Casual Friday Presents

Postural Orthostatic Tachycardia Syndrome (POTS)

FM Strategies: Physiology, Pathology, Interventions.

A BIOGENETIX CLINICAL PRESENTATION

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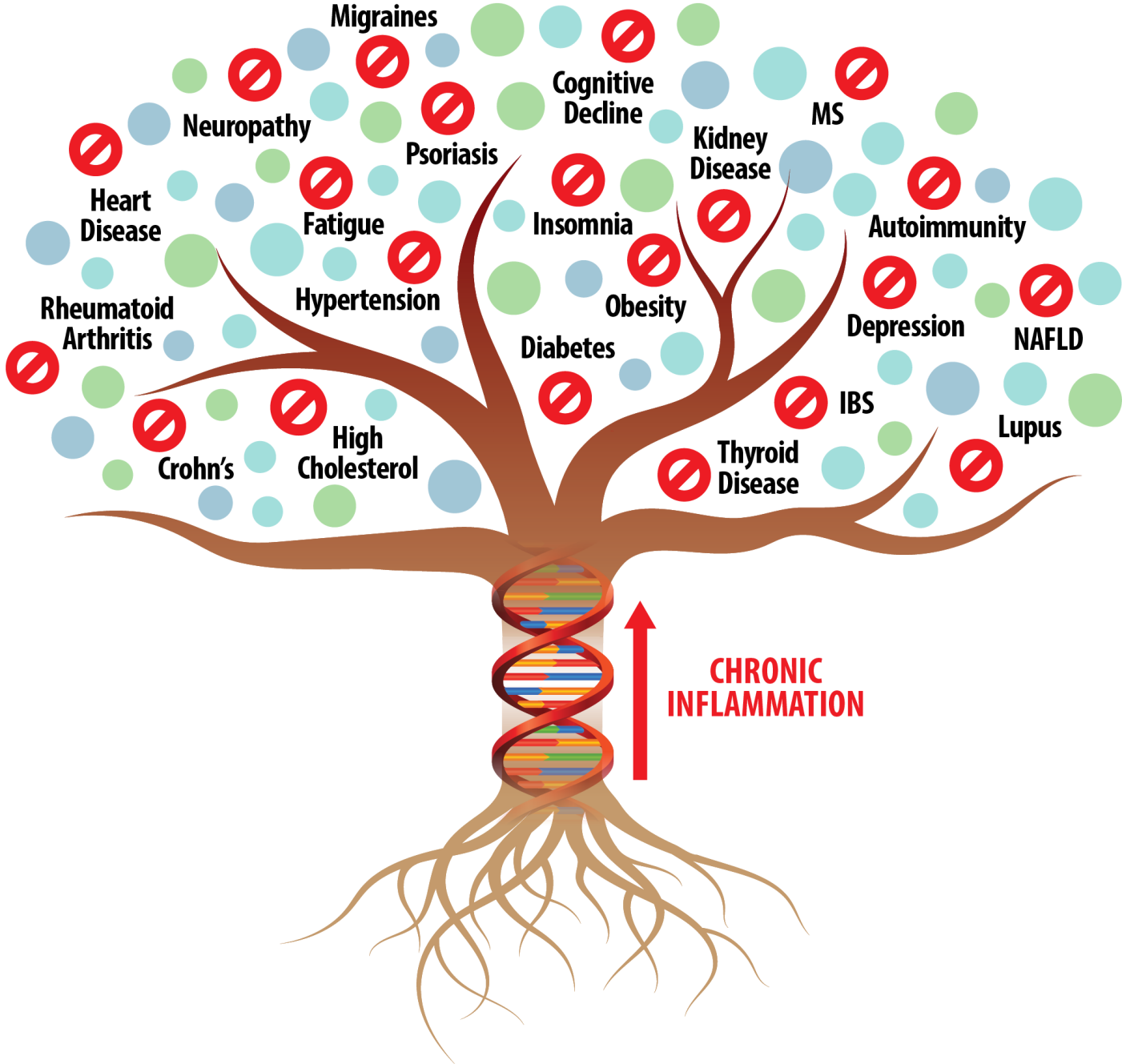
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION

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Postural orthostatic tachycardia syndrome (POTS) is a common form of autonomic dysregulation characterized as an excessive tachycardia upon standing in the presence of orthostatic intolerance.[1][2][3] Current adult diagnostic criterion requires a heart rate increase of greater than or equal to 30 bpm within the initial 10 minutes of standing or head-up tilt (HUT) in the absence of orthostatic hypotension.[4][5] POTS predominantly affects premenopausal females (5 to 1) between 15 and 50 years of age, manifesting with symptoms of fatigue, headache, palpitations, sleep disturbance, nausea, bloating, among others.[2][6][3] A multitude of pathophysiologic mechanisms including but not limited to disproportionate sympathoexcitation, volume depletion, autoimmune dysfunction, cardiac and physical deconditioning point to a heterogeneously complex etiology.[3][5][7] Most significantly, the debilitating nature of POTS predisposes patients to a high degree of functional impairment and decreased quality of life,[8] emphasizing the need for further investigation into the understanding and management of this increasingly prevalent clinical syndrome.

*Tachycardia: HR >100bpm at rest
*Orthostatic: relating to standing up straight

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A variety of proposed etiologies have led to the characterization of specific postural orthostatic tachycardia syndrome subtypes as described below, with a general consensus of excessive tachycardia in the setting of cardiovascular deconditioning as the final common pathway.[7]

Neuropathic

Neuropathic postural orthostatic tachycardia syndrome is a length-dependent autonomic neuropathy characterized by predominantly lower limb sympathetic denervation leading to reduced venoconstriction and venous pooling.[2][5] One study observed 50% of POTS patients exhibited peripheral sudomotor denervation correlated with a distal pattern of anhidrosis demonstrated by thermoregulatory sweat testing.[9] POTS patients have been observed to have decreased norepinephrine spillover in the lower extremities despite normal systemic norepinephrine spillover implicating dysfunctional norepinephrine reuptake due to injured terminal nerves.[10] Peripheral venous pooling evidenced by dependent acrocyanosis has also been observed.[11] Thus, an excessive cardiovascular response is necessary to maintain adequate mean arterial pressures.

*Norepinephrine: (also called **noradrenaline**) is a natural chemical in the body that acts as both a **stress hormone** and a **neurotransmitter**
*Acrocyanosis: smooth, wide blue vascular distribution demonstrating decreased blood flow.

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Hyperadrenergic

An estimated 30 to 60% of postural orthostatic tachycardia syndrome patients fall under the hyperadrenergic subtype, characterized by elevated standing plasma norepinephrine levels of greater than or equal to 600 pg/mL with predominant symptoms of increased sympathetic tone including palpitations, tremors, hypertension, anxiety, and tachycardia.[4][5] A norepinephrine transporter (NET) loss of function gene mutation (SLC6A2) resulting in deficient norepinephrine transport contributing to an increased mean supine heart rate was a feature in one case.[12] NET block is more frequently seen in the setting of pharmacologic inhibition by medications including tricyclic antidepressants, sympathomimetics (i.e., methylphenidate), and norepinephrine reuptake inhibitors (i.e., bupropion).[4][5] These medications are often useful in treating the associated cognitive effects of POTS such as depression, anxiety, and concentration difficulties. Therefore it is prudent to ensure patients are systemically clear of possible pharmacologic causes of elevated catecholamine levels and tachycardia throughout diagnostic evaluations.

Hypovolemic

Up to 70% of patients with postural orthostatic tachycardia syndrome exhibit decreased plasma, red blood cell, and total blood volumes, although the degree of hypovolemia varies between studies.[13][5][14] In POTS patients, this physiologic low volume state persists in association with a paradoxically low level of renin and aldosterone levels, suggesting a possible impairment of the renin-angiotensin-aldosterone axis that is crucial to maintaining adequate plasma volume [15]. Secondary hypovolemic states present in patients with co-existing gastrointestinal conditions culminating in excessive fluid loss and poor volume intake (nausea, vomiting, diarrhea).[4]

***Renin and aldosterone work together as part of a hormonal chain reaction to raise blood pressure and increase blood volume when your body detects a drop in fluid or salt levels.**

