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Vitamin B1 deficiency in patients with postural tachycardia syndrome (POTS)

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ABSTRACT

Objective: POTS is a heterogeneous disorder of the autonomic nervous system that can result from multiple etiologies. An increased prevalence of vitamin B12, vitamin D 25-OH and iron deficiencies has been observed in patients with POTS. This study examined the prevalence of vitamin B1 deficiency and assessed response to vitamin B1 supplementation in the deficient POTS patients.

Methods and Results: Medical records of 65 consecutive patients with POTS evaluated at our clinic were reviewed. In this cohort (mean age 32, range 13–54 years; 89% female), 6% had vitamin B1 deficiency, and one of four deficient patients experienced significant improvement of POTS after oral vitamin B1 supplementation.

Conclusion: A small subset of patients with POTS may have vitamin B1 deficiency. Testing for vitamin B1 deficiency and correcting the deficiency is recommended.

1. Introduction

Vitamin B1 (thiamine) is a water-soluble vitamin that plays a critical role in energy metabolism and, therefore, in the growth, development, and function of cells [1]. Since very little vitamin B1 is stored in the body and thiamine depletion can occur within 14 days, vitamin B1 needs to be continuously supplied from dietary sources. Foods that contain thiamine include beef, yeast, legumes, milk, nuts, oats, oranges, pork, rice, seeds, wheat, and whole-grain cereals. In industrialized countries, food made with white rice or white flour is typically enriched with thiamine [1].

Vitamin B1 deficiency is associated with alcoholism, malnutrition, eating disorders, hyperemesis gravidarum, and bariatric surgery complication [2,3]. Vitamin B1 deficiency can also occur in the elderly and in patients with congestive heart failure [4,5]. While there have been reports of vitamin B12, vitamin D and iron deficiencies in patients with POTS, the prevalence of vitamin B1 deficiency and response to vitamin B1 supplementation have not been determined [6–8].

2. Methods

2.1. Patients

Sixty-five consecutive patients with POTS who were evaluated and followed by the author at Dysautonomia Clinic between 2011 and 2012 were included in the study. Diagnosis of POTS was made through a tilt table test demonstrating a greater than 30 bpm increase in heart rate from supine to standing position within 10 min of tilting [9]. All patients had greater than 6 months history of symptoms of POTS [9].

Medical records were reviewed, and whole blood vitamin B1 test was extracted from the patient charts. Since we routinely obtain a thorough diagnostic workup for our patients, including a serum vitamin panel, all patients with POTS at our clinic have had a whole blood vitamin B1 test obtained through Quest Diagnostics Laboratory. Clinical features of patients with POTS who were found to have vitamin B1 deficiency on a blood test and their response to supplementation with oral vitamin B1 (thiamin hydrochloride) 100 mg daily for 4 weeks were assessed. Response to treatment was extracted from the clinical notes consisting of follow-up neurology visits, at which time the patients reported whether they noticed any changes in their symptoms or whether no changes had taken place since vitamin B1 supplementation.

2.2. Vitamin B1 testing

Whole blood vitamin B1 (thiamine) testing is considered superior to currently available alternative tests for assessing thiamine status [10]. Serum or plasma thiamine tests have poor sensitivity and specificity, and <10% of blood thiamine is contained in plasma. Transketolase determination, once considered the most reliable means of assessing thiamine status, is now considered an
inadequate method [10,11]. Transketolase is less sensitive than high-performance liquid chromatography, has poor precision, and specimen stability concerns [10–12]. High-performance liquid chromatography analysis of thiamine diphosphate in whole blood or erythrocytes is the most sensitive, specific, and precise method for determining the nutritional status of thiamine and is a reliable indicator of total body stores [12]. This assay specifically targets and quantitates the active form of vitamin B1 (thiamine diphosphate) as an indicator of vitamin B1 status [12].

3. Results

In a cohort of 65 consecutive patients with POTS, mean age 32 (age range 13–54 years), 89% female, 4 (6%) tested positive for vitamin B1 deficiency via whole blood vitamin B1 testing. The vitamin B1 deficiency was mild in all 4 patients, with values between 72–77 nm/L (normal range 78–185 nm/L). Clinical features of 4 patients with POTS and vitamin B1 deficiency are outlined in Table 1. Two patients also had confirmed small fiber neuropathy diagnosed via a skin biopsy, and two patients had co-morbid neurocardiogenic syncope. Record review was also remarkable for serum vitamin D25-OH deficiency in 3 of 4 patients. Other vitamin and mineral levels, including vitamin B12, vitamin B6, vitamin E, iron, copper, magnesium, folate and homocysteine level were within the normal range in all 4 patients. The patients also had negative markers of inflammation and autoimmunity, including CRP, ESR, RF and ANA.

