Original Article

Serum vitamin B-12 in children presenting with vasovagal syncope

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Background and Objectives: The present study aims to determine the serum vitamin B-12 in children presenting with vasovagal syncope. **Methods and Study Design:** This is a prospective review of 160 children presenting with vasovagal syncope. Subgroup analysis was done based on the results of head up tilt test. **Results:** Head up tilt test gave positive results in 80 children and yielded negative results in the remaining 80 children. The tilt test positive children had significantly lower thyroid stimulating hormone concentrations (p=0.06), total iron binding capacity (p=0.04) and serum vitamin B-12 (p=0.01). The prevalence of vitamin B-12 deficiency was significantly higher in the tilt positive group (80% vs 52.5%, p=0.001). Out of 80 children with positive tilt test, 8 children (10%) showed cardioinhibitory response, 22 children (27.5%) demonstrated a vasodepressor response, 24 children (30%) displayed mixed response and 26 children (32.5%) had the postural orthostatic tachycardia syndrome. Erythrocyte sedimentation rate was significantly lower in the mixed response group than in the vasodepressor group (6.2±0.8 mm/h vs 14.3±2.5 mm/h, p=0.001). Serum vitamin B-12 was significantly lower in the postural orthostatic tachycardia syndrome (POTS) group than in the vasodepressor group (240.8±38.2 pg/mL vs 392.7±27.1 pg/mL, p=0.001). The prevalence of vitamin B-12 deficiency was significantly higher in the POTS group than in the vasodepressor group (92.3% vs 45.5%, p=0.001). **Conclusions:** Vitamin B-12 deficiency causes reduction in myelinization, deceleration in nerve conduction and elevation in serum concentrations of noradrenaline. These factors may contribute to the impairment of autonomic functions which are involved in the pathogenesis of vasovagal syncope.

Key Words: children, head up tilt test, postural orthostatic tachycardia syndrome, vasovagal syncope, vitamin B-12

INTRODUCTION

Vasovagal syncope is usually defined by the sympathetic-parasympathetic imbalance, but its precise pathophysiology remains obscure. It has been hypothesized that the main underlying mechanism is the cardioinhibitory response resulting from either increased parasympathetic activation or a vasodepressor response due to inhibition of sympathetic activity, or a mixed response with both. Symptoms such as nausea, vomiting, abdominal pain, diaphoresis, pallor, palpitations and dizziness may precede syncopal attacks, especially in young individuals.[1-4]

Vasovagal syncope is most commonly observed in children and adolescents. Recent guidelines of the European Society of Cardiology report that a typical history of reflex syncope (a brief loss of consciousness with preceding symptoms in the presence of a trigger followed by spontaneous recovery), normal physical examination and electrocardiography findings are sufficient to diagnose neurocardiogenic syncope in children. The head-up tilt test is usually performed to provide more evidence for a diagnosis of reflex syncope if this diagnosis has not been proved initially. Positive results of this test can be classified as a vasodepressor response, cardioinhibitory response, mixed response or postural orthostatic tachycardia.[5-7]

Vitamin B-12 participates in the methylation reaction which is regulated by S-adenosyl-homocysteine and S-adenosyl-methionine. Since this reaction plays an essential role in myelin formation, vitamin B-12 deficiency may cause neurologic deficits. Accordingly, it has been postulated that vitamin B-12 is required for the physiologic function of sympathetic post-ganglionic fibers. Therefore, it is reasonable to assume that vitamin B-12 deficiency may affect the sympathetic regulation of blood vessels and the autonomic nervous system, similar to the situation observed in vasovagal syncope.[8,9]

The present study aimed to determine serum vitamin B-12 in children presenting with vasovagal syncope.

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METHODS

This prospective study was approved by the Institutional Review Board and Ethical Committee of Afyon Kocatepe University Hospital (grant no: 2017/2-75) where it was conducted at the Department of Pediatric Cardiology from May 2014 to May 2015. Written informed consent was obtained from all participants and their parents.

