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Review Article

Recent advances in the understanding of the mechanisms underlying postural tachycardia syndrome in children: practical implications for treatment

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Abstract Postural tachycardia syndrome is defined by a heart rate increment of 40 beats/minute (bpm) (or a heart rate that exceeds 125 bpm) within 10 minutes of change from the supine position to an upright position in the absence of obvious orthostatic hypotension. There are multiple pathophysiological mechanisms that underlie postural tachycardia syndrome, including peripheral denervation, β-receptor supersensitivity, hypovolaemia, and impaired muscle pump. Some children afflicted with postural orthostatic tachycardia syndrome and hypovolaemic dysregulation have been found to have perturbed renin–angiotensin–aldosterone profile, disturbed vascular endothelial function, and abnormal vasodilation. The hyperadrenergic state in some postural tachycardia syndrome patients is likely a driver for orthostatic tachycardia. Other mechanisms include the presence of treatable autonomic neuropathies. An understanding of these pathophysiological mechanisms might be helpful for the effective treatment of postural tachycardia syndrome.

Keywords: Postural tachycardia syndrome; blood volume; vasoactive peptides; vessel; heart; children

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Patients with postural tachycardia syndrome characteristically have problems maintaining an upright position in the face of a gravitational challenge. Orthostatic symptoms of postural tachycardia syndrome may occur after a postural change from the supine to an upright position. The diagnostic criterion in children is orthostatic symptom with an increment $\geqslant$40 beats/minute (bpm) (or a heart rate that exceeds 125 bpm) within 10 minutes of starting a standing test or a head-up tilt test.[1,2] Symptoms such as dizziness, headache, palpitations, weakness, tremulousness, nausea, or even syncope can be found in these children.[3,4] Postural tachycardia syndrome is increasingly recognised in children and adolescents. A negative influence on physical and emotional well-being has been reported.[5] Even daily activities may exacerbate symptoms.

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The pathophysiological mechanisms for postural tachycardia syndrome are not completely understood. Several mechanisms have been proposed including peripheral denervation, β-receptor hypersensitivity, hypovolaemia, and impaired cerebral autoregulation.[6] The purpose of this manuscript was to review recent advances in our understanding of the pathophysiological mechanisms underlying postural tachycardia syndrome in children.

Volume dysregulation

In healthy children and adolescents with normal vascular structure, intact vasomotor sensors, muscle pump ability, sufficient blood volume, and oxygen-carrying capacity, "standing up"-related reduced blood volume is usually well tolerated.[7,8] Circulatory deficits in postural tachycardia syndrome patients were first reported by MacLean and Allen,[9] and evidences for excessive venous pooling and anatomical or functional abnormalities of lower limb veins in postural tachycardia syndrome children were reported by Tanaka et al.[10]

During orthostasis, low 24-hour urinary sodium excretion may contribute to a change in blood volume.[11,12] Postural tachycardia syndrome patients were divided into three groups according to the pattern of blood flow measured in their lower extremities: low, high, and normal flow.

Low flow

In this group, increased peripheral resistance and reduced cardiac output were observed.[13] Typical signs and symptoms include paleness, acrocyanosis, and cool extremities. These symptoms increase when patients stand up.[14] Decreased peripheral blood flow and increased angiotensin II in low-flow postural tachycardia syndrome patients occur as a consequence of angiotensin II/angiotensin II type-1 binding and superoxide radical formation. This interaction leads to an important vasoconstrictive response through a reduction in bioavailable nitric oxide.[15] Frequencies of nitric oxide synthase-related genotypes (786CC and 298DD) were significantly lower in postural tachycardia syndrome patients than in control subjects.[16]

High flow

While standing up, this group of postural tachycardia syndrome children has decreased total peripheral resistance, which increases blood volume in lower extremities.[17] Local oedema is frequently observed, whereas acrocyanosis is rare.[17] Hyperkinetic circulation is an essential feature of this group;[18] moreover, symptoms are frequently exacerbated by a viral infection, suggesting that autoimmunity may play a role in this situation.

Normal flow

Splanchnic pooling is the main vascular change in normal-flow postural tachycardia syndrome children. Failure of venous and arterial constriction to increase splanchnic vascular compliance has been proposed as a causal mechanism.