Although vitamin B1 was supplemented in all four patients, only one patient (patient 1) reported significant improvement in all of her symptoms; the other patients noticed no significant change 4 weeks after supplementation. All four patients had their vitamin B1 level retested within 3–12 months after supplementation, and all four patients had vitamin B1 level within the normal range.

The patient whose symptoms improved with the use of vitamin B1 noted improvement at week 2 after supplementation, followed by continuous improvement thereafter. She was able to discontinue all her medications, return to college full-time, and subsequently begin an exercise training program. Prior to initiating vitamin B1, her clinical features included postural tachycardia, pre-syncope, shortness of breath, dizziness, fatigue, headaches, sleep disturbance and anxiety. She was home-bound and was unable to work, attend school, drive, or exercise. She frequently sought care at the emergency room for tachycardia, presyncope, migraine headaches, nausea and vomiting, and her medications prior to vitamin B1 supplementation included atenolol, topiramate, and lorazepam, with the doses being constantly adjusted depending on her symptom severity. After vitamin B1 supplementation, she reported a near complete resolution of all her symptoms and feeling ‘normal’. She continued with vitamin B1 100 mg once a day supplementation for the next 4 years, and her substantial improvement persisted. During this time, she did not experience any exacerbation of POTS, even after common viral infections, and did not require the use of beta blockers or benzodiazepines. She continued with non-pharmacologic measures of high sodium diet, liberal fluid intake and an exercise program.

4. Discussion

POTS is a heterogeneous disorder of the autonomic nervous system characterized by orthostatic tachycardia, presyncope, and non-orthostatic symptoms, such as weakness, headache, nausea, dizziness, sleep disturbance, and fatigue [13]. POTS affects an estimated 1 000 000–3 000 000 Americans, 80–85% of whom are women of reproductive age. POTS can be viewed as ‘the final common pathway’ syndrome, arising from multiple etiologies, one of which may include mitochondrial disorders [14,15]. Pathophysiologic mechanisms resulting in POTS consist of the autonomic neuropathy, hypovolemia, elevated sympathetic tone, mast cell activation, and an autoimmune process with the presence of various antibodies [15]. These mechanisms are not mutually exclusive and may occur in combination. About 50% of POTS patients have small fiber neuropathy, 20% have co-morbid autoimmune disorders, and at least 18% have Ehlers-Danlos syndrome [16–18]. POTS may be triggered by a virus, surgery, pregnancy, trauma or vaccination and can often result in significant disability and functional impairment for the patients, 25% of whom are unable to work or attend school [13,15,19].

Vitamin deficiencies have been described in patients with POTS. In a study of 125 adolescents, vitamin B12 levels were significantly lower in the patient group compared with the control group (47.2% vs. 18%, P <.001) [6]. In another study of 32 adolescents, patients with POTS, when compared with normal US pediatric population, had higher prevalence of low iron storage (50% vs. 14%), iron deficiency (25% of teenage girls vs. 9%, and 16% of teenage boys vs. 1%), and anemia (18% of teenage girls vs. 1.5%, and 43% of teenage boys vs. 0.1%)

### Table 1. Patients with POTS and vitamin B1 deficiency.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Diagnoses</th>
<th>WB Vit B1 (normal range 78–185 nm/L)</th>
<th>Response to oral vitamin B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24/F</td>
<td>POTS, migraine with and without aura</td>
<td>75</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>2</td>
<td>35/M</td>
<td>POTS, NCS, SFN</td>
<td>72</td>
<td>No change</td>
</tr>
<tr>
<td>3</td>
<td>45/M</td>
<td>POTS, migraine without aura</td>
<td>77</td>
<td>No change</td>
</tr>
<tr>
<td>4</td>
<td>32/F</td>
<td>POTS, NCS, SFN, chronic daily headache</td>
<td>76</td>
<td>No change</td>
</tr>
</tbody>
</table>

A study of 188 adolescents with fatigue and/or orthostatic intolerance found that 47% had iron insufficiency with low iron stores, 22% were iron deficient and 22% had hypovitaminosis D (25-hydroxyvitamin D ≤ 20 ng/mL) [8]. The authors reported a significant association between hypovitaminosis D and orthostatic intolerance ($p = 0.024$). In a case report, one patient with POTS presented with low plasma choline and betaine level and was found to have lower choline transporter-like protein 1/solute carrier 44A1 (CTL1/SLC44A1), mRNA expression and impaired mitochondria function [20]. In another case report, a patient with POTS and low I.25(OH)(2) vitamin D3 level, but normal 25(OH) vitamin D level, experienced significant improvement of POTS and was able to return to work full-time after initiation of calcitriol 0.25 mg orally daily for one month [21].

