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Original Article

Can Vitamin B12 Deficiency Really Cause Vasovagal Syncope? Retrospective Analysis of 469 Pediatric Vasovagal Syncope Cases

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ABSTRACT

Objective: Syncope is a frequent reason for referral to pediatric cardiology clinics. Vitamin B12 deficiency is frequently diagnosed in pediatric patients. In this study, we determined the frequency of vitamin B12 deficiency in pediatric vasovagal syncope (VVS).

Methods: This study was designed retrospectively. VVS patients were identified from the hospital registry system with ICD code 'R55, syncope, and fainting'. The frequency of VVS and vitamin B12 levels of the patients were evaluated. Below 200 ng/L was considered vitamin B12 deficiency.

Results: Eight hundred twelve patients were identified with ICD code R55, syncope, and fainting' in pediatric cardiology hospital records. Two hundred sixteen patients were excluded from the study due to insufficient hospital records. Four hundred and sixty-nine patients were diagnosed with VVS. One hundred and seventy-three patients were excluded from the study because of non-available vitamin B12 level. Ninety-six patients had epileptic sezure/suspected VVS, 28 patients had psychogenic syncope and 3 patients had cardiac syncope. Demographic characteristics, hemoglobin and vitamin B12 levels, and the frequency of vitamin B12 deficiency were similar in the patient and control groups ($p>0.05$). Two hundred and sixty-four patients had normal vitamin B12 level, whereas 32 patients were diagnosed with vitamin B12 deficiency. Fifty-six patients who had normal vitamin B12 levels experienced frequent VVS and 6 patients with vitamin B12 deficiency experienced frequent VVS (21.2% vs 23.0%, $p>0.05$).

Conclusion: Although VVS can cause serious concern in patients and families, it is unlikely to be a serious underlying disease. Vitamin B12 deficiency was not found at a high rate in this disease as in other studies.

Keywords: Vasovagal syncope, transient loss of consciousness, vitamin B12 deficiency

INTRODUCTION

Vasovagal syncope is one of the most common reasons for pediatric cardiology outpatient clinics. It is classified under the subheading of reflex (neurally mediated) syncope in the guidelines.[1] Since its clinical features overlap with many fatal or non-fatal diseases, it causes serious concern both in the physician and in the family. While history taking and physical examination is often sufficient for diagnosis, further investigations may be required.

The main pathophysiology of VVS is a sudden decrease in cardiac output and a transient decrease in cerebral perfusion (vasodepression and/or cardioinhibition) with any trigger. As a result, transient loss of consciousness occurs (TLOC). TLOC is a transient condition characterized by loss of consciousness, abnormal motor control, loss of response, and short-term amnesia.[1] The sudden decrease in cardiac output is caused by hypotension due to insufficient vasoconstriction (vasodepression) or bradycardia/asystole due to parasympathetic dominance (cardioinhibition).[2] Triggering factors are orthostatic changes (such as standing up) or emotional factors such as fear, pain (somatic or visceral) or blood phobia.

Studies have shown that vitamin B12 deficiency causes neurological deficits.[3,4] Although the neurological function of vitamin B12

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is from different enzymes and pathways, the most important mechanism is thought to be impaired myelin formation and the relation between demyelinating diseases and B12 deficiency has been revealed.[5,6] However, it has not been proven that there is a deterioration in myelination in vitamin B12 deficiency.[7] Although vitamin B12 deficiency has been shown to be an etiological cause of VVS, studies have been conducted with few patients or comparing the head-up tilt test (HUTT).[8-10] The sensitivity of the HUTT is variable and insufficient, especially in VVS with emotional stimuli.[11-13]

VVS is a well-defined disease in clinical practice and most cases do not require further investigation. However, vitamin B12 level is frequently studied in routine practice and sometimes even if the level is normal, it is considered an etiological cause and replacement therapy is given.[8-10] However, for treating VVS, education and lifestyle modifications are sufficient to treat many patients, while additional medical treatments (B-blockers, alpha agonists, etc.) are required in few severe patients.[14]

To our knowledge, there is no study evaluating vitamin B12 deficiency in such a large case series in pediatric patients presenting with VVS. Vitamin B12 deficiency appears to be overdiagnosed in these patients, resulting in ignoring the education and lifestyle modifications that are most beneficial in the treating of the disease. In this study, we determined the frequency of vitamin B12 deficiency in VVS patients.

MATERIALS AND METHODS

The study was conducted retrospectively in the Kayseri City Hospital, Clinic of Pediatric Cardiology. The permission was obtained from the Clinical Research Ethics Committee of Kayseri City Hospital (decision no: 654, date: 16/06/2022).

