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CASE REPORT

Stimulant medication and postural orthostatic tachycardia syndrome: a tale of two cases

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Abstract Stimulant medication may mimic the tachycardia of postural orthostatic tachycardia syndrome. Two case histories illustrate how missing the clinical distinction between a primary dysautonomia and a medication effect may have avoidable adverse consequences.

Keywords Postural orthostatic tachycardia syndrome · Tachycardia · Central nervous system stimulants · Isoproterenol · Tilt table test

Introduction

Postural orthostatic tachycardia syndrome (POTS) is defined by a heart rate increment of 30 beats/min or more within 10 min of standing or upright tilt in the absence of orthostatic hypotension, often exceeding a heart rate of 120 beats/min [1]. The postural tachycardia is typically accompanied by symptoms of cerebral hypoperfusion, such as lightheadedness, blurred vision, cognitive difficulties, and generalized weakness; and of sympathetic hyperactivity, such as palpitations, chest pain, and tremulousness. The symptoms are orthostatic, i.e., brought on by standing and relieved by recumbency.

Symptoms and signs of sympathetic hyperactivity may occur also in patients taking sympathomimetic drugs, either by prescription or over-the-counter, although in contrast to POTS they lack a strongly postural correlation. The following cases of tachycardia exemplify how psychostimulant use can potentially mislead patients or physicians to reach an incorrect diagnosis and to embark on a misdirected treatment plan.

Case one

A 33-year-old obese woman with an 8-month history of fatigue and palpitations was referred for evaluation of suspected POTS after a tilt table test showed a heart rate of 130. The palpitations and tachycardia were accompanied by hand tremors, occurred equally in all postures, and were not relieved by recumbency. The symptoms had begun shortly after she started taking phentermine 37.5 mg orally once daily, which over 2 years had resulted in more than 100 pounds of intentional weight loss.

On further questioning, it turned out that the patient had taken phentermine 1 h prior to undergoing the tilt table test, which showed a baseline supine heart rate of 98 beats/min that increased in the upright posture to 126–130 beats/min without hypotension. When repeated off of phentermine, the tilt table test showed a supine heart rate of 81 beats/min without symptoms that increased only to 99–104 beats/min upright (Fig. 1). A primary diagnosis of POTS was excluded on the basis of the normal heart rate off of phentermine and the lack of postural symptoms. Resolution of palpitations once phentermine was discontinued supported the conclusion that the tachycardia was primarily a medication effect.

Case two

A 34-year-old woman developed symptoms of lightheadedness while sitting at a ball game on a hot summer day at 99 °F. Thereafter she complained of fatigue and

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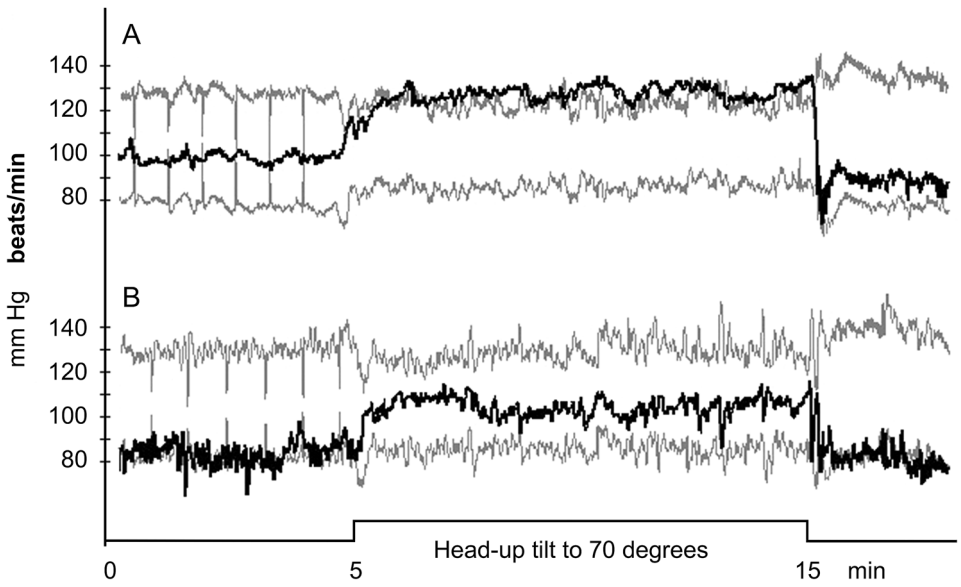