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Autoimmune

An autoimmunity hypothesis is one proposal for postural orthostatic tachycardia syndrome given the significant overlapping commonalities (female predominance, post-viral onset, elevated autoimmune markers) seen in other systemic autoimmune disorders such as rheumatoid arthritis, lupus, and Sjogren's syndrome.[4][6] Previous studies have demonstrated increased autoantibodies in POTS. Positive antinuclear antibodies were present in up to 25% of patients, with Hashimoto thyroiditis being the most prevalent.[1][16] One study demonstrated increased proinflammatory IL-6 levels in POTS patients associated with increased sympathetic drive, perhaps driven by chronic systemic immune activation.[17] Additionally, other autoimmune markers including ganglionic AChR, G-protein coupled receptor, and various nonspecific autoantibodies have presented in the POTS population.[1][3][18]

Deconditioning

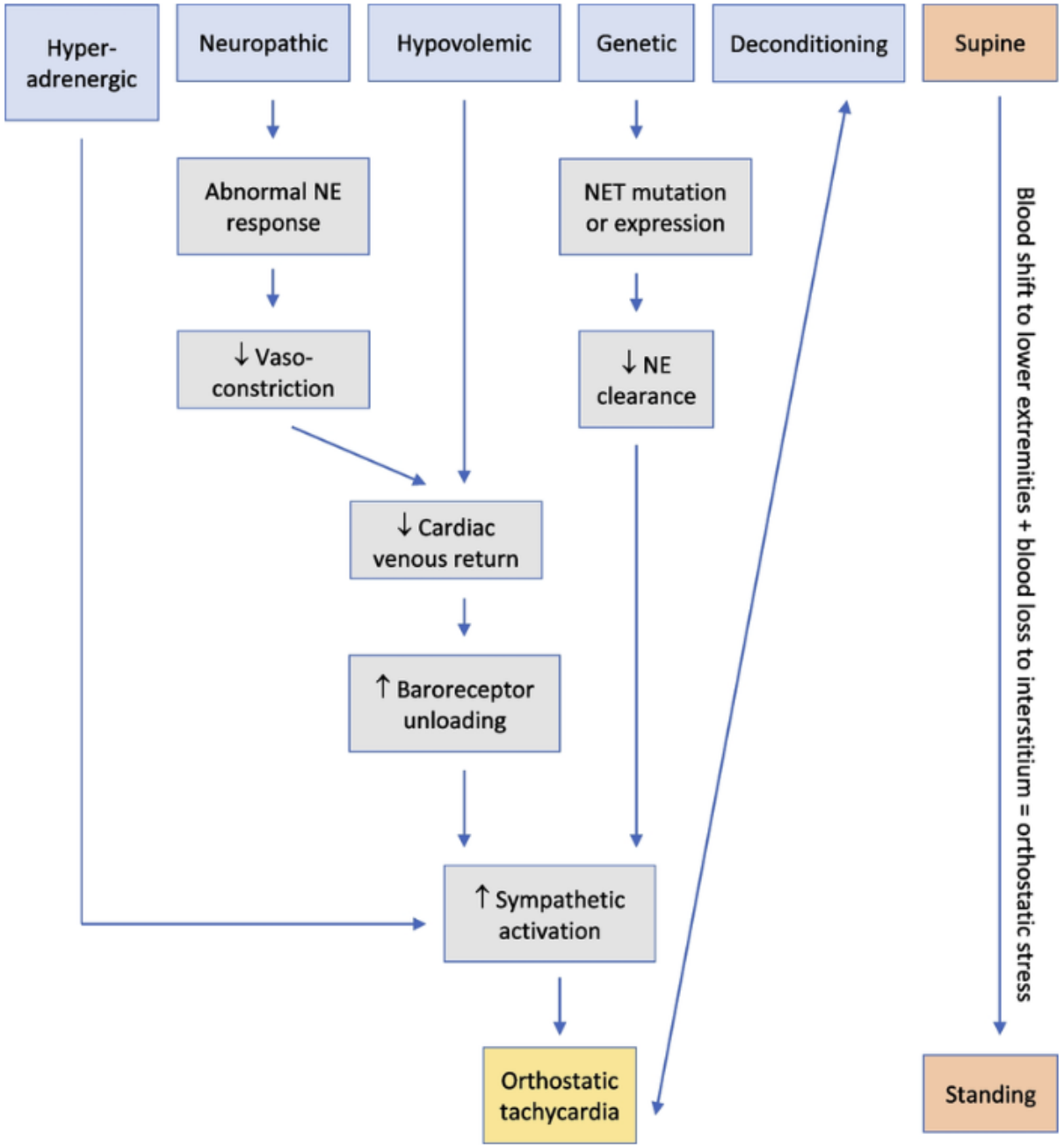
Physical and cardiovascular deconditioning is often evident in patients with postural orthostatic tachycardia syndrome, although its presence as either a cause or effect is unclear.[11][13] Moreover, it appears the severity of deconditioning does not necessarily correlate with objective laboratory or autonomic findings.[19] Similar POTS-like symptoms have been observed in otherwise healthy individuals placed in microgravity environments such as space flight, further implicating the physical and gravity dependent roles underlying POTS.[7] Decreased cardiac size and mass have been demonstrated in POTS patients compared to healthy controls, with an average decreased left ventricular mass of 16% and reduced plasma volume of 20%.[20][21] The well documented chronic fatigue, autonomic instability, and overall functional impairment give way to reduced physical activity and prolonged bed rest states, resulting in an unfavorable feedback cycle that exacerbates already prominent existing symptoms.

