REVIEW

Postural orthostatic tachycardia syndrome

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Postural orthostatic tachycardia syndrome (POTS) is an autonomic disturbance which has become better understood in recent years. It is now thought to encompass a group of disorders that have similar clinical features, such as orthostatic intolerance, but individual distinguishing parameters—for example, blood pressure and pulse rate. The clinical picture, diagnosis, and management of POTS are discussed.

Postural orthostatic tachycardia syndrome (POTS) is an autonomic disturbance[1] characterised by the clinical symptoms of orthostatic intolerance, mainly light-headedness, fatigue, sweating, tremor, anxiety, palpitation, exercise intolerance and near syncope on upright posture.[2] These are relieved on lying down. Patients also have a heart rate >120 beats/min (bpm) on standing or increase their heart rate by 30 bpm from a resting heart rate after standing for 10 min. The symptoms lead to the limitation of activities impacting on a patient's life on a day-to-day basis—for example, bathing, housework, feeding. The severity of symptoms is more pronounced compared to a condition like pure autonomic failure. Patients with POTS may not have blood pressure changes and can have fluctuation of blood pressure in either direction. Other conditions like chronic debilitating disorders, prolonged bed rest or medication that impair autonomic function have to be excluded.

HISTORY AND EPIDEMIOLOGY

POTS was first described 1940. Low *et al* from the Mayo clinic did the pioneering work on this condition.[3] Robertson of the Vanderbilt autonomic laboratories stated it was one of the most common conditions in young females.[4] Frolich *et al* reported patients who developed symptomatic postural tachycardia without any change in blood pressure.[5]

The condition is common in the age group 12–50 years with a female to male ratio of 5:1. It is common after stress such as sepsis, pregnancy, fever, surgery or trauma.[1 6] In some of the variants of POTS there is a functional mutation in the gene encoding for norepinephrine (noradrenaline) transportation. Ala 457pro mutation renders the transfers non-functional leading to altered heart rate as well as epinephrine (adrenaline) metabolites.[7]

PATHOGENESIS

Several theories have been suggested for the aetiopathogenesis of POTS.[8–11] Suggested factors that may lead to POTS include impaired vascular innervation, high plasma norepinephrine concentrations, α-receptor sensitivity, β-receptor hypersensitivity[5] and baroreceptor dysfunction.[12]

Impaired innervation of the veins or their response to sympathetic stimulation plays a key role in the aetiopathogenesis of POTS.[13 14] This leads to dependent venous pooling in the legs and reduced venous return to the heart. Thus there is redistribution of blood in the peripheral circulation. This could be worsened by capillary leakage, which leads to further hypovolaemia and causes reflex tachycardia. There is sympathetic cardiac activity without vasoconstriction, inducing a fall in central venous pressure. When this process continues, circulatory collapse may occur.

TYPES/VARIANTS

POTS can be classified as primary and secondary (box 1).[15] Partial dysautonomia can be caused by various stresses and has an immune mediated pathogenesis. Serum autoantibodies to α3 acetylcholine receptors of the peripheral ganglia have been found. The partial dysautonomic form can also affect adolescents. Symptoms initially worsen until the patient reaches 16 years of age and then gradually fade away. This is thought to be due to autonomic imbalance.

In some primary cases there is an hyperadrenergic state[16] leading to increased norepinephrine, which could be due to impaired clearance or decreased uptake by the synaptic cleft. These variants cause profuse sweating, anxiety and tremulousness and the diastolic pressure is high. This is thought to be a genetic disorder with involvement of family members. In these patients symptoms will be gradual and progressive. They will have orthostatic tachycardia as well as associated hypertension.

Evaluation

A detailed history of orthostatic intolerance (box 2), and specific findings on physical examination (box 3) and investigations (box 4), will give clues to the diagnosis.

