Evaluation of Relationship Between Tp-E Interval Values and QT Dispersion in Electrocardiogram in Children With B12 Vitamin Deficiency

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──────────── Abstract ────────────

Aim: B12 vitamin deficiency may cause cardiac autonomic dysfunction, heart rate variability, endothelial dysfunction and subclinical atherosclerosis, a significant degree of reduction in heart ejection fraction and deformation of the left ventricular myocardium. We aimed to investigate the effect of B12 deficiency in children on cardiac electrical activity by comparing the Tp-e and QT dispersion values between healthy children and children with B12 deficiency.

Methods: The demographic data, laboratory results electrocardiography and echocardiography results of isolated B12 patients (n=64) with vitamin B12 deficiency and control group (n=64) included in the study between 15.3.2020 and 15.06.2020 were prospectively recorded and comparatively analyzed.

Results: A total of 128 patients included in the study. Corrected QT (QTc) value and Tp-e interval, were statistically significantly higher in the patient group (p<0.05). Tp-e/QT and Tp-e/QTc ratios in the patient groups were statistically significantly higher than the ones in the control group (p<0.05).

Conclusion: Repolarization differences in B12 deficient children when compared to those of healthy children, might reflect subclinical symptoms.

Keywords: Child, vitamin B12 deficiency, QT dispersion, repolarization, Tp-e interval

Introduction

B12, a water-soluble vitamin, acts as a coenzyme in the synthesis of DNA required for cell division and proliferation, myelinization of neuronal cells and in the metabolisms of lipids and carbohydrates. By affecting the activity of the sympathetic and parasympathetic system, vitamin B12 deficiency causes heart rate variability and cardiac autonomic dysfunction and also results in endothelial dysfunction and subclinical atherosclerosis with its role in cellular metabolic pathways inhibiting homocysteine metabolism, lipid peroxidation and free radical formation. There are studies where vitamin B12 deficiency is associated with left ventricular myocardial deformation (1,2).

Left ventricular dysfunction plays a key role in the development of arrhythmias. Prolonged QT interval increases the sensitivity of the heart to ventricular arrhythmias. The QT dispersion and Tp-e interval values are recognized as an indicator for ventricular repolarization. (3,4). Prolonged QT dispersion and Tp-e interval values indicate a predisposition to ventricular arrhythmias.

In the literature, several studies show that vitamin B12 deficiency causes cardiac autonomic dysfunction and subclinical atherosclerosis in the pediatric age group (1,5). Autonomic dysfunction caused by vitamin B12 deficiency and cardiac dysfunction secondary to anemia, its role in pathways preventing the formation of free radicals, its effect on endothelial reconstruction and the associated cardiac complications may make the heart susceptible to arrhythmias (6-8).

In our study, we aimed to investigate the effect of vitamin B12 deficiency on cardiac electrical activity in children by comparing Tp-e interval and QT dispersion values of children with isolated vitamin B12 deficiency to Tp-e interval and QT dispersion values of healthy children.

Methods

Study Design

Ethical committee approval was obtained for our study from the Istanbul Training and Research Hospital, Clinical Research Ethics Committee of our hospital with the decision numbered 2020-06 and dated 11/03/2020. The families were informed about the study and their written consents were obtained.

Patients only with vitamin B12 deficiency were included in the study from among children who do not have any chronic disease (hypertension, diabetes mellitus, congenital or acquired heart disease, thyroid disease, chronic lung, liver and kidney disease, etc.) and whose other vitamin values (vitamin D, folate and ferritin) are in the normal range. The control group comprised of patients whose all vitamin values, including vitamin B12, were normal, and who did not have any additional chronic diseases and applied to the Pediatric Cardiology Outpatient Clinic for a routine pediatric examination or report for making sports and were not found to suffer from any problem and did not take any medication.

The demographic data of the patients were obtained from the patient files and the hospital information management system. Physical examinations, blood tests (hemogram, glucose, urea, creatinine, upper, lower, electrolytes, vitamin B12, folate, 25-OH vitamin D, ferritin, iron, iron-binding capacity, T4 TSH), age, gender, electrocardiography (ECG) and echocardiography (ECO) findings of the patients (taken prior to the initiation of the vitamin B12 deficiency treatment) between 15.3.2020 and 15.06.2020 were recorded prospectively in our clinical data registry form.

