Postural Orthostatic Tachycardia Syndrome (POTS) and Vitamin B$_{12}$ Deficiency in Adolescents

WHAT’S KNOWN ON THIS SUBJECT: Studies have shown dysfunction in the baroreflex mechanism and the autonomic nervous system, particularly in the sympathetic nervous system, in the pathophysiology of chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and syncope.

WHAT THIS STUDY ADDS: Vitamin B$_{12}$ deficiency is associated with postural orthostatic tachycardia syndrome in adolescence.

abstract

OBJECTIVE: Vitamin B$_{12}$ is involved in the production of adrenaline from noradrenaline. It is the cofactor involved in catecholamine degradation and plays a role in myelin synthesis. The current study aimed to investigate the association between vitamin B$_{12}$ levels and postural orthostatic tachycardia syndrome (POTS) during adolescence when accelerated myelin synthesis increases the vitamin B$_{12}$ need.

METHODS: One hundred twenty-five patients (mean age 11.1 ± 2.3 years; 60% female) reporting short-term loss of consciousness and diagnosed with vasovagal syncope based on anamnesis with a normal distribution and 50 control subjects (mean age 10.94 ± 2.5 years, 62% female) were included in this study. Serum vitamin B$_{12}$, folic acid, and ferritin levels were measured prospectively in addition to other tests. We defined vitamin B$_{12}$ deficiency as a serum level <300 pg/mL.$^{1-4}$

RESULTS: Vitamin B$_{12}$ levels were significantly lower in the patient group compared with the control group (47.2% vs 18%, $P<.001$). In the patient group, children with the POTS pattern had significantly lower vitamin B$_{12}$ levels compared with children without the POTS response ($P=.03$).

CONCLUSIONS: Vitamin B$_{12}$ deficiency in patients with POTS may lead to sympathetic nervous system baroreceptor dysfunction. Pediatrics 2014;133:e138–e142

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KEY WORDS: child, postural orthostatic tachycardia syndrome, tilt table test, vasovagal syncope, vitamin B$_{12}$

ABBREVIATIONS: CFS—chronic fatigue syndrome
CoA—coenzyme A
COMT—catecholamine-O-methyltransferase
HUTT—head-up tilt test
POTS—postural orthostatic tachycardia syndrome

Dr Öner designed the study, planned the concept, and prepared and edited the manuscript; Dr Guven contributed to data acquisition and analysis; Dr Tavli designed the study and contributed to manuscript design and review; Dr Mese reviewed the manuscript and contributed to the literature overview and data analysis; Dr Yilmazer contributed to the manuscript design and data analysis; and Dr Demirpence searched the literature and made statistical analysis.

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Postural orthostatic tachycardia syndrome (POTS) is one of the most common forms of chronic orthostatic intolerance in the general population. POTS is defined as a heart rate increase of at least 30 beats per minute (or a rate that exceeds 120 beats per minute) that occurs in the first 10 minutes of upright posture or the head-up tilt test (HUTT).

Patients diagnosed with POTS exhibit an abnormal sympathetic response. Despite the increased sympathetic response of the heart, there is a disrupted peripheral vascular response, and therefore selective peripheral neuropathy is considered present in patients with POTS.

A study in adolescents showed sympathetic nervous system dysfunction in the physiology of chronic fatigue syndrome (CFS) by demonstrating an abnormal catecholaminergic-mediated thermoregulatory response at resting state and in the local cooling test on skin. Furthermore, CFS has been associated with catecholamine-β-methyltransferase (COMT) and B2 adrenergic polymorphism.

Syncope, POTS, and CFS have similar etiologies but exhibit distinct clinical presentations. Previous studies have demonstrated that adolescent patients with CFS often exhibit POTS findings during the HUTT. Neurally mediated hypotension has been shown to be the most common cause of unexplained recurrent syncope, and overlapping findings have been found in CFS and neurally mediated hypotension.

When defining hyperadrenergic orthostatic hypotension with increased plasma levels of epinephrine and norepinephrine, Streeter found that orthostatic hypotension developed due to the accumulation of blood resulting from anatomic or functional postganglionic denervation in the lower-limb veins. Vitamin B₁₂ is involved in the methylation reaction regulated by S-adenosylhomocysteine and S-adenosylmethionine. This reaction plays a crucial role in the myelin formation associated with neurologic deficits in patients with vitamin B₁₂ deficiency. Dysfunction in unmyelinated sympathetic neurons, however, has not been shown. Toru et al suggested that vitamin B₁₂ is required for the physiologic function of sympathetic postganglionic fibers.