Abnormal vascular endothelial function

Relative hypovolaemia can occur in children with postural tachycardia syndrome because of venous pooling, capillary leakage, and impaired vascular function. Postural tachycardia syndrome patients have an abnormal response to hypovolaemia, which can be ascribed to renin–angiotensin–aldosterone axis abnormalities.[19]

Angiotensin II

Angiotensin II in postural tachycardia syndrome children was significantly higher than that of healthy subjects (105 ± 50 versus 84 ± 28 ng/L, $p = 0.041$), whereas impaired plasma renin and aldosterone responses were found in postural tachycardia syndrome children.[20] The so-called renin–aldosterone paradox could be a response to direct hormonal effect, low blood flow of the juxtaglomerular apparatus, sensor problem of the macula densa, or missing transmission of signal to the juxtaglomerular apparatus.[21]

Angiotensin-converting enzyme 2

Angiotensin 1–7 can be formed from angiotensin II through the angiotensin-converting enzyme. In postural tachycardia syndrome patients, high levels of angiotensin II did not cause any increase in angiotensin 1–7, suggesting the possibility of decreased activity of angiotensin-converting enzyme 2.[22]

Nitric oxide dysfunction

Nitric oxide is well recognised for its function in endothelial development. Liao confirmed that flow-dependent nitric oxide release was reduced in some children with postural tachycardia syndrome, suggesting an abnormal endothelial function.[23]

Plasma urotensin II and plasma intermedin

Low levels of urotensin II and plasma intermedin in postural tachycardia syndrome children leading to impaired vasoconstrictive response may play a role in the pathogenesis of postural tachycardia syndrome.[24,25]

Neuropathy

Index of valsalva manoeuver, heart rate change with deep respiration, and QT interval dispersion can be evidences for impaired autonomic nervous function in postural tachycardia syndrome children and adolescents.[26] Postural tachycardia syndrome may be a mild form of autonomic neuropathy caused by a preceding infection or vaccination history.[27] This was confirmed in different studies. Auto-antibodies against cardiac lipid raft-associated proteins were found in postural tachycardia syndrome patients;[28] moreover, the TT genotype (GNB3-C825T) encoding the G-proteinb3 subunit was more frequently found in postural tachycardia syndrome children.[29] α1-Adrenergic receptor activation, leading to vasoconstriction and concurrent β adrenergic receptor-mediated tachycardia, is present in autoimmune situations.[30] Acetylcholine acts as an important neurotransmitter in the autonomic nervous system.[31] Antibodies for acetylcholine receptor were positive in 24.39% of postural tachycardia syndrome children, and their symptoms were significantly more severe than in patients who were acetylcholine receptor antibodies

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negative. This may be caused by broken immune tolerance, abnormal immune reaction, or sensitised acetylcholine receptors of thymus cells.[32]

Hyperadrenergic status

Several studies have shown that postural tachycardia syndrome children and healthy subjects have similar levels of plasmatic norepinephrine and epinephrine at rest, whereas orthostatic plasma norepinephrine levels are different.[33] Dizziness, headache, fatigue, and tremulousness were frequent in hyperadrenergic postural tachycardia syndrome children and adolescents.[34] Pharmacological norepinephrine transporter blockade drugs produce postural tachycardia syndrome-like symptoms.[35] Increased synaptic norepinephrine concentrations can be observed in norepinephrine transporter deficiency families. Norepinephrine transporter deficient mice exhibited elevated blood pressure and increasing tachycardia when engaged in wakeful activities.[36] Ala457Pros, which can cause elevated heart rate and plasma norepinephrine transporter levels in the supine position, is the result of a mutation in the norepinephrine transporter SLC6A2. In the analysis of SLC6A2 gene polymorphisms, the norepinephrine transporter dysfunction of postural tachycardia syndrome children is still unexplained.[37] In 2012, Bayles described that epigenetic modification of this gene could decrease expression of the norepinephrine transporter protein, thus constituting a mechanism of postural tachycardia syndrome.[38] On the other hand, as excessive tachycardia is a main feature, treatment with β-adrenergic blockers is used. There is a large variation in the level of β-blockage efficiency, suggesting the existence of hyperadrenergic subgroups.[35]

Table 1. Mechanisms for postural tachycardia syndrome and related symptoms and laboratory findings.