Catecholamines should be measured in serum as well as in 24 h urine. In some variants of POTS there is a high concentration of catecholamines in blood as well as urine, and a high concentration of their metabolites like dihydroxyphenylglycol in urine. There is impaired response to tyramine with reduced clearance of norepinephrine at the

Abbreviations: CDC, US Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis; NMH, neurally mediated hypotension; NRI, norepinephrine reuptake inhibitor; POTS, postural orthostatic tachycardia syndrome; SSRI, selective serotonin reuptake inhibitor

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Box 1 Classification of postural tachycardia syndrome

Primary forms
- Partial dysautonomic
- Immune mediated pathogenesis
- Adolescence
- Hyperadrenergic state

Secondary forms
- Diabetes mellitus
- Amyloidosis
- Heavy metal poisoning
- Sjogren syndrome
- Hypermobility syndrome
- Paraneoplastic syndrome

Box 2 Symptoms of orthostatic intolerance

- Headache
- Fatigue
- Sleep disorder
- Weakness
- Hyperventilation/dyspnoea
- Tremulousness
- Sweating
- Anxiety/palpitation
- Dizziness/vertigo
- Pre-syncope/syncope

synaptic cleft. Sweat test as well as skin resistance can assess sudomotor function.

The 70° head up tilt table study has become the standard stress test for orthostatic integrity and thus of neurovascular competence. Patterns of heart rate as well as blood pressure response will be the key to identifying which type of orthostatic intolerance is present and thus for planning treatment for further management. In a control population there is an increase of only 15 bpm in heart rate in the first minute of standing and a further increase for 9 min. In POTS supine heart rate is greater than the normal control population and an increase of more than 30 bpm takes place between 1–5 min on 70° head uplift.[10 17]

DIFFERENTIAL DIAGNOSIS

Inappropriate sinus tachycardia syndrome

This is a clinical condition in which the heart rate increases out of proportion to physical needs. The automaticity of the sinus node is increased with increased cardiac sympathetic tone and blunted cardiac parasympathetic tone. Most of the features are similar to POTS, but in inappropriate sinus tachycardia syndrome, unlike POTS, the heart rate never exceeds 100 bpm in the supine position and increases on standing.

Chronic fatigue syndrome

In Europe, chronic fatigue syndrome (CFS) is called myalgic encephalomyelitis (ME). Orthostatic intolerance is a broad title for blood pressure abnormalities such as neurally mediated hypotension (NMH) and POTS. Orthostatic intolerance is a symptom of CFS. CFS is a chronic condition associated with high morbidity. The US Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of CFS include chronic debilitating fatigue lasting for 6 months or more, associated cognitive difficulties, pharyngitis, muscle pain, joint pain, headache, sleep disturbance and post-exercise malaise that is unexplained by other illness.

Patients with CFS have findings similar to the findings in patients with POTS during the head up tilt table test.[18 19] Patients with POTS may also have fatigue as a prominent clinical feature. Orthostatic tachycardia and autonomic abnormalities are present in both conditions, which is qualitatively difficult to differentiate. The heart rate variability and blood pressure variation is similar in both conditions. POTS fails to satisfy CDC criteria for CFS.[20]

TREATMENT

Drugs to avoid

Review all the drugs which the patient is taking. Drugs which can aggravate the symptoms of POTS are angiotensin-converting enzyme inhibitors, α- and β-blockers, calcium channel blockers, diuretics, monoamine oxidase inhibitors, tricyclic antidepressants and phenothiazines. Any such drugs should be stopped first. Once the diagnosis is confirmed aggravating factors such as dehydration, extreme heat and excess consumption of alcohol should be avoided.

Non-pharmacological measures

Patients should be advised to take aerobic exercise on a regular basis so that venous return from the lower extremities can be increased.[21] Patients with dysautonomic syncope can be advised to wear graded compressive hosiery extending up to the waist, thus helping to increase static pressure at the calf and decrease venous pooling. A high fluid intake should be encouraged with at least 3–5 g of common salt.

Pharmacotherapy

There is no specific drug treatment for POTS and it depends on the type of aetiology responsible for the syndrome.

Fludrocortisone has been tried with success.[22] It helps by increasing sodium and fluid retention as well as by sensitising α-adrenergic receptors. There are volume-expanding agents like vasopressin, and vasoconstriction drugs like midodrine, which can be gradually titrated upward until the maximum dose is reached. Midodrine is an α-1 receptor stimulating agent which helps to improve orthostatic tolerance.[23] Methylphenidate, a long acting α-agonist, also has been found to be effective.[24] Erythropoietin, which helps in volume expansion as well having a direct vasoconstrictive effect, is worth trying in patients who are refractory to other treatment. The major disadvantages of using erythropoietin are that it is expensive and has to be given subcutaneously.[25]

The hyperadrenergic form of POTS can be treated by β-blocking agents or drugs like labetalol, which have both α- and β-receptor blocking effects. In selected patients drugs such as clonidine can be used which act as sympatholytic agents.