Electrocardiogram Assessments

Their ECGs were assessed by the same pediatric cardiologist. ECGs were taken by a 12-lead device (Schiller Cardiovit At-102 plus) with velocity 25 mm/sec and amplitude 10 mm/mV. A magnifying glass and a manual ruler were used during the examination of ECG samples in order to increase the sensitivity of P wave, PR interval, QRS complex, QT interval, Corrected QT (QTc), Tp-e, Tp-e/QT, Tp-e/QTc, QT dispersion, and QTc dispersion calculations. The waves and intervals measured in our study are shown in Figure 1.

Echocardiographic examinations were performed with 2-dimensional and color Doppler echocardiography device (GE Vivid S5®). Echocardiographic assessment of all cases included in the study was performed by the same experienced pediatric cardiologist. In all cases, classical echocardiographic measurements, i.e., left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), end-diastolic interventricular septal diameter (IVSd), end-diastolic left ventricular posterior wall
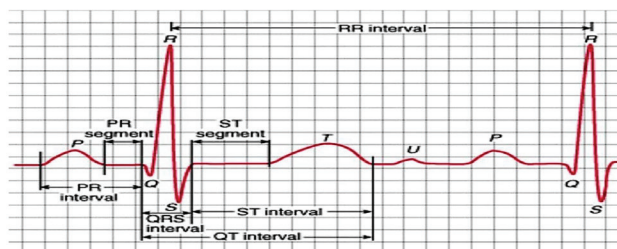
Figure 1: Waves and intervals making up the ECG
ECG: Electrocardiography

diameter (LVPWd), ejection fraction (EF) and shortening fraction (SF) measurements were made.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics: Categorical variables are expressed in numbers and percentages and numerical variables are expressed in mean, standard deviation, minimum and maximum values. When the numerical variables met the normal distribution condition, the Student's t-test was used for the comparison of two independent groups, and the Mann-Whitney U test was used when the normal distribution condition was not met. In independent groups, the rates were compared by chi-square test. The relationships between numerical variables were analyzed with Pearson's correlation analysis when the normal distribution condition was met, and when the normal distribution condition was not met, Spearman correlation analysis was used. The significance level alpha was accepted $p<0.05$.

Results

A total of 128 patients (64 patients and 64 controls) were included in the study. Of the 64 patients included in the study, 33 (51.6%) were female and 31 (48.4%) were male. The control group consisted of 33 (53.9%) girls and 31 (48.4%) boys. No statistically significant difference was found between the two groups in terms of gender distribution (p=1). The mean age of the patient group was 11±2.7 years and the mean age of the control group was 10.8±2.3 years. No statistically significant difference was found between the patient and control groups in terms of the mean age (p=0.428).

In the patient group, the mean vitamin B12 level was 144±30.3, whereas in the control group, the mean vitamin B12 level was 310.6±131.9. Folate level was found to be statistically significantly lower in the patient group compared to the control group (p=0.035). However, it remained in the range of normal values in both groups (Table 1).

When all cases were evaluated, a weak positive correlation was found between vitamin B12 level and white

Table 1. The distribution of vitamin and iron variables of the patient and control groups

	B12 deficiency group		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
Vitamin B12 (180-914 (pg/mL)	144.0±30.3	50-191	310.6±132	200-862	<0.001[a]
Folate (5.9-24 ng/mL)	10.0±2.8	4.69-17.68	11.1±2.9	5.21-18.2	0.035[b]
Ferritin (11-316 ng/mL)	23.5±7.4	12-49.6	27.3±13.1	11.7-79.6	0.179
TIBC1 (250-450 mcg/dL)	285.8±49.1	210-418	283.3±49.2	172-433	0.778
Iron (60-180 mcg/dL)	78.1±26.8	23-170	79.1±26.3	37-160	0.832
25-OH Vitamin D (14-50 ng/mL)	17.1±3.7	12-37.5	18.5±4.3	13.5-33.8	0.079

