CASE REPORT

A Tale of Two Syndromes: Lyme Disease Preceding Postural Orthostatic Tachycardia Syndrome

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The pathogenesis of postural orthostatic tachycardia syndrome (POTS) is poorly understood. However, it has been suggested that altered immune activity or denervation of the autonomic system following illness may be an important trigger. Patients infected with Lyme disease have a small incidence of post-Lyme disease syndrome that share similar characteristics to POTS. We report a short series of two women who present with persistent symptoms of orthostatic intolerance consistent with POTS after treated Lyme disease.

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postural orthostatic tachycardia syndrome; Lyme disease

INTRODUCTION

Postural orthostatic tachycardia syndrome (POTS) often presents as debilitating orthostatic intolerance characterized by orthostatic tachycardia in the absence of hypotension.^{1–5} Reflex sympathetic stimulation to decreased vascular tone plays a key role in the pathogenesis of POTS^{1–6} and leads to the characteristic symptoms in POTS patients. The initiation of this process is not well understood, however some have proposed that there is an infectious source to the pathophysiology of POTS.^{1,2,7} Lyme disease (LD) may contribute to the development of POTS. However, posttreatment LD syndrome (PLDS) represents a decline in the quality of life with symptoms that frequently overlap with those seen in POTS. Therefore, recognition and differentiation of the two is essential in long-term management of the symptomatic patient.

We present a two-case series of patients who suffered from LD and were successfully treated initially with antibiotics, but later developed orthostatic intolerance, eventually diagnosed as POTS.

CASE: #1

A 37-year-old female was seen in the emergency department with a 6-month history of progressively worsening episodic palpitations and lightheadedness upon standing from a sitting position. She stated that the palpitations were regular and fast without associated chest pain or shortness of breath, but her symptoms were accompanied with constant thirst and diaphoresis and occurred mostly premenstrual. She denied fever, abdominal pain, nausea, or diarrhea. Her medical history was significant for a completed treatment course of 100 mg doxycycline by mouth (PO) two time daily for 14 days for LD after noticing an erythema migrans rash 1-year prior at an outside hospital. Her surgical history includes two cesarean sections and a cholecystectomy. Her father had early heart disease with a myocardial infarction at the age of 42 and her mother had syncopal episodes associated with low blood pressure (BP). The patient was not taking any prescribed or over the counter medications, and has no allergies. She denied tobacco use, but occasionally uses alcohol, however states she had not used in 7 days. Notably,

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she adds that she recently quit her job in a bakery due to the above symptoms, as the conditions made her symptoms worse. Physical exam findings revealed an afebrile patient with a supine BP of 117/60 mmHg and a heart rate of 79 beats per minute (BPM), a sitting BP of 122/63 mmHg with a pulse of 95 BPM, and a standing BP of 132/79 mmHg with a pulse of 158 BPM. She had normal heart sounds, with a regular rhythm and rate and no murmurs or gallops. There was no jugular vein distension and her lungs were clear to auscultation. The rest of her physical exam was unremarkable including no neurologic deficits.

She was admitted to the hospital for workup of her symptoms. Initial laboratory data obtained revealed a normal complete blood count, serum potassium of 3.5 mEq and an otherwise normal chemistry panel. Her creatinine kinase was 246 U/L (24–173 U/L) and troponin-I was <0.30 (<0.30 ng/mL). Further testing revealed a thyroid-stimulating hormone of 2.28 mIU/L (0.27–4.20 mIU/L), a cortisol of 6.4 ug/dL (6.2–19.4 ug/dL), plasma renin of 0.27 ng/mL per hour (0.25–5.82 ng/mL per hour), an 8 am upright aldosterone level of 3 ng/dL (<28 ng/dL), and a aldosterone/plasma renin activity ratio of 7.4 (0.9–28.9). Venous catecholamine levels were examined in the supine and standing position. Supine serum metanephrine was 54 pg/mL (<57 pg/mL), normetanephrine of 145 pg/mL (<148 pg/mL), and total metanephrine was 199 pg/mL (<205 pg/mL). Supine levels were also within normal limits revealing a serum metanephrine, normetanephrine, and total metanephrine of 53, 125, and 178 pg/mL, respectively. Urinary toxicology was positive for cannabinoids. Lyme titers were not obtained. An electrocardiogram revealed sinus tachycardia with normal PR, QRS, and QT intervals and without ST-T wave changes.