The study was conducted with pediatric patients (8-18 years) referred to the pediatric cardiology clinic with syncope between October 2018 and October 2021 and a healthy control group. The patients were identified by searching the records of the pediatric cardiology outpatient clinic from the hospital registry system with the "ICD code R55, syncope, and fainting". The control group consisted of patients who were referred to the pediatric cardiology clinic with murmur, palpitation, or any other reason, whose transthoracic echocardiography (TTE) and electrocardiography (ECG) examinations were normal, and whose vitamin B12 levels were studied.

Patients who were referred to the pediatric cardiology clinic due to syncope and diagnosed with VVS according to the criteria of the European Society of Cardiology (ESC) (2018)[1] and who met the following criteria were included in the study as the patient group.

- Measuring the vitamin B12 levels in the pediatric cardiology clinic or the referral clinic,
- The VVS event had occurred within the last month.

Patients who met any following criterion were excluded from the study;

- Patients who could not be diagnosed with VVS at their first admission and who required further investigations such as HUTT and electroencephalography,
- Patients diagnosed with epileptic seizure, cardiogenic syncope, breath holding, psychogenic syncope,
- Patients with a head trauma history,
- Receiving B12 replacement therapy before the vitamin B12-level study [checked from patient history and ministry of health prescription registration system (e-prescription)],
- History of infection.

Vitamin B12 levels were measured by electrochemiluminescence immunoassay “ECLIA” in the hospital clinical laboratory on the same day and the intra-assay coefficient of variation (CVs) was 2.2%. Two hundred ng/L was accepted as cut-off value for deficiency.[3]

Each patient referred with syncope was evaluated with 12-lead ECG and TTE, and abnormalities were recorded. Patients with suspected arrhythmia were evaluated with 24-hour Holter ECG. The exercise stress test was applied to patients who experienced exercise-related syncope. Patients whose convulsion-VVS-psychogenic syncope distinction could not be made clearly were referred to another center for HUTT and were excluded from the study.

The patients were divided into 2 groups as those who had VVS attack only once and those who had recurrent attacks (2 or more).

Statistical Analysis

The normality of the distribution of vitamin B12 levels, demographic features were assessed with Kolmogorov-Smirnov test. Results are expressed as means for continuous variables and percentages for categorical variables. Continuous variables were compared between groups with Student’s t-test. The percentage of vitamin B12 deficiency and syncope frequency (one vs 2 or more) were analyzed with chi-square test. P-values <0.05 were considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (ver. 22.0; SPSS Inc., Chicago, IL, USA).

RESULTS

During the past 3 years, 812 patients aged 8-18 years with ICD code "R55, syncope, and fainting" were identified in pediatric cardiology hospital records. Two hundred and sixteen patients were excluded from the study due to insufficient hospital records (Figure 1).

Twenty-eight patients were diagnosed with psychogenic syncope and 3 patients with cardiac syncope (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and coronary artery course anomaly). Ninety-six patients described epileptic seizures or suspected VVS. According to the ESC 2018 guideline, 469 patients were diagnosed with VVS (Figure 1).

Twenty-nine patients were evaluated with 24 h Holter ECG and 17 patients were evaluated with an exercise stress test. Cardiac syncope was not diagnosed with these tests.

Vitamin B12 levels and the frequency of vitamin B12 deficiency were similar in the patient and control groups (n=142) (10.8% vs 11.2%, Table 1).

The vitamin B12 level of 264 patients was normal, it was below 200 ng/L in 32 patients. One hundred and seventy-three VVS patients were excluded from the study (due to not evaluating vitamin B12 levels, receiving treatment, etc.). Fifty-six (21.2%) patients with normal vitamin B12 levels and 6 (23.0%) patients with low vitamin B12 levels experienced frequent (2 or more in the last 3 months) VVS (Figure 1). There was no statistical difference between the two groups (Table 2).

Following the diagnosis, patient education and lifestyle modification recommendations were made as the first therapy. Medical treatment was started at the time of diagnosis for 4 patients. Medical treatment was started for 12 patients because their complaints persisted despite education and lifestyle modifications. B-blockers were started as medical treatment, no other drug was needed in any patient.

Vitamin B12 replacement therapy was administered to 32 patients with vitamin B12 deficiency. However, only 6 of these patients complained of frequent VVS. These patients were not evaluated for the frequency of syncope as they also received other treatments.

DISCUSSION

In this study, we revealed that many patients were referred to the pediatric cardiology clinic with VVS, and vitamin B12 levels were frequently studied in the pediatric cardiology clinic or in the other centers, but vitamin B12 deficiency was not a common etiological cause in this disease as thought. VVS is a common disease in children and adolescents and causes serious anxiety in parents and patients. The similarity of the disease with epilepsy or other potentially fatal cardiac diseases in terms of clinical findings compels physicians to conduct further investigations.