Fig. 1 Tilt table tests in case #1. Beat-to-beat blood pressure and heart rate tracings of tilt table tests in case #1 performed **a** on phentermine 37.5 mg daily and **b** off of phentermine. Systolic and diastolic blood pressures are indicated in *gray*, and heart rate is indicated in *black*

intermittent warm and tingling sensations throughout her body. Her symptoms were not associated with standing or relieved by recumbency.

Evaluation by her local cardiologist included a tilt table test at 80° inclination for suspected dysautonomia. The findings were normal at baseline, with heart rate in the 90 s, but when repeated during intravenous infusion of isoproterenol at 5 μg/min, heart rate increased to 180 beats/min with symptoms of panic, palpitations, and lightheadedness. On that basis she was diagnosed with POTS and treated with a series of interventions for dysautonomia. When her symptoms persisted on increased fluid intake and salt supplementation, her cardiologist implemented increasingly aggressive interventions. Despite treatment efforts, her symptoms worsened. She began to collapse without warning 3–4 times daily, resulting in frequent falls, all without injury. During the apparent syncopal episodes, she exhibited no seizure-like behavior, and glucose, blood pressure, and monitored electrocardiogram were normal. She stopped working, as did her husband to stay home and care for her full time.

She subsequently underwent a series of three atrioventricular junction ablation procedures for atrial tachycardia. When her symptoms continued, she received a peripherally inserted central catheter for daily intravenous saline infusions. The central line became infected with methicillin-resistant *Staphylococcus aureus* and was removed. Although she received intravenous vancomycin, the infection progressed to tricuspid valve endocarditis requiring surgical bioprosthetic tricuspid valve replacement. Postoperatively she developed atrial fibrillation and was treated with warfarin. She then underwent epicardial placement of a pacemaker with unipolar right atrial, right ventricular, and two left ventricular leads. The pacemaker was revised twice within the year because of painful lateral and superficial migration.

The patient traveled to our clinic for a second opinion, arriving by wheelchair. Her medications at that time consisted of fludrocortisone 0.4 mg daily, midodrine 15 mg thrice daily, pyridostigmine 60 mg twice daily, pindolol 2.5 mg twice daily, spironolactone or hydrochlorothiazide 25 mg as needed for swelling caused by fludrocortisone, and erythropoietin 6000 units weekly. As her symptoms were seemingly intractable despite this regimen, her referring physician inquired about adding droxidopa.

Neurological examination was normal. Blood pressure supine was 102/70 mmHg and heart rate 67 beats/min. During active standing there was no significant change in blood pressure or heart rate, even though at 3 min she complained that she felt that she was about to pass out. With encouragement she was able to continue standing for 5 min, at which time she became less responsive. Her head dropped forward, her eyes closed, her arms became limp, and she appeared to be on the verge of losing consciousness, during which her standing blood pressure was 104/76 mmHg and heart rate 70 beats/min and regular.

Testing included electrocardiography, which showed normal sinus rhythm at a rate of 82. Electroencephalography was normal. Quantitative sudomotor axon reflex responses were normal. Adrenergic responses to the Valsalva maneuver obtained by photoplethysmography demonstrated normal phase II and phase IV responses with a pressure recovery time of 1.6 s. Tilt table testing to 70° while off her usual medications, and without isoproterenol, demonstrated a stable hemodynamic profile. Baseline supine blood pressure was 103/61 mmHg and heart rate

60 beats/min. Her typical symptoms were reproduced at 3 min upright, at which point she reported that she was feeling extremely dizzy and tingly and on the brink of passing out. Beat-to-beat blood pressure measurements did not decline but remained steady at 111/68 mmHg at the climax of symptoms, while heart rate also remained normal at 68 beats/min.

