Phenicell, we offer intravenous mesenchymal stem cells from umbilical cord blood as well as iv exosomes which are derived from Mesenchymal stem cells. Contact us for me details.

IX. Refs:

a. Eduardo E Benarroch: Review Mayo Clin Proc 2012 Dec;87(12):1214-25. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder

b. Mohammed T Numan , Ankur Kamdar , Jane Young , Ian J Butler: Case Reports Stem Cells Dev: 2017 Mar 15;26(6):391-393. Autologous Adipose Stem Cell Therapy for Autonomic Nervous System Dysfunction in Two Young Patients

c. William T. Gunning, et al: Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. J Am Heart Assoc. 2019 Sep 17; 8(18):

d. Amy C. Arnold MD 2018. Auton Neurosci 215: 3-11. Diagnosis, physiology and prognosis. has great review article on POTS I will refer you to. See PDF on my website