Study group

The study group included 160 children presenting with vasovagal syncope. The children presenting with vasovagal syncope had at least two unexplained syncope attacks. The diagnosis of vasovagal syncope was based on history and symptoms. To exclude any cardiac structural disease, American Society of Echocardiography guidelines were used to carry out echocardiographic examination which included two-dimensional, M-mode, and Doppler studies covering systolic and diastolic parameters.[10] Patients with cardiac, neurologic, and psychiatric illness, chronic disease and arrhythmia, and any drug use that can alter cardiac conduction velocity heart rate and blood pressure were excluded from the study.

Head up tilt test

After the procurement of 24 h electrocardiography monitoring, all patients presenting with vasovagal syncope underwent a head-up tilt test. The tilt test was performed in a quiet room with low lighting after 12 h of patient fasting from 8 PM to 8 AM. No intravenous fluid infusions or pharmacological provocation was used during the test. Patients were monitored for continuous assessment of heart rate and rhythm and conventional automatic arm cuff blood pressure measurement in every 5 min. The tilt test protocol consisted of the patient lying in a supine position for 10 min while baseline electrocardiogram and blood pressure recordings were performed; then the patient was subsequently tilted to a head-up position at 70° for 20 min. Whenever symptoms or alterations in blood pressure or heart rate were observed, blood pressure was recorded more frequently manually (in 30 s intervals).[11,12]

Eighty patients reproducing syncope or pre-syncope during tilting were identified as tilt test-positive while 80 patients with no response at the end of 20 minutes were defined as tilt test-negative according to the Guidelines of Syncope of the European Society of Cardiology (version 2009).[7] Positive response was also defined as at least one of the following signs with or without syncope: (1) bradycardia, which was characterized by heart rate <75 bpm in children of 4–6 years old, heart rate <65 bpm in children of 7–8 years old, heart rate <60 bpm in children over 8 years old, sinus arrest, second degree atrioventricular block or higher, and asystole for 3 seconds; (2) hypotension defined as <80 mmHg in systolic blood pressure or decrease of >15 mmHg and/or diastolic blood pressure <50 mmHg; and (3) junctional rhythm together with escaped rhythm and accelerated idioventricular rhythm.[11,12]

There are several different possible positive responses to a head-up tilt test: (1) Vasodepressor - the blood pressure falls but the heart rate does not fall by more than 10% from its peak; (2) Cardioinhibitory - the heart rate falls to less than 40 beats/min for more than 10 s but asystole of more than 3 s does not occur (type A) or there is asystole of more than 3 s (type B); (3) Mixed - mixture of vasodepressor and cardioinhibitory responses (type A); (4) Postural orthostatic tachycardia syndrome (POTS) - heart rate rises both at the onset of upright position and throughout its duration before syncope (greater than 130/min).[12]

Out of 80 children with a positive tilt test, 8 children (10%) showed a cardioinhibitory response, 22 children (27.5%) demonstrated a vasodepressor response, 24 children (30%) displayed mixed response and 26 children (32.5%) had POTS.

Laboratory studies

From all children, two samples of 20 mL venous blood were drawn by standard phlebotomy one day later. The first sample was used to evaluate hemoglobin, mean corpuscular volume (MCV), leukocyte count, platelet count, mean platelet volume (MPV) by an automated commercial counter (Coulter counter, Max Instruments Laboratory, Milan, Italy).

The second blood samples of the participants were allowed to clot and centrifuged at 3000 rpm for 3–5 min within 30 min. Serum iron, ferritin, total iron binding capacity and vitamin B-12 levels were estimated immediately, using an automated electrolyte analyzer (Siemens Healthcare Diagnostics, Germany). The intra-assay coefficients of variation (CVs) were 5.3%, 3.8%, 7.8% and 6.2% whereas the inter-assay CVs were 1.8%, 1.5%, 10.0% and 5.7% for serum concentrations of iron, ferritin, total iron binding capacity and vitamin B-12 respectively. Vitamin B-12 deficiency was defined as serum concentration was < 300 pg/mL.

As for the third blood samples of the participants, serum levels of C-reactive protein (CRP) were measured by sandwich enzyme immunoassay whereas serum concentrations of thyroid-stimulating hormone (TSH) and free thyroxine were recorded by radioimmunoassay (DSL Diagnostic Systems Laboratories, USA). The intra-assay CVs were 9.6%, 9.7% and 8.2% whereas the inter-assay CVs were 6.6%, 6.2% and 7.4% for serum levels of CRP, TSH and free thyroxine respectively.