It is suggested that the disturbances in central serotonin production and regulation affects the blood pressure and heart rate. Selective serotonin reuptake inhibitors (SSRIs) increase nerve communication and stimulation of the standing vasoconstriction reflex.[26 27] This reduces venous blood pooling and increases orthostatic tolerance. This effect is beneficial in controlling the symptoms in patients with POTS. SSRIs have been used in the past for the treatment of neurally mediated hypotension and syncope.[16] In symptomatic patients with POTS, the addition of an SSRI or a norepinephrine reuptake inhibitor (NRI) would be beneficial. An NRI is more beneficial in patients with POTS. Bupropion can be used and gradually titrated upward.

Combination of drugs such as SSRI and NRI (venlafaxine and duloxetine) are also effective in treating selected patient

Box 3 Signs to look for in suspected orthostatic intolerance

- Pallor
- Tachycardia
- Hypoxia
- Postural hypotension
- Arrhythmia
- Focal neurological deficit

Box 4 Investigations in a case of suspected orthostatic intolerance

- Blood: FBC, glucose levels, electrolytes, thyroid function tests, bone profile, serum cortisol
- ECG
- Cervical spine *x* ray
- Catecholamine levels (blood and urine)
- 70° head tilt table test
- EEG
- Brain CT scan
- Sweat test
- Sudomotor function test

CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; FBC, full blood count.

with POTS.[28] Patients are able to tolerate these agents with minimal side effects. Sometimes the combination of an SSRI with bupropion can be also used.

Pyridostigmine, an acetylcholine esterase inhibitor, has shown promising results in the management of POTS caused by post-viral infection and autoimmune disorders.[29] Low dose combination therapy is better than high dose monotherapy.

As patients' activities of daily living can become so compromised that they require help in all aspects, a multi-disciplinary approach to their treatment is required. It is essential to involve social workers, occupational therapists and clinical psychologists as well as legal counsellors.

PROGNOSIS

Prognosis depends on aetiology. Patients may have continuous symptoms. They may be unable to cope with their employment or normal daily activities. After post-viral episodes around 50% of patients recover in 2–5 years. Prognosis is good in adolescent patients. In the majority >90% respond to a combination of physical methods as well as pharmacotherapy. In the hyperadrenergic state patients will require life long treatment. In the secondary form the causative disorder has to be treated in order for patients to become symptom-free.

CONCLUSION

POTS is a heterogeneous disorder that disturbs normal autonomic control. This is a well-known disease entity which is under diagnosed and also underestimated. It is under diagnosed because symptoms mimic vasovagal syndrome. However, it is being diagnosed more and more by tilt table study or at syncope assessment clinics. Finally, treatment is dependent upon identifying the subtype and then pursuing a comprehensive management plan.