[a]Student's t-test, there is a significant difference between the groups in terms of vitamin B12.
[b]Student's t-test, there is a significant difference between the groups in terms of folate. TIBC: Total iron-binding capacity, SD: Standard deviation

Table 2. Electrocardiographic findings of the patient and control groups

	B12 group deficiency		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
Heart rate (minute)	83.8±14.8	54-135	88.1±16.0	59/127	0.118
P (sec)[1]	0.09±0.01	0.07-0.12	0.09±0.01	0.06-0.12	0.835
PR (sec)[1]	0.12±0.01	0.09-0.15	0.12±0.02	0.09-0.16	0.977
QRS (sec)[1]	0.08±0.01	0.07-0.10	0.08±0.01	0.07-0.11	0.877
QT (msec)[2]	327.9±23.2	273-396	328.3±44.7	33-388	0.164
QTc (msec)[2]	393.5±18.8	335-430	405.5±18.7	360-445	<0.001[a]

[1]Second
[2]Millisecond
[a]Student's t-test, there is a significant difference between the groups in terms of corrected QT distances. SD: Standard deviation

blood cell (WBC) and platelet values (r=0.044; r=0.016, respectively). No statistically significant relationship was found between other hemogram parameters and vitamin B12 level (p>0.05). No statistically significant difference was found in laboratory parameters in both groups (p>0.05).

QTc was found to be significantly higher in the group with vitamin B12 deficiency compared to the control group (p<0.001). There were no patients with a QTc value >445 ms in both the patient and control groups (Table 2).

In the patient group, the mean Tp-e interval was found to be 81.4±4.4 ms. In the control group, the mean Tp-e interval was found to be 72.3±6.9 ms. Tp-e interval was found to be statistically significantly higher in the patient group compared to the control group (p<0.001) (Table 3).

In the patient group, the Tp-e/QT ratio and the Tp-e/QTc ratio were found to be statistically significantly higher than the control group (p<0.001 and p=0.001) (Table 3).

QTd and QTcd values were found to be statistically significantly higher in the patient group compared to the control group (p=0.009 and p<0.001) (Table 4). The minimum value of QTc in the patient group was found to be statistically significantly lower than the control group (p<0.001) (Table 4).

No significant difference was found in both groups in terms of EF and SF (p=0.408 and p=0.062). In the patient

Table 3. Comparison of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in the patient and control groups

	B12 group deficiency		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
Tp-e	81.4±4.4	68-90	72.3±6.9	56-88	<0.001[a]
Tp-e/QT	0.25±0.02	0.19-0.33	0.22±0.02	0.17-0.27	<0.001[b]
Tp-e/QTC	0.21±0.01	0.16-0.24	0.18±0.02	0.13-0.26	<0.001[c]

[a]Student's t-test, there is a significant difference between the groups in terms of Tp-e interval
[b]Student's t-test, there is a significant difference between the groups in terms of Tp-e interval/QT distance ratio
[c]Student's t-test, there is a significant difference between the groups in terms of Tp-e interval/ corrected QT distance ratio OTc: Corrected QT, SD: Standard deviation

group, IVSd and LVPWd (Left ventricular posterior wall diameter) values were found to be statistically significantly higher than the control group (p=0.013; p=0.040).

A statistically significant negative correlation was found between vitamin B12 level and age in all cases included in the study (r=-0.175) (Table 5). In all cases, a statistically significant negative correlation was found between vitamin B12 level and Tp-e interval, Tp-e/QT, Tp-e/QTc values (r=-0.580; r=-0.511; r=-0.549, respectively) (Table 5).

Heart rate was found to be statistically significantly lower in boys than in girls (p=0.043). In terms of

echocardiography measurements, LVESD (Left ventricular end-diastolic diameter) value was found to be statistically significantly higher in boys compared to girls (p=0.042) (Table 6).

In the control group, heart rate was found to be statistically significantly lower in boys compared to girls (p=0.034). There was no statistically significant difference in other ECG and ECO parameters (p>0.05).