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) and categorical variables were denoted as numbers or percentages where appropriate. Smirnov-Kolmogorov test was used to test the normality of the data distribution. Student t-test, chi-square test, Mann-Whitney U test and Kruskal-Wallis test were used for the comparisons. A post hoc analysis was made to determine the two variables between which there is a statistically significant difference. Two-tailed p values less than 0.05 were considered to be statistically significant.

RESULTS

This is a prospective review of 160 children presenting with vasovagal syncope. The head-up tilt test gave positive results in 80 children and yielded negative results in the remaining 80 children. Table 1 compares the demo-

Table 1. Demographic, clinical and biochemical characteristics of the study group

	Head up tilt test negative (n=80)	Head up tilt test positive (n=80)	*p*
Age (years)	13.2±0.1	13.5±0.1	0.138
Men/women	20/60 (25.0%/75.0%)	22/58 (27.5%/72.5%)	0.592
Height (m)	1.56±0.2	1.59±0.2	0.654
Weight (kg)	47.8±1.7	48.7±1.9	0.380
Body mass index (kg/m^2)	19.3±0.5	18.9±0.5	0.257
Hemoglobin (g/dL)	13.0±1.9	13.6±1.7	0.213
Mean corpuscular volume (fL)	84.4±0.7	83.8±0.6	0.490
Leukocyte count (x10^3/mm^3)	7.31±0.23	7.34±0.29	0.866
Neutrophil/Lymphocyte ratio	1.9±0.1	2.1±0.1	0.188
Platelet count (x10^6/mm^3)	2.82±0.75	279.2±0.59	0.774
Mean platelet volume	8.1±0.1	8.2±.1	0.955
Sedimentation rate (mm/h)	10.0±0.8	11.7±1.1	0.192
C-reactive protein (mg/L)	0.4±0.2	0.3±0.1	0.597
Serum iron (µg/dL)	91.1±6.2	93.4±4.8	0.771
Ferritin (ng/mL)	35.3±3.6	41.7±3.2	0.135
Total iron binding capacity (µg/L)	39.2±0.7	37.3±0.7	0.040
Thyroid stimulating hormone (U/mL)	2.92±0.56	1.93±0.26	0.006
Free thyroxine (ng/dL)	1.35±0.14	1.32±0.15	0.346
Vitamin B-12 (pg/dL)	3.58±0.21	2.82±0.16	0.010
Vitamin B-12 deficiency	42 (52.5%)	64 (80.0%)	0.001

All variables were expressed as mean±standard deviation except the variables men/women and vitamin B-12 deficiency which were denoted as numbers and percentages.

graphic, clinical and biochemical characteristics of the tilt test negative and the tilt test positive children. The tilt test positive children had significantly lower TSH concentrations (p=0.06), total iron binding capacity (p=0.04) and serum vitamin B-12 (p=0.01). The prevalence of vitamin B-12 deficiency was significantly higher in the tilt positive group (80% vs 52.5%, p=0.001).

Out of 80 children with positive tilt test, 8 children (10%) showed a cardioinhibitory response, 22 children (27.5%) demonstrated a vasodepressor response, 24 children (30%) displayed a mixed response and 26 children (32.5%) had POTS. Table 2 demonstrates the demographic, clinical and biochemical characteristics of the tilt test positive children with respect to the different possible positive responses. The erythrocyte sedimentation rate was significantly higher in the vasodepressor group than in the mixed response group (6.2±0.8 mm/h vs 14.3±2.5 mm/h, p=0.001). Serum vitamin B-12 was significantly lower in the POTS group than in the vasodepressor group (240.8±38.2 pg/mL vs 392.7±27.1 pg/mL, p=0.001). The prevalence of vitamin B-12 deficiency was significantly higher in the POTS group than in the vasodepressor group (92.3% vs 45.5%, p=0.001).