Clinical features of severe vitamin B1 deficiency include cardiovascular and neurologic complications, such as heart failure, neuropathy, ataxia, paralysis, delirium and confusion. Wernicke's encephalopathy, defined as a triad of encephalopathy, ataxic gait and oculomotor dysfunction, typically occurs in patients with chronic alcohol abuse or severe malnutrition. Although the full-blown classical vitamin B1 deficiency syndromes occur relatively rarely in the United States and only in patients with severe thiamine deficiency, marginal deficiency (in which thiamine stores are sufficiently depleted to affect a patient's well-being and to be detected on laboratory tests, but not depleted enough to create the classical clinical signs) may give rise to symptoms that are more vague and often overlooked [22]. These symptoms include mental fatigue, emotional lability, paresthesias, chest pain, tachycardia, generalized weakness, myalgias, back pain, nausea, vomiting, and decreased ability to perform physical activity or work [22]. Most of these non-specific symptoms commonly occur in patients with POTS and other neurologic disorders, including small fiber neuropathy, fibromyalgia and chronic fatigue syndrome, and as such, it is important to rule out vitamin B1 deficiency in this patient population.

In this study, the prevalence of vitamin B1 deficiency in patients with POTS was 6%, which is higher than what may be expected in the healthy non-elderly population in the developed countries where thiamine is widely available through fortified food. The patients in our study had no risk factors for vitamin B1 deficiency since they consumed no alcohol, had no significant GI disorders that would affect thiamine absorption, no history of bariatric surgery or eating disorders and no co-morbid diabetes or congestive heart failure. Currently, the relationship between vitamin B1 deficiency and POTS in these patients is unclear. We hypothesize that in a subset of patients with POTS, energy production and metabolism may be altered, whether through mitochondrial dysfunction or genetic abnormalities at the cellular level. Furthermore, there is substantial evidence that aside from its critical role in metabolism of simple carbohydrates and the citric acid cycle, thiamine is an important modulator of acetylcholine release, thereby affecting synaptic transmission [23]. Thiamine deficiency is also found to induce an early functionally significant central muscarinic cholinergic lesion, affect neuronal transmission at the peripheral ganglia and cause vascular dysfunction via reduced nitric oxide production [24–26]. These findings suggest that thiamine plays an important role in the function of the autonomic nervous system and may be a factor in the pathophysiology of POTS. Precisely how thiamine deficiency can potentially lead to POTS needs to be investigated further.

Limitation of this study is a lack of healthy, age-matched controls with measured whole blood vitamin B1 test results. However, we believe, based on the available data of prevalence of vitamin B1 deficiency in healthy population, that if we were to have a control group, their vitamin B1 level would be in the normal range, given the widespread availability of vitamin B1 in the American diet. Another limitation is that we did not assess whether there were any objective improvement in the outcomes of a tilt table test or a skin biopsy after vitamin B1 was replaced. Both of these limitations would be best addressed in the context of a future prospective randomized placebo-controlled trial investigating the efficacy of vitamin B1 supplementation in patients with POTS.

In this cohort, only one of four patients (25%) had significant improvement with oral vitamin B1 supplementation. Since the choice of pharmacotherapy for POTS is quite limited, with many patients experiencing various adverse effects from medications, treatment with vitamins and supplements may present a potentially effective, well-tolerated, and cost-effective option for selected patients. Further research is necessary to determine the utility and efficacy of vitamin B1 supplementation, as well as other vitamins and supplements commonly used in patients with POTS.

Disclosure statement
No potential conflict of interest was reported by the author.

Notes on contributor
Blitshteyn, PhD, is a clinical assistant professor of neurology and director of Dysautonomia Clinic. His research interests include neurology, autonomic disorders, POTS, headache medicine and women's health.

References