Discussion

In our study, we found that in ECGs of children with isolated vitamin B12 deficiency, QT intervals and Tp-E intervals, which can increase the predisposition to arrhythmia, were statistically significantly prolonged.

By affecting the activity of the sympathetic and parasympathetic system, vitamin B12 deficiency causes heart rate variability and cardiac autonomic dysfunction and also results in endothelial dysfunction and subclinical atherosclerosis with its role in cellular metabolic pathways inhibiting homocysteine metabolism, lipid peroxidation and free radical formation. There are studies where vitamin B12 deficiency is associated with left ventricular myocardial deformation (1,2).

Herzlich et al. (9) found that left ventricular EF was significantly lower in the vitamin B12 deficient patients in the adult group. Kaya et al. (7) report that global and segmental myocardial deformation is impaired in patients with vitamin B12 deficiency and this disorder is associated with vitamin B12 levels.

The autonomic nervous system is the key regulator of the physiological functions of the cardiovascular system. It is known that vitamin B12 deficiency leads to the impairment of neuron myelinization and thus, causes cardiac autonomic dysfunction. In their study that was conducted with a group of patients with B12 deficiency, Beitzke et al. (10) evaluated the hemodynamic and autonomic responses of the patients with the tilt-table test. It was found that the baroreflex response was impaired in the vitamin B12 deficient group and a significant decrease was observed in the blood pressure measured after the tilt table test (10). In the paediatric patient group, the vitamin B12 deficiency was shown to cause the heart rate variability by affecting the activity of the sympathetic and parasympathetic system (2,11). Öner et al. (12) compared low levels of vitamin B12 with the findings of postural orthostatic tachycardia syndrome (POTS) pattern in their study on adolescent children diagnosed with vasovagal syncope. It was reported that the deficiency may cause POTS with sympathetic system baroreceptor dysfunction in children with vitamin B12 deficiency (12).

Vitamin B12 has been associated with endothelial dysfunction and subclinical atherosclerosis with its role in cellular metabolic pathways that inhibit lipid peroxidation and free radical formation (1,6). In their study on the paediatric group with vitamin B12 deficiency, Çelik et al. (1) report a significant relationship between carotid intima-media thickness values measured in the early detection of atherosclerosis and the autonomic modulation of heart rate variability (HRV) (1).

Vitamin B12 deficiency is detected in various chronic diseases that develop with immune and inflammatory processes. Studies show that inflammation-related factors such as oxidative stress, nitric oxide production and exposure to various cytokines are associated with

Table 4. QT dispersion and QTc dispersion values of the patient and control groups

	Vitamin B12 deficiency group		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
QT Minimum	315.8±23.8	261-384	321.6±27.3	228-376	0.204
QT Maximum	340.9±25.5	278-418	344.0±24.4	288-400	0.476
QTd	25.8±10.7	7-49	20.8±10.9	4-52	0.009[a]
QTc Minimum	376.8±20.5	326-423	392.8±22.2	341-454	<0.001[b]
QTc Maximum	413.1±19.1	367-453	419.2±17.9	377-460	0.077
QTcd	36.1±13.0	16-79	27.4±14.7	1-69	<0.001[c]

[a]Student's t-test, there is a significant difference between the groups in terms of QT dispersion value
[b]Student's t-test, there is a significant difference between the groups in terms of corrected QT minimum value
[c]Student's t-test, there is a significant difference between the groups in terms of corrected QT dispersion value
OTc: Corrected QT, SD: Standard deviation

Table 5. Evaluation of vitamin B12 levels, age and electrocardiographic findings in all cases

	B12	
	r	p
Age	-0.175	0.048[a]
ECG		
Heart Rate	0.103	0.246
Tp-e	-0.580	<0.001[b]
Tp-e/QT	-0.511	<0.001[c]
Tp-e/QTC	-0.549	<0.001[d]

[a]Pearson correlation, there is a significantly negative correlation between vitamin B12 and age.
[b]Pearson correlation, there is a significantly negative correlation between vitamin B12 and Tp-e interval.
[c]Pearson correlation, there is a significantly negative correlation between vitamin B12 and Tp-e interval/QT distance ratio.
[d]Pearson correlation, there is a significantly negative correlation between vitamin B12 and Tp-e interval/corrected QT distance ratio.
ECG: Electrocardiography, OTc: Corrected QT