The pathophysiology underlying postural orthostatic tachycardia syndrome is heterogeneous, encompassing excess sympathetic tone, impaired peripheral autonomic function, volume dysregulation, cardiovascular deconditioning, and autoimmune dysfunction.[4][5][7][11] In normal healthy subjects, a shift of the intravascular volume to the interstitial space reduces the total effective circulating blood volume, reflecting the gravity-dependent physiology seen in orthostatic-related pathologies. As expected, a subsequent reduction in stroke volume results in a compensatory increased sympathetic drive augmenting cardiac contractility, heart rate, and systemic vascular resistance. POTS patients exhibit persistent decreased stroke volume despite an exaggerated sympathetic response with postural changes such as standing, culminating in a final common pathway of tachycardia in the presence of orthostatic intolerance on standing.[4][7]

The mechanisms as mentioned earlier are not mutually exclusive but instead overlap in a complex interaction of cause and effect. Affected physiologic systems include neuropathic, cardiovascular, renal, immune, and hematologic; this widespread implication of complex systems have added a certain degree of difficulty in constructing a comprehensive framework in the understanding of POTS. Common symptoms include chronic fatigue, dizziness, sleep disturbance, headache, tremors, tachycardia, anxiety, depression, gastrointestinal disturbances, syncope, and vision changes.[1][6][13][22]

TABLE 1

Medication	Mechanism	Adverse effects
Fludrocortisone	Synthetic mineralocorticoid increasing renal sodium reabsorption and loss of potassium	Hypertension, hypokalemia, headaches, heart failure, edema
Midodrine	α1-adrenergic agonist increases arteriolar and venous tone	Supine hypertension, paresthesias, urinary retention and urgency
Clonidine, α-methyldopa	Centrally acting α2-agonist reduces sympathetic tone decreases peripheral vascular resistance, blood pressure, and heart rate	Sedation, cognitive clouding, fatigue, headache, skin rash
Propranolol, metoprolol	Blocks β-adrenergic receptor activation decreasing heart rate, cardiac contractility; non-selective β-blockers (propranolol) also reduce splenic vasoconstriction via β_2 inhibition	Bradycardia, hypotension, fatigue, syncope
Pyridostigmine	Inhibits action of acetylcholinesterase leading to increased acetylcholine at autonomic ganglia and peripheral muscarinic receptors	Abdominal pain, diarrhea, vomiting, dysmenorrhea



***NET mutation** refers to a mutation in the **norepinephrine transporter (NET)** gene, **SLC6A2**.

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https://www.researchgate.net/figure/Convergence-of-common-POTS-pathophysiological-theories-partially-adapted-from-Arnold-et_fig1_334175297

More on the NET Mutation

When NET mutation is impactful:

- NE stays in the synapse much longer.
- More NE spills into the bloodstream.
- Adrenergic receptors are stimulated excessively.
- The sympathetic nervous system becomes overactive.

This leads to symptoms such as:

- tachycardia
- palpitations
- anxiety
- tremor
- sweating
- orthostatic intolerance
- hyperadrenergic POTS

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Review > Heart Rhythm. 2022 Nov;19(11):1880-1889. doi: 10.1016/j.hrthm.2022.07.014.
Epub 2022 Jul 16.