In our clinic, in addition to the 12-lead ECG, as a routine practice, all patients are evaluated with TTE, although there is no murmur and no structural heart disease is suspected. If cardiac syncope is suspected, also 24-hour ambulatory Holter ECG examination can be performed. However, unnecessary tests do not reduce anxiety, in contrast, incidentally detected pathologies increase anxiety even more.

It has been shown that vitamin B12 deficiency causes different neurological findings.[3] However, histopathologically, myelination disorder could not be demonstrated in vitamin B12 deficiency.[7] It has been reported that vitamin B12 is low in VVS patients, but these studies were evaluated with a limited number of patients or according to the positive-negative HUTT.[8,15,16] However, the HUTT is recommended for the differential diagnosis of this disease only in suspicious cases, and the HUTT does not provide an idea about

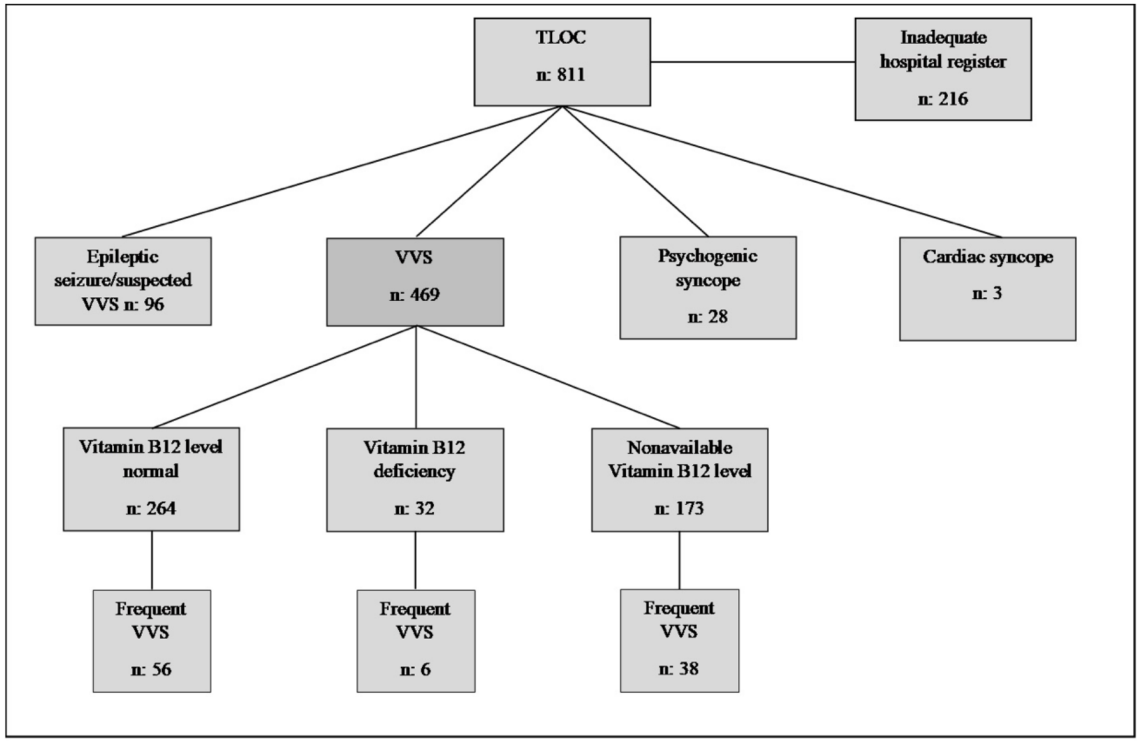

Figure 1. Number of patients referred with TLOC according to their diagnosis and vitamin B12 deficiencies

TLOC: Transient loss of consciousness, VVS: Vasovagal syncope, frequent VVS: 2 or more VVS in the last 3 months

Table 1. Demographic characteristics and vitamin B12 levels of the patient and control groups. Values are expressed as mean±SD, ratios and percentage

	Patient group (n=296)	Control group (n=142)	p-value
Body weight (kg)	36.4±12.3 (n=112)	42.7±9.8 (n=87)	0.487
Age (years)	13.3±4.2	15.7±6.3	0.128
Gender (Male/Female)	0.8	0.68	0.346
Hemoglobin (g/dL)	12.1±6.3	11.8±4.8	0.634
Vitamin B12 level (ng/L)	322.4±58.3	296.8±34.1	0.096
Vitamin B12 deficiency	32 (10.8%)	16 (11.2%)	0.854

SD: Standard deviation

Table 2. Demographic characteristics and vitamin B12 levels of patient groups. Values are expressed as mean±SD, ratios and percentage

	One syncope (last 3 months) (n=245)	Two or more syncope (last 3 months) (n=51)	p-value
Age (years)	31.5±3.6	41.1±9.3	0.078
Gender (Male/Female)	1.2	0.9	0.068
Hemoglobin (g/dL)	11.7±5.9	12.4±3.9	0.097
Vitamin B12 level (ng/L)	298.2±26.4	338.72±38.5	0.128
Vitamin B12 deficiency	26 (77%)	6 (23%)	0.517

SD: Standard deviation

the severity of the disease.[12,13,17] Additionally, cardioinhibition or vasodepression in VVS may occur not only with orthostatic changes but also with emotional triggers.[18,19] In our study, we did not find a relationship between vitamin B12 deficiency and VVS, as well as the diagnosis and severity of the disease. The neurological side effects of vitamin B12 may not be controversial, but its relationship with VVS may not be as obvious as be expected.