Table 6. Electrocardiographic and echocardiographic findings by gender in the vitamin B12 deficiency group

	Male			Female	
	Mean ± SD	Minimum to Maximum	Mean ± SD	Minimum to Maximum	p
ECG					
Heart rate	79.9±11.8	56-107	87.4±16.5	54-135	0.043[a]
QTc (msec)	395±14.8	366-430	391.5±21.9	335-429	0.391
Tp-e	82.4±4.5	68-90	80.5±4.3	72-90	0.084
Tp-e/QT	0.25±0.02	0.20-0.27	0.25±0.02	0.19-0.33	0.320
Tp-e/QTC	0.21±0.01	0.16-0.24	0.21±0.01	0.17-0.23	0.647
ECG					
LVEDD (mm)	43.0±4.9	33-52	40.6±5.0	32-48	0.057
LVESD (mm)	25.7±6.5	17-55	23±3.1	16-31	0.042[b]
EF (%)	74.4±5.6	63-86	73.7±7.3	64-89	0.518
SF (%)	41.7±5.0	34-53	41.9±7.0	34-60	0.549
IVSd (mm)	8.32±1.70	6-11	8.33±1.57	5-11	0.881
LVPWd[6] (mm)	8.32±1.64	6-11	8.33±1.85	4-12	0.908

LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, EF: Ejection fraction, SF: Shortening fraction, IVSd: Interventricular septum diameter, LVPWd: Left ventricular posterior wall diameter, ECG: Electrocardiography, SD: Standard deviation
[a]Mann-Whitney U test, heart rate was found to be statistically significantly lower in boys than in girls (p=0.043).
[b]Mann-Whitney U test, left ventricular end-diastolic diameter value was found to be statistically significantly higher in boys compared to girls

increased intestinal permeability. Increased intestinal permeability is observed in another study conducted on patients with Behcet's syndrome and it is reported that the absorption of folate and vitamin B12 due to subclinical gastrointestinal inflammation may decrease (13). Vitamin B12 prevents oxidative stress with its role in cellular metabolic pathways that inhibit lipid peroxidation and free radical formation (14). In a study where the relationship between rheumatoid arthritis that develops with immune and inflammatory processes and vitamin B is examined, the detection of Th1-immune response and oxidative stress stimulated in parallel with decreased levels of vitamins B suggests that the immune activation may be accountable for homocysteine accumulation (15). Studies have been conducted in the childhood group to evaluate chronic diseases in which immune and inflammatory mechanisms play a role in the pathogenesis and their effects on the electrical activity of the heart. A significant relationship was found between Qt dispersion and Tp-e interval values in patients with Familial Mediterranean Fever, Kawasaki, hypothyroidism, celiac disease, ulcerative colitis and Crohn's disease (16-19).

In the study conducted by Isakov et al. (20) on 120 individuals between the ages of 40-70, one group was administered a multivitamin containing vitamin B12 and the other group was administered placebo for 8 weeks. The blood values and homocysteine levels showed that the cardiovascular risk parameters decreased in the group receiving vitamin supplements (20).

Several ECG parameters provide preliminary information on current or likely clinical situations. QT interval and T wave are significant as they indicate cardiac repolarization. It is shown that the increase in QT dispersion, which is considered to indicate regional heterogeneity in myocardial repolarization, causes serious ventricular arrhythmias and sudden cardiac death by way of re-entry (21). The Tp-e interval corresponds to the ventricular repolarization dispersion. Any increase in ventricular repolarization dispersion is regarded as an important risk factor for ventricular arrhythmias. The prolonged Tp-e interval represents the abnormal dispersion of ventricular repolarization and is associated with an increased risk of ventricular arrhythmia (14). Therefore, the Tp-e interval is a non-invasive screening method for arrhythmogenesis. Tp-e interval, the Tp-e/QT ratio and Tp-e/QTc ratio are parameters that represent the increase in the ventricular repolarization dispersion in recent studies. The prolonged Tp-e interval is associated with increased mortality in patients with long QT syndrome, Brugada syndrome and acute myocardial infarction. Since Tp-e/QT ratio is not affected by the heart rate and body weight, it is a more sensitive marker than others (4).