Postural orthostatic tachycardia syndrome as a sequela of COVID-19

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Affiliations + expand

PMID: 35853576 PMCID: PMC9287587 DOI: 10.1016/j.hrthm.2022.07.014

Abstract

Postural orthostatic tachycardia syndrome (POTS) is a complex multisystem disorder characterized by orthostatic intolerance and tachycardia and may be triggered by viral infection. Recent reports indicate that 2%-14% of coronavirus disease 2019 (COVID-19) survivors develop POTS and 9%-61% experience POTS-like symptoms, such as tachycardia, orthostatic intolerance, fatigue, and cognitive impairment within 6-8 months of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Pathophysiological mechanisms of post-COVID-19 POTS are not well understood. Current hypotheses include autoimmunity related to SARS-CoV-2 infection, autonomic dysfunction, direct toxic injury by SARS-CoV-2 to the autonomic nervous system, and invasion of the central nervous system by SARS-CoV-2. Practitioners should actively assess POTS in patients with post-acute COVID-19 syndrome symptoms. Given that the symptoms of post-COVID-19 POTS are predominantly chronic orthostatic tachycardia, lifestyle modifications in combination with the use of heart rate-lowering medications along with other pharmacotherapies should be considered. For example, ivabradine or β-blockers in combination with compression stockings and increasing salt and fluid intake has shown potential. Treatment teams should be multidisciplinary, including physicians of various specialties, nurses, psychologists, and physiotherapists. Additionally, more resources to adequately care for this patient population are urgently needed given the increased demand for autonomic specialists and clinics since the start of the COVID-19 pandemic. Considering our limited understanding of post-COVID-19 POTS, further research on topics such as its natural history, pathophysiological mechanisms, and ideal treatment is warranted. This review

Clin Auton Res. 2025 Jan 22;35(2):285–299. doi: 10.1007/s10286-025-01106-y

Long-COVID and postural orthostatic tachycardia syndrome: a preliminary comparison of neuropsychological performance

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PMCID: PMC12000172 PMID: 39838139