Pathophysiology	Symptoms	Laboratory findings
Volume dysregulation	Paleness, acrocyanosis, cool extremities, local oedema, hyperkinetic circulation[14,17,18]	Increased angiotensin II,[20,22] low 24-hour urinary sodium,[11,12] low levels of standing plasma renin activity, or no difference[20,41]
Abnormal vascular endothelial function	Dizziness, weakness, and pallor[3]	Larger vascular flow-mediated dilation,[23] high plasma nitric oxide and nitric oxide synthase levels,[23] decreased plasma urotensin II, and intermedin levels[24,25]
Neuropathy	Cool extremities, sweating, migraine headache	Positive acetylcholine receptor antibody,[31] low index of valsalva manoeuver, longer QT interval dispersion[26]
Hyperadrenergic state	Frequent dizziness, headache, fatigue, tremulousness[34,42]	High levels of upright plasma norepinephrine[34–36]
Muscle pump defects	Paleness, acrocyanosis, and cool extremities[40]	Low calf blood flow[40]

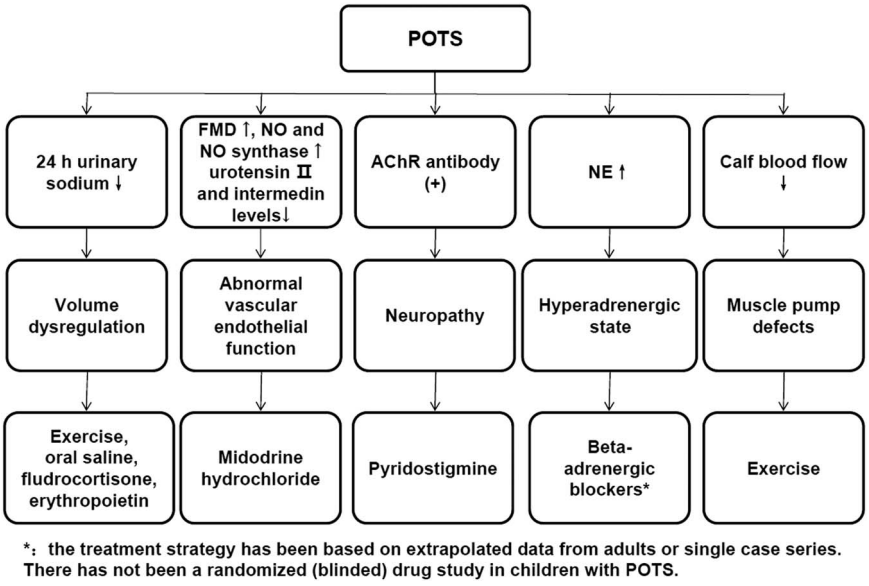

Figure 1.
Laboratory investigation, pathophysiology and therapeutic options for postural tachycardia syndrome in children. AChR, acetylcholine receptor; POTS, postural tachycardia syndrome.

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Muscle pump defects

Against orthostatic challenge, muscle blood flow increases, and contraction of leg and gluteal muscles drive venous blood back to the heart, so that arterial pressure can be maintained in healthy children.[39] Some researchers have stressed the importance of muscle pump activity in postural tachycardia syndrome patients. Decreased calf circumference, calf ejection fraction, and calf venous capacity may play a role in this type.[40] Some scholars take the presence of venous valves that are incomplete or congenitally absent into consideration.

Conclusions

In recent years, an in-depth understanding has accumulated on the underlying mechanisms of postural tachycardia syndrome in children. These can be divided into five categories: volume dyregulation, abnormal vascular endothelial function, neuropathy, hyperadrenergic state, and muscle pump defects. When deciding treatment strategies for patients with postural tachycardia syndrome, it is useful to try and understand which pathophysiological mechanism or combination of pathophysiological mechanisms are contributing to the symptoms (Table 1 and Fig 1).[41–43] Non-pharmacological treatments should be recommended at first.[43] If possible, healthcare providers should consider discontinuing medications that exacerbate the tachycardia. A regular structured exercise programme, oral rehydration saline, and a multidisciplinary approach with β-blockers or midodrine should be selected, depending on the pathophysiological status of the patients (Fig 1).[43] Common mechanisms such as volume dysregulation, disturbed vascular endothelial function, abnormal vasodilation, and hyperadrenergic state require further research; moreover, more research is necessary to fully understand autoimmune and inflammation mechanisms to facilitate treatment options. It is unclear whether there are postural tachycardia syndrome patients who might have mixed underlying mechanisms or subtypes in various proportions, which would be worthy of investigation.

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Conflicts of Interest

None.

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