DISCUSSION

The prevalence of vitamin B-12 deficiency is relatively higher among adolescents and young adults. This may be due to an imbalance between increased need for vitamin B-12 and its decreased intake. An increased need for vitamin B-12 is associated with accelerated growth, whereas decreased intake is due to unsatisfactory food intake, sometimes also reflected in obesity and possibly to the use of drugs like metformin, oral contraceptives and proton pump inhibitors.[13-17]

Vitamin B-12 acts as a co-factor for three enzymes: (1) phentolamine N-methyltransferase which is needed for the conversion of noradrenaline to adrenaline, (2) catecholamine-O-methyltransferase which is required for the degradation of catecholamines, (3) methylmalonyl coenzyme A (CoA) mutase which catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA in myelin synthesis. Therefore, myelinization is decreased, nerve conduction is decelerated and serum noradrenaline levels are elevated in vitamin B-12 deficiency.[18] Sympathetic postganglionic nerves require vitamin B-12 for their functions but the demyelination of sympathetic fibers does not occur in vitamin B-12 deficiency.[19]

Dysfunction of the sympathetic nervous system has been considered to be the main factor in vasovagal syncope and POTS. Plasma noradrenaline concentrations are found to be higher in tilt test positive children than in tilt negative children and this alteration has been considered as evidence for excessive sympathetic stimulation as a trigger in vasovagal syncope.[20] The relatively frequent observation of vasovagal syncope attacks in the morning hours can be attributed to diurnal variation in autonomic function in children and adolescents who present with vasovagal syncope and whose head-up tilt test is positive.[21]

As for POTS, serum levels of noradrenaline are increased, but the response to noradrenaline is inadequate in lower extremities veins. Thus, venous blood accumulates in the lower limbs as the heart rate increases during the head up tilt test. This mechanism resembles the mechanism which is involved in vitamin B-12 deficiency.[8,9,11]

Autonomic dysfunction may also contribute to the pathophysiology of chronic fatigue syndrome. Postural changes may trigger abnormal cardiovascular responses (such as orthostatic hypotension, vasovagal syncope, and POTS) in some 33% of patients considered to have the chronic fatigue syndrome and vitamin B-12 can be used to treat this syndrome.[22,23]

Autonomic dysfunction has been demonstrated in adults with vitamin B-12 deficiency during the tilt test

Table 2. The characteristics of participating chefs and cooks (n=90)

	Cardioinhibitory Response (n=8)	Vasodepressor Response (n=22)	Mixed Response (n=24)	POTS (n=26)
Age (years)	13.9±0.6	13.2±0.3	13.2±0.2	13.0±0.2
Male / Female	1/7 (12.5/87.5%)	6/16 (27.3/72.7%)	6/18 (25.0/75.0%)	9/17 (34.6/65.4%)
Height (cm)	157.5±1.9	160.3±1.8	158.4±1.8	159.2±1.7
Weight (kg)	48.5±2.2	49.9±1.9	48.6±1.9	47.5±1.7
BMI (kg/m^2)	19.7±0.8	18.5±0.6	19.3±0.5	18.6±0.5
Hemoglobin (g/dL)	13.9±0.6	13.2±0.3	13.8±0.2	13.8±0.2
MCV (fL)	86.8±1.3	83.3±1.5	86.5±1.1	85.2±0.9
Leukocyte count ($x10^3/mm^3$)	8.22±0.12	7.74±0.42	7.16±0.38	7.07±0.45
NLR	2.0±0.4	2.0±0.2	2.0±0.2	1.8±0.2
Platelet count ($x10^6/mm^3$)	28.7±0.13	26.4±0.11	27.3±0.11	26.5±12.2
Mean platelet volume	7.5±0.5	8.3±0.2	7.7±0.2	8.3±0.2
Sedimentation rate (mm/h)	14.5±0.5	14.3±2.5*	6.2±0.8*	10.3±1.2
CRP (mg/L)	0.2±0.1	0.3±0.1	0.2±0.1	0.3±0.1
Serum iron (µg/L)	12.6±2.8	7.7±1.0	7.8±0.8	9.3±0.7
Ferritin (ng/mL)	73.2±18.0	36.5±7.0	30.9±3.8	44.1±5.5
TIBC (µg/L)	35.6±0.9	39.8±1.2	38.0±1.0	36.2±0.9
TSH (U/mL)	1.59±0.14	1.87±0.26	2.04±0.39	2.23±0.31
Free thyroxine (ng/dL)	1.13±0.17	1.44±0.29	1.43±0.12	1.35±0.16
Vitamin B-12 (pg/dL)	2.31±1.0	3.93±0.3**	2.42±0.2	2.40±0.4**
Vitamin B-12 deficiency	8 (100%)	10 (45.5%)**	22 (91.7%)	24 (92.3%)**