In vitamin B₁₂ deficiency, myelin synthesis is disrupted and may lead to baroreflex dysfunction, affecting the sympathetic regulation of blood vessels and the autonomic nervous system, as observed in demyelinating disorders. Furthermore, the blood level of noradrenaline is particularly increased because of the dysfunction of enzymes requiring vitamin B₁₂, such as phenylethanolamine n-methyltransferase (involved in the conversion of noradrenaline to adrenaline) and COMT (involved in adrenaline-noradrenaline-dopamine degradation).

On the basis of these findings, we investigated the association between B₁₂ levels and POTS in adolescents.

METHODS

This prospective study covers the period between November 2009 and May 2010. We included 125 patients who were admitted to our unit for an evaluation of vasovagal syncope. Fifty healthy subjects who underwent a cardiovascular assessment for an innocent murmur were also included in this study. The parents of the patients and subjects in the control group were informed about the clinical condition and the possible causes. Informed consent was obtained from the patients for the tilt test and the blood tests and from the control subjects for the blood tests. A comprehensive anamnesis, complete physical examination, 12-lead electrocardiogram, transthoracic echocardiogram, tilt table test, and blood tests were performed in all patients. Patients with neurologic, psychiatric, and cardiovascular disorders were excluded from the study. The inclusion criteria were as follows: (1) history of vasovagal syncope; (2) aged <18 years; (3) <6 months between the index episode of syncope, presyncope, and the first assessment; and (4) no history of infection at the time of blood collection.

The physical examination, 12-lead electrocardiography, and transthoracic echocardiography were normal in all subjects enrolled in the study.

Study Design

The history of the initial attack was obtained from the patient, parents, and other bystanders. All children were reevaluated and classified according to the tilt table results. Within the patient group, patients with a positive tilt test (36 of 125) were compared with those with a negative tilt test (69 of 125), and patients with POTS (35 of 125) were compared with those without POTS (90 of 125). We also compared vitamin B₁₂ levels between the groups.

Tilt Table Test

All children were tested in the morning after fasting for 8 hours. Heart rate was monitored continuously, and blood pressure was recorded every 2 minutes by using an automatic sphygmomanometer. The children were kept in a supine position for 10 minutes. They were then tilted to a head-up position at 85° for 20 minutes. Previous reports showed that this protocol was associated with optimal and adequate sensitivity rates. A positive response was defined as the occurrence of syncope or presyncope during the HUTT, accompanied by ≥1 of the following signs: (1) bradycardia, characterized by a heart rate <75 beats per minute in children aged 4 to 6 years, a heart rate <65 beats per minute in children aged 7 to 8 years, and a heart rate <60
beats per minute in children aged >8 years, sinus arrest, degree II or greater atrioventricular block, and asystole for 3 seconds; (2) hypotension, defined as a systolic blood pressure ≤80 mm Hg or a drop of >15 mm Hg and/or a diastolic blood pressure <50 mm Hg. A cardioinhibitory response was defined as an abrupt decrease in heart rate. A vasodepressor response was defined as a decrease in blood pressure. The mixed pattern was characterized by a decrease in both heart rate and blood pressure. The vasodepressor response was defined as a decrease in blood pressure. The cardioinhibitory response was defined as a decrease in heart rate. A vasodepressor response was defined as a decrease in blood pressure. The mixed pattern was characterized by a decrease in both heart rate and blood pressure.

POTS was diagnosed on the basis of a heart rate increase >30 beats per minute or a maximum heart rate >120 beats per minute, causing lightheadedness, fatigue, presyncope, and dizziness in the absence of profound hypotension.

**Analytical Methods**

Blood samples were obtained from each patient for the analysis of serum B12 levels, the folic acid level, the ferritin level, hemoglobin, hematocrit, and mean corpuscular volume. All samples were collected after 8 hours of fasting. A low vitamin B12 level was defined as <300 pg/mL. An ABX Pentra 120 (Horiba) device was used for the blood count, and a Roche E-601 analyzer was used for the detection of vitamin B12 levels.

**Statistical Analysis**

SPSS for Windows 15.0 (SPSS, Chicago, IL) was used for the statistical analysis. The results of the descriptive analysis were expressed as the mean ± SD for numerical variables. The mean values of variables with normal distribution were compared between groups using Student’s t test; variables with abnormal distribution were assessed using the Mann-Whitney U test. The Kruskal-Wallis test was used to determine significant differences between continuous variables. If the overall P value was significant, the Mann-Whitney U test was conducted to evaluate differences among groups. The χ² test was performed for each categorical variable.