The consistently normal heart rate and blood pressure measurements during symptoms established that her symptoms were not caused by a disorder of the autonomic nervous system. Her medications were subsequently weaned, which resulted in improvement of symptoms.

Commentary

Both of these patients fulfilled the diagnostic criteria for POTS [1], but the tachycardia was largely explained by psychostimulant medications that have known dose-dependent chronotropic effects. Phentermine, like its parent drug, amphetamine, is a trace amine-associated receptor 1 agonist that releases norepinephrine into the synapse and increased heart rate in the first case in both supine and upright postures. Isoproterenol is a β_1- and β_2-adrenoreceptor agonist that has the primary effect of increasing heart rate and is routinely used as a provocative agent to increase the sensitivity of tilt table testing in detecting neurally mediated syncope. Shen et al. found that, in patients with vasovagal syncope, isoproterenol resulted in a mean heart rate of 102 ± 19 beats/min as compared to 72 ± 13 beats/min without isoproterenol [2]. Sheldon found a similar effect in nomal subjects, whose heart rate reached 136 ± 20 beats/min on isoproterenol [3].

Many drugs, including those available over-the-counter, by prescription, or illicitly, are known to have the property of increasing the heart rate (Tables 1, 2). As atrial tachycardia is among their recognized adverse affects, some of these could potentially contribute to the clinical phenotype of POTS in susceptible patients. In particular, drugs that inhibit the norepinephrine transporter (NET) and increase plasma norepinephrine concentrations can induce hyperadrenergic symptoms including orthostatic tachycardia [4]. The combined literature of adults taking stimulants for attention deficit hyperactivity disorder indicates a typical increase in heart rate of 4–10 beats/min [5, 6]. Whereas there is good evidence that stimulant medications at prescribed doses in children, adolescents and adults are not associated with an increased risk of adverse cardiovascular events [5, 7, 8], outliers having larger changes in heart rate have been noted in approximately 5–10 % of patients [5, 6]. The frequency of emergency department visits for tachycardia is slightly increased among children prescribed stimulants [8]. Supraventricular tachycardia is an

Table 1 Adrenergic drugs that may contribute to sinus tachycardia

Norepinephrine releasing agents		
Amphetamine		
Dextroamphetamine		
Methamphetamine		
3,4-Methylenedioxymethamphetamine (MDMA)		
Phentermine		
Norepinephrine transporter inhibitors		
Drug	**K_i (nmol)**	**Classification**
High affinity ($K_i < 5$ nmol)		
Mazindol	1.1	NDSRI
Protriptyline	1.4	SNRI
Nortriptyline	1.7	SNRI
Desipramine	2.3	NRI
Moderate affinity (K_i 5–10 nmol)		
Atomoxetine	5.0	NRI
Lofepramine	5.4	SNRI
Duloxetine	5.9	SNRI
Tapentadol	8.8	NRI
Low affinity (K_i 10–500 nmol)		
Maprotiline	11.1	NRI
Reboxetine	13.4	NRI
Amoxapine	16.0	SNRI
Doxepin	29.5	SNRI
Clomipramine	45.9	SRI[a]
Imipramine	51.7	SNRI
Amitriptyline	61.3	SNRI
Milnacipran	111	SNRI
Viloxazine	155	NRI
Methylphenidate	345	NDRI
Very low affinity ($K_i > 500$ nmol)		
Tramadol	1242	SNRI
Desvenlafaxine	1491	SNRI
Cocaine	1720	NDSRI
Venlafaxine	2753	SNRI
Bupropion	>6000	NDRI
β1 and β2 adrenoreceptor agonists		
Albuterol		
Ephedrine		
Epinephrine		
Formoterol		
Isoproterenol		
Phenylpropanolamine		
Pirbuterol		
Pseudoephedrine		
Salmeterol		
Terbutaline		

Table 1 continued

Adenosine receptor antagonists
Caffeine
Theophylline
Monoamine oxidase A inhibitors
Isocarboxazid
Phenelzine
Trancypromine