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REFERENCES

1 **Grubb BP**, Kosinski DJ, Boehm K, *et al.* The postural orthostatic tachycardia syndrome: a neurocardiogenic variant identified during head-up tilt table testing. *Pacing Clin Electrophysiol* 1997;**20**(9 Pt 1):2205–12.
2 **Karas B**, Grubb BP, Boehm K, *et al.* The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *Pacing Clin Electrophysiol* 2000;**23**:344–51.
3 **Low PA**, Schondorf R, Rummans TA. Why do patients have orthostatic symptoms in POTS? *Clin Auton Res* 2001;**11**:223–4.
4 **Robertson D**, Shannon JR, Biaggioni I, *et al.* Orthostatic intolerance and the postural tachycardia syndrome: genetic and environment pathophysiologies. Neurolab Autonomic Team. *Pflugers Arch* 2000;**441**(2–3 Suppl):R48–51.
5 **Frohlich ED**, Dustan HP, Tarazi RC. Hyperdynamic beta-adrenergic circulatory state. An overview. *Arch Intern Med* 1970;**126**:1068–9.
6 **Kanjwal Y**, Kosinski D, Grubb BP. The postural orthostatic tachycardia syndrome: definitions, diagnosis, and management. *Pacing Clin Electrophysiol* 2003;**26**:1747–57.
7 **Stober G**, Nothen MM, Porzgen P, *et al.* Systematic search for variation in the human norepinephrine transporter gene: identification of five naturally occurring missense mutations and study of association with major psychiatric disorders. *Am J Med Genet* 1996;**67**:523–32.
8 **Fouad FM**, Tadena-Thome L, Bravo EL, *et al.* Idiopathic hypovolemia. *Ann Intern Med* 1986;**104**:298–303.
9 **Pasternac A**, Tubau JF, Puddu PE, *et al.* Increased plasma catecholamine levels in patients with symptomatic mitral valve prolapse. *Am J Med* 1982;**73**:783–90.
10 **Jacob G**, Robertson D, Mosqueda-Garcia R, *et al.* Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. *Am J Med* 1997;**103**:128–33.
11 **Streeten DH**, Anderson GH Jr, Richardson R, *et al.* Abnormal orthostatic changes in blood pressure and heart rate in subjects with intact sympathetic nervous function: evidence for excessive venous pooling. *J Lab Clin Med* 1988;**111**:326–35.
12 **Muenter Swift N**, Charkoudian N, Dotson RM, *et al.* Baroreflex control of muscle sympathetic nerve activity in postural orthostatic tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2005;**289**:H1226–33.
13 **Low PA**, Caskey PE, Tuck RR, *et al.* Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol* 1983;**14**:573–80.
14 **Schondorf R**, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology* 1993;**43**:132–7.
15 **Grubb BP**, Kosinski DJ, Kanjwal Y. Orthostatic hypotension: causes, classification, and treatment. *Pacing Clin Electrophysiol* 2003;**26**(4 Pt 1):892–901.
16 **Goldstein DS**, Eldadah B, Holmes C, *et al.* Neurocirculatory abnormalities in chronic orthostatic intolerance. *Circulation* 2005;**111**:839–45.
17 **Furlan R**, Jacob G, Snell M, *et al.* Chronic orthostatic intolerance: a disorder with discordant cardiac and vascular sympathetic control. *Circulation* 1998;**98**:2154–9.
18 **Rowe PC**, Bou-Holaigah I, Kan JS, *et al.* Is neurally mediated hypotension an unrecognised cause of chronic fatigue? *Lancet* 1995;**345**:623–4.
19 **Stewart JM**, Gewitz MH, Weldon A, *et al.* Orthostatic intolerance in adolescent chronic fatigue syndrome. *Pediatrics* 1999;**103**:116–21.
20 **Fukuda K**, Straus SE, Hickie I, *et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;**121**:953–9.
21 **Grubb BP**. Dysautonaumic syncope. In: Grubb BP, Olshansky B, eds. *Syncope:mechanisms and management.* Armonk, New York: Futura Press, 1988:107–26.
22 **Freitas J**, Santos R, Azevedo E, *et al.* Clinical improvement in patients with orthostatic intolerance after treatment with bisoprolol and fludrocortisone. *Clin Auton Res* 2000;**10**:293–9.
23 **Grubb BP**, Karas B, Kosinski D, *et al.* Preliminary observations on the use of midodrine hydrochloride in the treatment of refractory neurocardiogenic syncope. *J Interv Card Electrophysiol* 1999;**3**:139–43.
24 **Grubb BP**, Kosinski D, Mouhaffel A, *et al.* The use of methylphenidate in the treatment of refractory neurocardiogenic syncope. *Pacing Clin Electrophysiol* 1996;**19**:836–40.
25 **Grubb BP**, Karas B. Preliminary observations on the use of erythropoietin in the treatment of refractory postural tachycardia syndrome. *Clin Auton Res* 1999;**9**:228.
26 **Vincent S**, Bieck PR, Garland EM, *et al.* Clinical assessment of norepinephrine transporter blockade through biochemical and pharmacological profiles. *Circulation* 2004;**109**:3202–7.
27 **Schroeder C**, Tank J, Boschmann M, *et al.* Selective norepinephrine reuptake inhibition as a human model of orthostatic intolerance. *Circulation* 2002;**105**:347–53.
28 **Grubb BP**, Karas BJ. The potential role of serotonin in the pathogenesis of neurocardiogenic syncope and related autonomic disturbances. *J Interv Card Electrophysiol* 1998;**2**:325–32.
29 **Raj SR**, Black BK, Biaggioni I, *et al.* Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. *Circulation* 2005;**111**:2734–40.