**RESULTS**

Among the 125 patients with syncope, 50 (40%) were boys, and 75 (60%) were girls. There was no difference between the patient and control groups in terms of age or gender distribution (Table 1). During the HUTT, a cardioinhibitory response was observed in 9 of the 125 children in the neurally mediated syncope group, a vasodepressor response was observed in 5, a mixed pattern response was observed in 22, and the POTS pattern was observed in 35. The hematologic parameters (hemoglobin, hematocrit, mean corpuscular volume) and the folic acid, ferritin, and vitamin B12 levels of the groups are displayed in Table 1. Vitamin B12 levels were significantly lower in children with vasovagal syncope compared with healthy subjects (352.75 ± 160 vs 411.32 ± 134, respectively, P < .001). By contrast, there was no significant difference between the 2 groups regarding hemoglobin, hematocrit, mean corpuscular volume, folic acid, or ferritin values. A low vitamin B12 level was found to be more prevalent in children with vasovagal syncope (47.2% vs 18%, P < .01). In the vasovagal syncope group, children with the POTS pattern had significantly lower vitamin B12 levels compared with children with syncope without the POTS response. However, the number of patients with low vitamin B12 levels was significantly higher among children with the POTS response, P < .05 (Table 2). There was no significant difference between tilt-positive patients and tilt-negative patients regarding vitamin B12 levels (377.00 ± 180 vs 342.9 ± 152.16, respectively, P > .05).

Patients with low levels of vitamin B12 were referred to the hematology poly- clinic for treatment and follow-up, and those with persisting complaints after normalization of B12 levels were referred to our department again. During

### TABLE 1 Demographic and Clinical Characteristics of Patients and Healthy Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Syncope Group</th>
<th>Healthy Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>125</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age range (mean, median)</td>
<td>5–16 (11.1±2.3), 11</td>
<td>6–15 (10.94 ± 2.5), 11</td>
<td>NSa</td>
</tr>
<tr>
<td>Gender distribution</td>
<td>60% females</td>
<td>62% females</td>
<td>NSc</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.41 ± 0.73</td>
<td>12.72 ± 0.63</td>
<td>NSa</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>84.42 ± 4.68</td>
<td>83.57 ± 3.76</td>
<td>NSa</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36.24 ± 5.47</td>
<td>37.41 ± 4.78</td>
<td>NSa</td>
</tr>
<tr>
<td>Vitamin B12 level (pg/mL)</td>
<td>352.75 ± 160</td>
<td>411.32 ± 134</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Children with low B12 levels, n (%)</td>
<td>59 (47.2)</td>
<td>9 (18)</td>
<td></td>
</tr>
<tr>
<td>No. of children aged &gt;10 y</td>
<td>93 (74.4%)</td>
<td>39 (74%)</td>
<td>NSc</td>
</tr>
<tr>
<td>Folic acid level (ng/mL)</td>
<td>9.2 ± 3.1</td>
<td>8.9 ± 2.7</td>
<td>NSa</td>
</tr>
<tr>
<td>Ferritin level (ng/mL)</td>
<td>28.9 ± 18.4</td>
<td>31.3 ± 20.9</td>
<td>NSa</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. NS, not significant.

a P values calculated by t test.

b P values calculated by Mann-Whitney U test.

c P values calculated by χ² analysis.

### TABLE 2 Comparison of Vitamin B12 Levels and Number of Patients With Low Vitamin B12 Levels in Both Children With POTS Pattern and Patients With Syncope Who Had No POTS Pattern

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With POTS Pattern (n = 35)</th>
<th>Patients With Syncope Who Had No POTS Pattern (n = 125)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12 levels</td>
<td>312.60 ± 155.9</td>
<td>352.75 ± 160.9</td>
<td>&gt;.05c</td>
</tr>
<tr>
<td>Children with low vitamin B12 levels, n (%)</td>
<td>22 (62.8%)</td>
<td>59 (47.2%)</td>
<td></td>
</tr>
</tbody>
</table>

* P values calculated by Mann-Whitney U test.

** Intermediate Approval**

Participants were included in the study. There were no significant differences in the demographic characteristics between the groups. The statistical analysis was conducted using SPSS software. The results of the descriptive analysis were expressed as the mean ± SD for numerical variables. The mean values of variables with normal distribution were compared between groups using Student’s t test; variables with abnormal distribution were assessed using the Mann-Whitney U test. The Kruskal-Wallis test was used to determine significant differences between continuous variables. If the overall P value was significant, the Mann-Whitney U test was conducted to evaluate differences among groups. The χ² test was performed for each categorical variable.

