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## Invited Editorial / *Davetli Editöryal Yorum*

# Postural orthostatic tachycardia: A syndrome requiring detailed search for associated conditions

## Postural ortostatik taşikardi: Eşlik eden durumların ayrıntılı araştırılmasını gereken bir sendrom

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Postural orthostatic tachycardia syndrome (POTS) is a clinical syndrome usually characterized by

*(1)* symptoms such as light-headedness, palpitations, tremor, generalized weakness, blurred vision, diminished concentration, exercise intolerance, and fatigue, that occur upon standing;

*(2)* an increase in heart rate ≥30 bpm when moving from recumbent to standing position (or ≥40 bpm in individuals 12 to 19 years of age); and

*(3)* the absence of orthostatic hypotension (≥20 mm Hg drop in systolic blood pressure).

Association of POTS with syncope is not clear and not frequent, but presyncope is frequently observed. It also has a diurnal variation, occurring more frequently in the morning hours. POTS is predominantly (75%) observed in women of childbearing age, and is considered to be a chronic disease with eventual improvement and without known mortality.[1,2] There is important relationship between POTS and use of contraceptive drugs, and worsening of POTS symptoms during menstruation.

Despite the absence of a definite classification, POTS is generally divided into primary and secondary forms.

Primary form describes conditions with no identifiable causes. Pathophysiology of primary POTS is complex and there is no single mechanism explaining the underlying pathology. Different combinations of co-existing factors may be involved in the same patient. These factors include autonomic denervation (partial dysautonomic or neuropathic POTS), hypovolemia (hypovolemic POTS), hyperadrenergic stimulation (hyperadrenergic POTS), deconditioning, and hypervigilance. The most frequent form of primary POTS is the "partial dysautonomic" form. These patients frequently report an abrupt onset of symptoms associated with acute viral febrile illness, pregnancy, surgery, sepsis, or trauma. Peripheral autonomic neuropathy is suggested to be the underlying mechanism in these patients.[3] Less frequent form of POTS is hyperadrenergic POTS. This group of patients experiences slower, gradual onset and progression of symptoms over time. They also have increased serum norepinephrine levels on standing and are very sensitive to isoproterenol infusion. Hyperadrenergic POTS is frequently associated with a strong family history, orthostatic hypertension, tremor, anxiety, increase in urine output on standing, acrocyanosis and migraine-type headaches.[4]

**Abbreviation:**

*POTS Postural orthostatic tachycardia syndrome*

Secondary form of POTS refers to clinical conditions in which POTS is considered to evolve due to other clinical disorders that lead to peripheral au-

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tonomic denervation or vascular unresponsiveness (Table 1). Another proposed mechanism is production of autoantibodies to the acetylcholine receptors of the autonomic ganglia by tumor cells.[5,6]

Investigation of POTS should include a complete history and physical examination with orthostatic vital signs and 12-lead electrocardiogram, complete blood count, and thyroid function studies. Positional serum norepinephrine levels, 24-hour Holter monitoring, exercise stress testing, transthoracic echocardiogram, and autonomic testing can be useful in individual patients, but are not mandatory and should not be routinely performed.[1]

Despite the fact that POTS is a clinical condition that significantly affects quality of life and approximately 25% of these patients are disabled and unable to work, there is still no specific therapy approved for the treatment of this clinical entity.[5] Patients should be informed about the need for long-term therapy. Reassurance, education and motivation of the patient, strict adherence to physicians' recommendations, treatment of underlying secondary causes, and avoidance and/or withdrawal of drugs are the mainstay of initial management. Exercise training is the first step in nonpharmacological management of these patients. Exercise programs should initially be supine or at least non-upright exercises, such as swimming and cycling, with some resistance training for the thighs.[1] Upright exercises will probably worsen symptoms and lead to discontinuation of physical activity and demoralization of patients. Short-term decompensation in clinical condition can be managed with acute intravenous infusion of up to 2 L of saline. The effect of this approach may last from several hours up to 2 days. Other, less proven treatment options include consumption of 2–3 L of water and 10–12 g of sodium chloride daily, or administration of drugs, such as fludrocortisone, pyridostigmine, midodrine, or low-dose propranolol. Clonidine or alpha-methyldopa can be prescribed to patients with POTS who have prominent hyperadrenergic features. In an open-label study, administration of ivabradine resulted in symptom improvement in up to 60% of patients with POTS.[7] Our earlier experience with this drug supports the results of this study.[8]