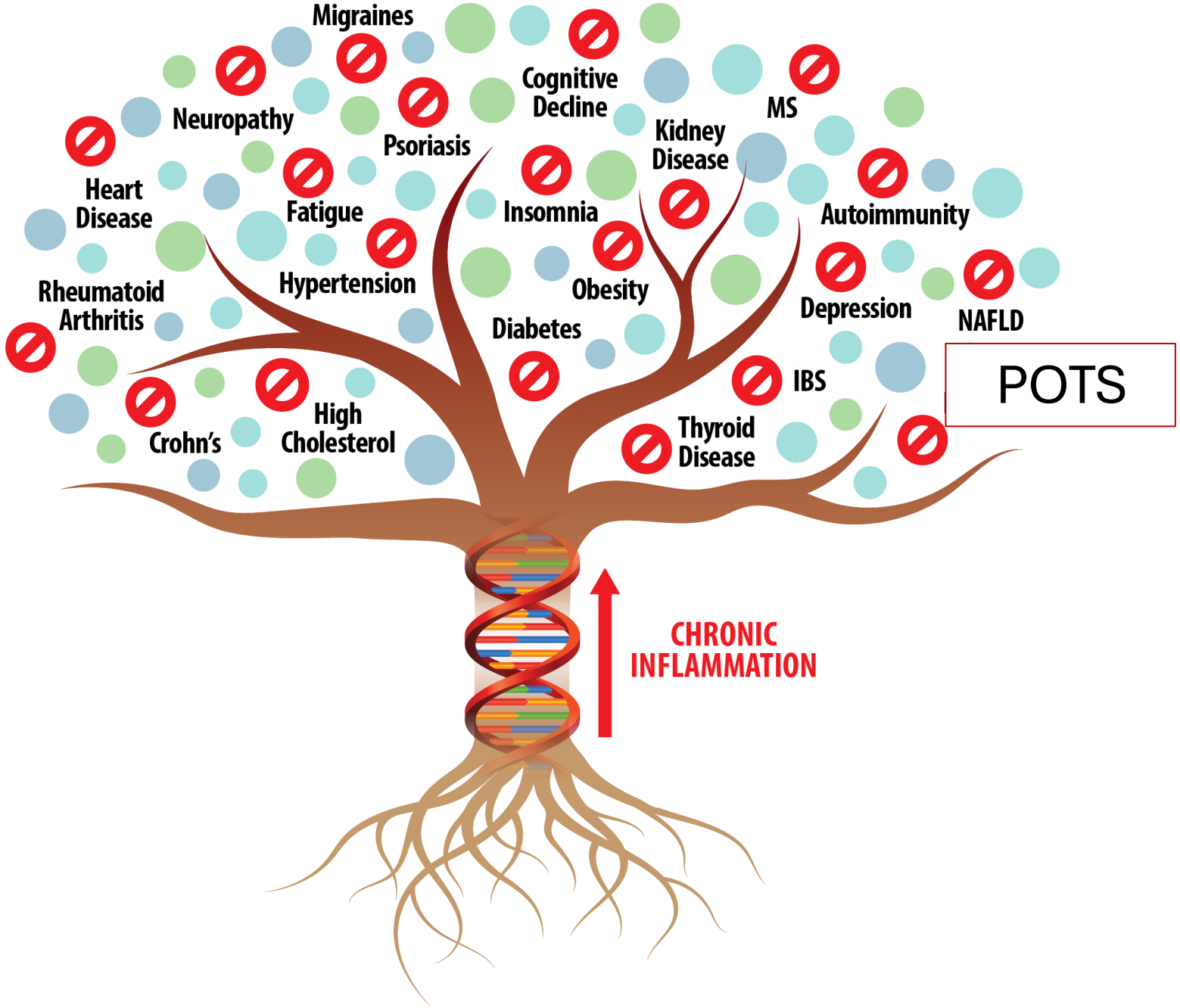
Abstract

Purpose

The aim of the study is to analyze and compare the cognitive profile between 59 patients with long-COVID [LC; 30 of them with and 29 without a positive coronavirus disease 2019 (COVID-19) confirmatory test] and 31 patients with postural orthostatic tachycardia syndrome (POTS) and a matched group of 39 healthy control participants.

Methods

Participants were examined on a battery of neuropsychological tests, including verbal


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
Rheumatoid Arthritis
Diabetes
NAFLD
IBS
Crohn's
High Cholesterol
Thyroid Disease
POTS
CHRONIC INFLAMMATION

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Workup Flow

Orthostatic Symptoms

↓

Confirm POTS

↓

Determine Physiologic Subtype

↓

Search for Contributing Systems

↓

Prioritize Treatable Drivers

↓

Build Individualized Support Plan

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Functional Organization of Contributing Systems

1. Autonomic nervous system.
2. Immune system.
3. Mast cell activation.
4. Autonomic neuropathy.
5. Blood volume.
6. Mitochondria.
7. Connective tissue.
8. Gut-immune axis.
9. Environmental factors.

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The Questions

1. Is this primarily hyperadrenergic, neuropathic, or hypovolemic?
2. Is there evidence of autoimmunity?
3. Is mast cell activation contributing?
4. Is small fiber neuropathy present?
5. Is blood volume reduced?
6. Is mitochondrial dysfunction limiting exercise tolerance?
7. Is hypermobility or connective tissue laxity increasing venous pooling?
8. Are gut or immune factors amplifying symptoms?
9. What individualized interventions address the dominant physiologic drivers?

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Test Selection

1. What have the primaries discovered? (adrenergic, neuro, or hypovolemic)
2. Cyrex Array 5 (evidence of autoimmunity?)
3. Cytokine mapping (MCAS)
4. B vitamins and mineral (neuropathies?)
5. CBC, BP, etc (blood volume evidence?)
6. Organic acids (mitochondrial)
7. Observations (hypermobility)
8. Stool (gut involvement)
9. Tox (environmental involvement)

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Tests Considered:

1. Biogenetix general screen
2. CytoDx (cytokine response profile from Dx Solutions)
3. DUTCH Complete
4. Organix (Genova)
5. GI Effects (Genova)
6. Tox panel (Vibrant)

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We Want to Hear from You!

Give us your Casual Friday feedback
with this short 5-question survey.

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