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Patients with low levels of vitamin B12 were referred to the hematology poly-clinic for treatment and follow-up, and those with persisting complaints after normalization of B12 levels were referred to our department again. During
commonly in girls aged >10 years in this study. Orthostatic hypotension was not invariably observed in the group with low levels of vitamin B<sub>12</sub>. Whereas vitamin B<sub>12</sub> deficiency was observed in 47.2% of the patients, the rate of orthostatic hypotension was 12.6%. In addition, 28.8% of the patients had a positive tilt test, and POTS was observed in 28%. Low levels of vitamin B<sub>12</sub> were observed in 62.8% of the patients with POTS.

The tilt test may be affected by various factors, including the discomfort of being in the examination room, the discomfort caused by the intravenous or intra-arterial interventions, the tiredness and relative volume depletion related to long-lasting electrophysiological examinations performed before the procedure, and the prolonged duration of the procedure. Therefore, patients with similar laboratory data may respond differently during the tilt test. Generally, the results obtained from controlled studies have demonstrated that the HUTT is highly specific, although there are contradicting publications regarding the sensitivity of this test, with values ranging from 32% to 85% in reported series. Therefore, “tilt” test protocols that are pharmacologically induced with isoproterenol are commonly used to increase the diagnostic value of the test.

Vitamin B<sub>12</sub> deficiency is known to be more common among the elderly, although there is a currently increasing prevalence among adolescents worldwide. This is due to the increased need associated with accelerated development, decreased intake related to inadequate diet (vegetarian diet, obesity), and the side effects of medications (metformin used in the treatment of obesity, oral contraceptives, and antireflux medications such as proton pump inhibitors). Vitamin B<sub>12</sub> is a cofactor for the following enzymes: (1) methylmalonyl coenzyme A (CoA) mutase, catalyzing the isomerization of methylmalonyl-CoA to succinyl-CoA, which is required for myelin synthesis; (2) phenolamine N-methyltransferase, which is required for the conversion of noradrenaline to adrenaline; and (3) COMT, which is required for the degradation of catecholamines. Decelerated demyelination and nerve conduction and increased serum levels of noradrenaline have been observed in vitamin B<sub>12</sub> deficiency.

Some studies have shown that the functions of sympathetic postganglionic nerves require vitamin B<sub>12</sub>, although the presence of demyelinated sympathetic nerves has not been demonstrated in vitamin B<sub>12</sub> deficiency. Additionally, autonomic dysfunction, POTS, and syncope have been shown to be common in diseases related to myelinization deficits.

Studies have shown dysfunction in the baroreflex mechanism and the autonomic nervous system, particularly in the sympathetic nervous system, in the pathophysiology of CFS, POTS, and syncope. Therefore, despite the increased serum levels of noradrenaline, an inadequate noradrenaline response has been found in the lower-limb veins. Venous pooling occurs in the lower limbs as the heart rate increases during the HUTT. Because similar mechanisms are involved in vitamin B<sub>12</sub> deficiency, we believe that patients with CFS, POTS, and syncope should be screened for vitamin B<sub>12</sub> deficiency.

In their study in 2002, Beitzke et al demonstrated autonomic dysfunction in vitamin B<sub>12</sub> deficiency during the HUTT, similar to that observed in diabetic autonomic neuropathy. In these patients, there was a reduced increase in the cardiac index and in the total peripheral resistance index, and the baroreceptor sensitivity was disrupted. Patchell et al reported syncope episodes without orthostatic hypotension in the presence of vitamin B<sub>12</sub> deficiency in a patient diagnosed with anorexia nervosa.

An article by Skrabal emphasizes that neurologic findings may occur without anemia in the elderly population with frequent presyncope and falling due to vitamin B<sub>12</sub> deficiency and that it is inaccurate to assume vitamin B<sub>12</sub> deficiency cannot present without anemia. Both peripheral and autonomic neuropathy develop in vitamin B<sub>12</sub> deficiency, and treatment improves autonomic nervous system functions more rapidly.

Other studies have demonstrated that the change of posture may lead to an abnormal cardiovascular response (orthostatic hypotension, POTS, syncope) in one-third of patients and that CFS is most likely associated with sympathetic dysfunction. There are also studies supporting the similarity of the autonomic dysfunctions observed in CFS and POTS. Hägglöf in 2000 and Björkgren in 1999 demonstrated that CFS could be treated with vitamin B<sub>12</sub>.

CONCLUSIONS

Our study shows the association between the etiopathogenesis of POTS and the vitamin B<sub>12</sub> deficiency–induced sympathetic nervous system-baroreceptor dysfunction.
REFERENCES


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