The prevalence of vitamin B12 deficiency differs significantly from country to country studies. The main reason for this difference may be socioeconomic status and different cut-off values. In Turkey, Varkal[20] reported this rate as 4.1% in a study evaluating 3115 children. Much higher prevalences have been reported in different countries, possibly due to low socio-economic status.[21,22] Although the B12 level was slightly higher in the control group, it was not statistically significant. In the study by Pektas et al.[8], 52.5% in the group with negative HUTT and 80% in the positive group. Our rates are far from the results.

A cut-off level of 100 ng/L, at which significant clinical findings occur, has been suggested for the vitamin B12 level.[3] However, there may be false positive or negative results. Therefore, homocysteine levels should also be checked in the evaluation of vitamin B12 levels. Additionally, considering that folic acid plays a role together with vitamin B12 in the remethylation of homocysteine, it would be more accurate to evaluate vitamin B12, folic acid, and homocysteine levels together.[3] Kovalchuk and Boyarchuk[9] evaluated 40 pediatric patients with a diagnosis of VVS and found that vitamin B12 levels were lower and homocysteine levels higher than the healthy control group. However, since our study was retrospective, we do not know the homocysteine levels. Folic acid levels were measured in very few patients and their levels were in the normal range. However, statistical analysis was not performed due to the small number.

The most valuable tool in the diagnosis of VVS is history taking from the patients and eyewitnesses of syncope. If the TLOC occurs with orthostatic changes or emotional stimuli (pain, fear, fear of blood, etc.) and consciousness quickly returns, further investigation is not required and the diagnosis is clear.

The recommended first-line therapy for treating VVS is education and lifestyle modifications. If known, it is recommended to stay away from the triggering factor (irritating smell, blood phobia etc.), and to sit or lie down when there are prodromal symptoms.[1] Increasing fluid and salt intake also reduces the recurrence of syncope.[23,24] In many patients, these measures are sufficient without medical treatment. If syncope recurrence is frequent, medical treatment is recommended. Parekh et al.[10] claimed that VVS patients with vitamin B12 deficiency and HUTT-positive VVS improved after vitamin B12 replacement and the HUTT became negative. However, the HUTT is not a good tool for evaluating the response to treatment.[25] In our series, few patients were treated with beta-blockers (metoprolol) and these patients benefited from medical therapy. The medical treatment of those whose symptoms decreased significantly for 1 year was discontinued. There are also patients who are given vitamin B12 replacement, but it is unclear whether these patients benefit from B12 replacement or from education and lifestyle modifications.

Study Limitations

The most important limitation was the retrospective design of our study. This is because hospital records may not be recorded properly. Although patients with insufficient records were excluded from the study, different physicians may not have paid enough attention to the disease and did not obtain sufficient and reliable patient histories. Vitamin B12 levels can be studied frequently by doctors and replacement therapy can be given. Although replacement therapy recipients are identified from the hospital registry and excluded from the study, there may be patients who are overlooked and these patients may affect the results. Since vitamin B12 and folic acid play a role in homocysteine remethylation, their levels may affect each other. Very few patients had folic acid levels and we did not perform statistical analysisIt would be best to evaluate VVS patients with vitamin B12, folic acid, and homocysteine levels in a prospective case-controlled study with a large number of cases.

CONCLUSION

Almost every patient experiencing syncope is referred to pediatric cardiology clinics. The concern of both the family and physician that there will be an underlying mortal disease leads to unnecessary tests. Of course, there are neurological manifestations of vitamin B12 deficiency. However, it does not seem to be an etiological cause as often as it is considered in a common disease such as VVS. VVS patients with vitamin B12 deficiency should be given replacement therapy. However, education, lifestyle modifications and medical treatments should not lag behind vitamin B12 replacement. Long-term prospective, case-controlled studies should be conducted to better understand the role of vitamin B12 in the pathophysiology of VVS.

Ethics

Ethics Committee Approval: The permission was obtained from the Clinical Research Ethics Committee of Kayseri City Hospital (decision no: 654, date: 16/06/2022).

Informed Consent: This study was designed retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., M.A., Concept: S.S., M.A., Design: S.S., M.A., Data Collection or Processing: S.S., Analysis or Interpretation: S.S., Literature Search: S.S., Writing: S.S.

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