In this issue of the journal, Atik and colleagues[9] report their experience with the diagnosis and treatment of POTS, as well as vasovagal syncope and inappropriate sinus tachycardia in children. Diagnosis of POTS was established in 7 of 132 patients evaluated due to complaints of syncope, presyncope, and lightheadedness. Three of them had comorbidities, including hypertrophic cardiomyopathy, homocystinuria, and Reynaud's phenomenon. These associations are reported for the first time (except homocystinuria, which had been reported in a previous article of the authors[10]), but unfortunately, causative relationships and suggested underlying mechanisms could not be established. Among them, Reynaud's phenomenon might have been explained by abnormal adrenergic vasoconstriction, but the clinical evaluation of the patient did not support this hypothesis. One of the

**Table 1. Secondary causes of postural orthostatic tachycardia syndrome**

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| Chronic diabetes mellitus (most frequent cause) |
| Amyloidosis |
| Sarcoidosis |
| Autoimmune diseases |
| • Autoimmune autonomic ganglionopathy |
| • Sjogren's syndrome |
| • Systemic lupus erythematosus |
| • Antiphospholipid syndrome |
| Chiari malformation type I |
| Storage diseases |
| Ehlers-Danlos syndrome |
| Genetic disorders/abnormalities |
| Infections |
| • Viral diseases |
| • Mononucleosis |
| • Lyme disease |
| • Extrapulmonary Mycoplasma pneumonia |
| • Hepatitis C |
| Multiple sclerosis |
| Mitochondrial diseases |
| Mast cell activation disorders |
| Paraneoplastic syndromes |
| Toxicity from alcoholism, chemotherapy, and heavy metal poisoning |
| Trauma, pregnancy, or surgery |
| Vaccinations |
| Vitamin deficiencies (vitamin D deficiency) |
| Anemia (iron deficiency) |

frequent physical signs in patients with POTS is position-dependent acrocyanosis in the lower extremities, observed in up to 50% of patients. This finding can be accompanied by Reynaud's phenomenon in upper extremities as a result of redistribution of blood, hypovolemia, hyperadrenergic stimulation, and/or underlying disease, such as scleroderma. The underlying mechanism of this phenomenon has been suggested to represent abnormalities in nitric oxide activity in the skin of these patients.[11] Unfortunately, the location of Reynaud's phenomenon in the patient was not described, and it is also not clear why the patient received beta-blocker and angiotensin receptor blocker medication. These drugs should be avoided in patients with POTS, as they frequently worsen orthostatic tolerance and may worsen Raynaud's phenomenon. Only low-dose propranolol (10–20 mg) can be used in these patients, with very limited scientific evidence of proof.[1] Other drugs that should be avoided in POTS patients include alpha blockers, angiotensin converting enzyme inhibitors, bromocriptine, calcium channel blockers, diuretics, ethanol, ganglionic blocking agents, hydralazine, monoamine oxidase inhibitors, nitrates, opiates, phenotiazines, phosphodiesterase inhibitors, tricyclic antidepressants, and most importantly, contraceptive drugs containing high concentration of progesterone. The last item decreases aldosterone level and worsens symptoms of POTS.

The association of POTS with hypertrophic cardiomyopathy also needs more discussion. Relying on the findings of tilt-testing, the authors suggested that syncope in this patient was related to POTS. However, POTS patients generally have no cardiac abnormalities. Furthermore, previous studies suggested that the sensitivity, specificity, and accuracy of tilt-testing to evaluate the origin of syncope in patients with hypertrophic cardiomyopathy is poor due to altered autonomic response related to heterogeneous areas of hypertrophy.[12]

In conclusion, there is relatively limited information about the etiology and treatment of POTS and other orthostatic problems in the young population. The study of Arik et al. published in this issue of the journal adds some new information about the etiology of syncope and presyncope in a Turkish pediatric population. We need more data from multicenter studies or surveys to establish the real incidence and underlying causes of syncope in the region.

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