NRI norepinephrine reuptake inhibitor, *SRI* serotonin reuptake inhibitor, *SNRI* serotonin norepinephrine reuptake inhibitor, *NDRI* norepinephrine dopamine reuptake inhibitor, *NDSRI* norepinephrine dopamine serotonin reuptake inhibitor

[a] Whereas clomipramine has low affinity for NET, its active metabolite desmethylclomipramine has high NET affinity. K_i indicates dissociation constant [15]. This list is not exhaustive

increasingly recognized complication of consuming excessive amounts of caffeinated energy drinks [9]. On the basis of these observations, it seems possible that some of the tachycardic outliers might have had preexisting POTS that went unrecognized.

On the other hand, not all sympathomimetic drugs cause tachycardia. Patients vary in their heart rate responses to stimulant medications, and some other stimulants, such as modafinil, may not worsen baseline or standing tachycardia [10]. Another example is the norepinephrine prodrug droxidopa, which increases blood pressure but has been shown not to increase heart rate [11].

The problem with making a diagnosis of POTS in a patient with tachycardia who is taking stimulant medication is that it follows a path of circular reasoning, i.e., the conditions of the diagnostic test may create the very profile of the disorder the physician is looking for. Whereas in these two cases the diagnosis of POTS was correct strictly by heart rate criteria, further variables were relevant to the critical distinction between a primary dysautonomia and a potentially reversible drug-induced disorder. First, the patients' symptoms were inconsistently related to postural changes. Second, symptoms were not responding to treatment. Third, syncopal symptoms in the presence of stable blood pressure and heart rate measurements were suggestive of a psychological condition. In this regard it is noteworthy that isoproterenol is considered a reliable and valid precipitator of symptomatic attacks in patients with panic disorder [12]. Unlike the tachycardia of panic disorder, that of POTS tends to be sustained while in the upright posture and is less likely to be accompanied by cognitive psychological symptoms such as fear [13]. The second case illustrates some of the potential medical hazards of missing this distinction and subjecting the patient to a series of escalating interventions.

Table 2 Anticholinergic drugs that may contribute to sinus tachycardia

Cholinergic receptor antagonists
Amantadine
Anisotropine
Atropine
Belladonna
Benztropine
Bornaprine
Brompheniramine
Butylscopolamine
Cimetropium
Chlorpheniramine
Clidinium
Darifenacin
Dicyclomine
Diphenhydramine
Glycopyrrolate
Hydroxyzine
Hyoscyamine
Ipratropium
Isopropamide
Mepenzolate
Methantheline
Methscopolamine
Orphenadrine
Oxybutynin
Pirenzepine
Prifinium
Propantheline
Propiverine
Scopolamine
Solifenacin
Terodiline
Tiotropium
Tolterodine
Triyexphenidyl
Trospium
Umeclidinium

Anticholinergic drugs increase heart rate by inhibiting vagal influence on the sinus node and include medications used to treat overactive bladder, irritable bowel syndrome, chronic obstructive pulmonary disease, and Parkinson's disease. This list is not exhaustive

Consideration of the effect of stimulant drugs on heart rate is even more important now that patients increasingly are investigating their symptoms on social media or medical websites or are monitoring their heart rates with inexpensive portable devices [14]. Additionally, healthcare professionals who are unfamiliar with autonomic disorders may not recognize the effects of medications on heart rate.

Although naming nonspecific or drug-induced symptoms "dysautonomia" may seem to provide explanatory value or medical validation, it is important to note that dysautonomia is not a discrete diagnosis or a single entity, but rather a broad category, much like weakness, fatigue, or dizziness.

In conclusion, evaluation of the patient with suspected POTS should include a careful history correlating symptoms with postural changes, consideration of the pharmacology of the patient's medications, and objective measurements of heart rate and blood pressure during postural challenge. Treatment of POTS requires an individualized and rational approach including a search for potentially reversible causes.

Compliance with ethical standards

Conflict of interest The corresponding author states that there is no conflict of interest.

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