A diagnosis of POTS was suspected, and electrophysiology input helped to support the diagnosis. This patient underwent symptomatic treatment focused on intravascular volume expansion and adrenergic antagonism. Propranolol, 40 mg twice daily was initiated. Patient was instructed to increase oral intake to nine glasses of water daily and to avoid concentrated carbohydrates. Outpatient conditioning training program was recommended and was started during her admission. At the time of discharge, the patient had symptomatic improvement.

CASE: #2

A 17-year-old female with a history of treated LD has had complaints of dizziness, headache, difficulty with memory, and presyncope for approximately 5 months is now seen in the emergency department with palpitations and shortness of breath for 1 week. Her medical history includes acne and scoliosis. Her LD was treated with a complete course of 100 mg doxycycline PO two times daily for 14 days after the manifestation of a erythema migrans rash 8 months ago. She had been using minocycline for 2 years for her acne of which she recently discontinued 2 weeks prior to presentation; around the time her symptoms began. Other medications included naprosen 550 mg as needed for her headache. She denies tobacco, alcohol, or drug use, but states occasional caffeine use. She is a high school student and lives at home with her parents. Her father has a history of hypertension, but there is no family history of arrhythmia, syncope, or sudden cardiac death.

On physical exam the patient was resting comfortably and was found to be afebrile with a respiratory rate of 16 breaths per minute, and a supine heart rate of 74 BPM, and a BP of 131/74 mmHg, which changes to a heart rate of 98 BPM and a BP of 116/73 mmHg upon standing. She has a normal head and neck exam with clear lungs to auscultation. Her cardiac exam reveals normal heart sounds and a regular rhythm with no added heart sounds and normal jugular venous pressure. Her pulses were equal 2+ in all extremities. She was alert and oriented with no focal neurologic deficits including no vertigo.

Her labs revealed normal serum chemistry values, as well as a normal complete blood count. Her Lyme antibody had an index of 0.50 (0.91–1.09 is equivocal with >1.1 being positive). Venous catecholamine levels were not investigated. An ECG showed normal sinus rhythm with no conduction defects. An MRI of her head revealed no abnormalities. Additionally, a transthoracic echocardiogram revealed no structural abnormalities and had an ejection fraction of 65%.

Tilt table testing was performed in clinic after the discharge from the emergency room. Her supine heart rate and BP was 88 BPM and 127/72 mmHg, respectively. At 60° head up tilt, her BP became 124/84 mmHg with her heart rate increasing to 120

Table 1. Overlapping Symptoms of POTS and PLDS

PLDS ⁸	POTS (Ref. 2)
Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy	Sustained heart rate increase of ≥ 30 BPM or increase of heart rate to ≥ 120 BPM within 10 minutes of assuming an upright posture
Fatigue	Fatigue
Widespread musculoskeletal pain	Light headedness or dizziness
Anxiety	Anxiety and migraine headaches
Impaired quality of life	Impaired quality of life
Complaints of cognitive difficulties	Palpitations

PLDS = post-Lyme disease syndrome; POTS = postural orthostatic tachycardia syndrome; BPM = beats per minute.

BPM accompanied with dizziness for 25 minutes. The tilt was then ended with a repeat supine BP of 114/65 mmHg and a heart rate of 80 BPM. The diagnosis of POTS was made and she was medically treated with midodrine 7.5 mg in the morning and early afternoon, with another 5 mg in the late afternoon and again in the evening. She was educated to maintain a gluten free diet with water supplementation of two 8 ounce glasses of water every 2 hours to be consumed over 5 minutes for a total of 10 glasses, and to begin an exercise routine.

DISCUSSION

Borrelia burgdorferi, the spirochete responsible for the tick-borne illness LD, results in a multisystem disorder that frequently begins with erythema migrans and may later involve the nervous, musculoskeletal, and cardiovascular systems. While LD usually responds to antibiotic treatment, there is a subgroup of patients who later develop PLDS. The syndrome describes patients who experience prolonged subjective symptoms of myalgias, headache, fatigue, irritability, and cognitive dysfunction following treated LD.⁸ This condition of subjective complaints is defined by a *Borrelia*-associated infection adequately treated with antibiotics while objective findings of other diseases are absent.⁹ These patients initially improve with the use of antibiotics and have resolution of physical symptoms and signs of LD. However, after a quiescent period, they again develop symptoms of fatigue, pain, and cognitive dysfunction. Interestingly, these symptoms usually develop within 6 months following successful treatment with antibiotics.⁸ The exact etiology of this syndrome remains unclear. The best estimates of the prevalence of PLDS come from studies

of patients with erythema migrans who received appropriate antibiotic treatment, of which 10–20% of such patients have persistent or intermittent subjective symptoms of mild to moderate intensity 12 months after completion of therapy.^{10–13}