We could not find any study in the literature in English that evaluates the relationship between vitamin B12 and QT dispersion, which is used as an indicator of susceptibility to ventricular arrhythmia, and Tp-e interval in the adult or paediatric population. However, studies that evaluate these parameters with iron deficiency and vitamin D in the paediatric population are available. Karadeniz et al.

(22) report a significant negative correlation between the level of ferritin and Tp-e interval and QT dispersion values, which was thought to be associated with impaired cardiac hemodynamics due to iron deficiency anaemia. In their study conducted with 100 adolescent patients with the aim of investigating the relationship between vitamin D and ventricular repolarization abnormalities, Bagrul et al. (23) reported that the effects of vitamin D on cardiac contractility and calcium haemostasis of the myocardium and QT dispersion and Tp-e interval values were found to be high. Tp-e interval and the Tp-Te/QT ratio were found significantly increased in patients with ventricular tachycardia and ventricular fibrillation more than other in patients with ventricular premature complexes (VPC) and may be used as a novel non-invasive marker of differentiating malignant and benign VPC (24). In another article, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, in patients with newly diagnosed COVID-19, were prolonged compared with normal healthy individuals (25). Our study suggests that both autonomic nervous system dysregulation and its function in cellular metabolic pathways and its endovascular damaging effects result in changes in the cardiac electrical activity.

In our study, QT dispersion and QTc dispersion values in the patient group were found to be statistically significantly higher compared to the control group (p=0.009; p<0.001, respectively). Tp-e interval was statistically significantly higher in the patient group compared to the control group (p<0.001). In the patient group, the Tp-e/QT ratio and the Tp-e/QTc ratio were statistically significantly higher than in the control group (p<0.001; p<0.001, respectively). In our study, no statistically significant difference was found in the heart rate in the patient group compared to the control group (p=0.118). No significant difference was found between the patient and control groups in terms of P wave, PR interval, QRS complex and QT interval values.

In a study in which vitamin B12 and echocardiographic markers were evaluated in 367 patients who underwent angiography, a significantly decreased left ventricular EF was found in the B12 deficient group (9). In our study, LVEDD, LVESD, end-diastolic IVSd, end-diastolic LVPWd, EF and SF measurements were made in the patient and control groups as classical echocardiography measurements. No significant difference was not found in the EF and SF values in both groups. The mean IVSd and LVPWd values of the patient group were statistically significantly higher compared to the control group (p=0.013 and p=0.040, respectively).

A statistically significant negative correlation was found between the level of vitamin B12 and age in all cases included in the study (r=-0.175). It is known that atherosclerosis resulting from endothelial dysfunction starts in childhood (6). The correlation between age and ECG parameters was evaluated in all cases. Any statistically significant correlation was not found between age and Tp-e interval, Tp-e/QT, Tp-e/QTc values.

Study Limitations

The sample size of the study is small. Our study is not planned for long term and thus, it does not provide the opportunity to evaluate the clinical findings of ECG changes in the future. Possible changes in the post-treatment ECG findings of the vitamin B12 deficient group could not be assessed due to time restrictions. However, our study is important for revealing the effect of isolated vitamin B12 deficiency on the electrical activity of the heart in order to eliminate the effect of other vitamin values on ECG findings, considering that iron deficiency and vitamin D deficiency and ECG changes were examined in previous studies.

Conclusion

In conclusion, our study provides significant findings to detect early signs of cardiovascular events that may occur in the childhood age group with vitamin B12 deficiency. Repolarization differences compared to the normal population may reflect early subclinical findings associated with Vitamin B12 deficiency. Further prospective studies with larger samples are needed to identify these early period changes and their clinical significance.

Authorship Contributions

Concept: C.Y., N.S., Design: C.S., M.E., Data Collection or Processing: N.S., C.Y., Analysis or Interpretation: C.Y., K.S., M.E., Literature Search: C.Y., N.S., Writing: C.Y., K.S., M.E., N.S.

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