POTS: postural orthostatic tachycardia syndrome; BMI: body mass index; MCV: mean corpuscular volume; NLR: neutrophil/lymphocyte ratio; CRP: C-reactive protein; TIBC: total iron binding capacity; TSH: thyroid stimulating hormone.
*There was statistically significant difference between vasodepressor and mixed response groups (p=0.001).
**There was statistically significant difference between vasodepressor response and POTS groups (p=0.001).

and such dysfunction has also been observed in diabetic patients with autonomic neuropathy. Collectively, baroreceptor sensitivity is impaired, the increased cardiac index is less and total peripheral resistance index decreased.[24]

Elderly people who have vitamin B-12 deficiency may present with neurological symptoms, pre-syncope and falling attacks. This may or may not occur without B-12 associated anemia. Where vitamin B-12 deficiency contributes to autonomic and peripheral neuropathy, its supplementation helps improve neurological functions more rapidly.[25]

Oner et al evaluated 50 healthy adolescents and 125 adolescents presenting with vasovagal syncope. Approximately 29% of the patients had positive tilt test and POTS was diagnosed in 28% of the tilt positive patients. Vitamin B-12 deficiency was detected in 62.8% of the patients with POTS. The prevalence of orthostatic hypotension did not change significantly in individuals with low serum vitamin B-12.[26]

The present study indicates that serum vitamin B-12 is significantly lower and vitamin B-12 deficiency significantly higher in children with a positive tilt test. There is POTS in 32.5% of tilt positive patients and vitamin B-12 deficiency in 92.3% of the children with POTS. This relatively higher prevalence seems to be due to the relatively higher prevalence of vitamin B-12 deficiency among young Turkish women. Vitamin B-12 deficiency was present in 81% of young Turkish women in late pregnancy and this prevalence only reduced to 60% during the postnatal period.[27]

The autonomic nervous system and endocrine system have a close mutual relationship. As a part of the endocrine system, the thyroid gland is involved in autonomic nervous system function. Whenever an abnormality occurs in the synthesis and/or secretion of thyroid hormones, autonomic dysfunction occurs and the thyroid gland becomes activated if autonomic nervous system is stimulated excessively.[28,29] Significantly lower TSH concentrations in the tilt positive children in this study may be attributed to the activation of thyroid activity in response to an excessive stimulation of sympathetic nervous system.

A decrease in iron stores usually precedes and predicts overt iron deficiency during childhood and adolescence. Such a decrease may lead to a reduction in oxygen carrying capacity of hemoglobin which eventually results in an increase in cardiac output. The underlying pathogenesis is poorly understood, although it has been proposed that certain metabolites (e.g. lactate, adenosine, and hydrogen ions) and/or hypoxia sensed through carotid baroreceptors can trigger a reflex mechanism which partially stimulates the sympathetic innervations of the heart.[30,31] Significantly lower iron binding capacity in the tilt positive children of this study may reflect an underlying, if subtle, reason for autonomic dysfunction.

The vasodepressor response in the tilt test occurs as a result of vasodilatation which is probably induced by the withdrawal of sympathetic nervous system tone.[12] Inflammation is an immunovascular response which is characterized by marked vascular changes such as vasodilatation.[32,33] A significantly higher sedimentation rate in the vasodepressor group may be the consequence of a systemic inflammatory process, which is closely related with the pathophysiology of vasovagal syncope.

The findings of the present study should be interpreted cautiously as power is limited by a relatively small cohort size, the lack of a control group, the lack of longitudinal data and the biased grouping of tilt positive patients. The reliability of the head-up tilt test may be affected by various factors including the psychological stress of the examination room, the discomfort caused by the intravenous

or intra-arterial interventions, prolonged duration of the procedure and the exhaustion and relative dehydration related with pre-procedural preparation. Patients with similar demographic, clinical and biochemical characteristics may have different tilt test results. Further research is warranted to clarify the role of vitamin B-12 in children presenting with vasovagal syncope.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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