There are approximately 500,000 patients in the United States known to suffer from POTS,^{1,2,14} with the majority of cases showing a female predominance of 5:1, and ages between 20 and 50 years.^{1–3,6,14,15} The symptoms of POTS frequently include palpitations, fatigue, weakness, and impaired quality of life in more than 50% of patients.^{3,4} Many of these symptoms can be vague and may overlap with the symptoms seen in other diseases, but importantly with PLDS¹⁶ (Table 1). The etiopathogenesis between the two syndromes may have a common immunological connection, though remains theoretical at this time. Theories suggest bacterial persistence or autoimmune phenomena such as molecular mimicry causing antibody reactivity to borrelial antigens from the original spirochetal infection that may exist in PLDS.^{17,18} Antineural antibody reactivity was found to be significantly higher in the patients suffering from PLDS (49%) as compared to post-Lyme healthy individuals (18.5%) or healthy individuals without a history of LD (15%) with a $P < 0.01$.¹⁹ The relationship between PLDS and POTS may be explained by this interaction.

Primary neuropathic and secondary type POTS is commonly reported to be precipitated by a febrile illness, often viral,^{1–3,5} and peripheral autonomic deinnervation, and has been observed with medical illnesses and autoimmune diseases.^{1–3} Studies suggest that the pathophysiology in some POTS patients is related to the production of enzyme-linked immunosorbent assay positive autoantibodies that block the acetylcholine receptor,²⁰ and against muscarinic

and $\beta 1/2$ -adrenergic receptors.²¹ The activation of autoantibodies to these receptors produce vasodilation of the vasculature that may contribute to the autonomic changes seen in POTS.²² Additionally, patients with LD have shown evidence of lymphoplasmocellular infiltrates in the autonomic ganglia,²³ resulting in sympathetic denervation in the lower extremities and kidneys causing significant sympathetic stimulation related to prolonged orthostatic stress. Consequently, the increased redistribution of blood in the peripheral circulation and relative hypovolemia, cause venous return to the heart to abruptly fall leading to a reflex tachycardia and sympathetic cardiac activity without vasoconstriction.^{1, 15, 17, 24}

The patients above report a quiescent period of greater than 1 year after their initial infection with LD. Their persistent or relapsing symptoms greater than 6 months after LD categorizes them into the PLDS,⁸ resulting in orthostatic intolerance seen in POTS. Only one other case series linking PLDS and POTS has been described,²⁵ thus appreciation and recognition of orthostatic intolerance in this subset of patients may contribute to early and directed management.

The treatment of PLDS associated POTS most often consists of both pharmacologic and nonpharmacologic corrections of autonomic imbalance with treatment tailored towards educating the patient about avoidance of aggravating and precipitating factors. Several double-blinded controlled trials of patients with PLDS have shown no benefit after repeat antibiotic treatment,^{26, 27} and no effective therapies have been identified. Intravascular volume expanders are used effectively in POTS, and include fludrocortisone (Grade 2C).²⁸ Commonly, β -adrenergic receptor antagonists such as propranolol and vasoconstrictors such as midodrine are also effective in the pharmacologic treatment of POTS. Our patients underwent a variety of symptomatic treatments focused on intravascular volume expansion, adrenergic antagonism, and avoidance of activities that negatively impact the patient's quality of life.

Each of our patients had an acute episode of LD presenting with erythema migrans without cardiac complications, and with an initial response to the course of antibiotics leading to an asymptomatic period ranging from 6 months to 1 year, however, subsequently developed symptoms consistent with POTS.

Some limitations should be acknowledged in our study. This was a retrospective report on a small number of patients. We did not check for synaptic antibodies, as the report was retrospective in nature. Also, questions such as why few patients with PLDS may develop POTS remains unanswered from this report. However, having a high index of suspicion for POTS in this subset of patients may lead to the initiation of appropriate treatment in patients with PLDS and subsequent improvement in their symptoms and quality of life.

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