ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Vitamin B12 Level in Children

Çocuklarda B12 Vitamin Seviyesi

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Abstract

Introduction: Vitamin B12 deficiency may have serious results and surplus vitamin may be guiding in the process/follow-up of some diseases. It was aimed to determine the vitamin B12 level (by retrospective screening) in children without chronic disease who applied to our outpatient clinic.
Materials and Methods: After excluding acute and chronic diseases, vitamin B12 levels, age, gender, and the season of presentation were investigated in all patients who applied to the general pediatric outpatient clinic, only in children with complaints of fatigue, decreased appetite, and healthy child examination.
Results: Three thousand one hundred and sixty three children were included in the study. Vitamin B12 deficiency was present in 5.5% individuals, vitamin B12 insufficiency was present in 23.6% individuals, and high vitamin B12 level was present in 2.1% individuals. The age range with the lowest vitamin B12 levels in both female and male children was found to be 14-18 years ($p<0.001$). Vitamin B12 deficiency and borderline deficiency were mostly seen in August and July ($p<0.001$).
Conclusion: Vitamin B12 deficiency and borderline deficiency were observed in approximately one third of patients, most frequently in the age group of 1-3 years, and in the adolescent age group in summer season.

Öz

Giriş: B12 vitamini eksikliği ciddi sonuçlar doğurabilir. Yüksek B12 vitamini seviyeleri bazı hastalıkların takip sürecinde yol gösterici olabilir. Polikliniğimize başvuran kronik hastalığı olmayan çocuklarda vitamin B12 düzeyinin (retrospektif taranarak) belirlenmesi amaçlandı.
Gereç ve Yöntem: Genel çocuk polikliniğine başvuran tüm hastaların dosyası retrospektif tarandı sadece halsizlik, iştahsızlık şikayeti ile başvuran kronik hastalığı olmayan, sağlıklı çocuk muayenesi tanılı hastalar çalışmaya alındı.
Bulgular: Çalışmaya üç bin yüz altmış üç çocuk dahil edildi. Çocukların %5,5'inde B12 vitamini eksikliği, %23,6'sında B12 vitamini yetersizliği (sınırda eksikliği) ve %2,1'inde yüksek B12 vitamini düzeyi mevcuttu. Hem kız hem de erkek çocuklarda vitamin B12 düzeyinin en düşük olduğu yaş aralığı 14-18 yaş olarak bulundu ($p<0,001$). Vitamin B12 eksikliği ve borderline eksikliği en çok Ağustos ve Temmuz aylarında görüldü ($p<0,001$).
Sonuç: B12 vitamini eksikliği ve borderline eksikliği hastaların yaklaşık üçte birinde, en sık 1-3 yaş grubunda ve adölesan yaş grubunda yaz mevsiminde gözlendi.

Keywords
Vitamin B12, childhood, age, season

Anahtar kelimeler
B12 vitamini, çocukluk çağı, yaş, mevsim

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Introduction

Vitamin B12, which is required in the healthy neurometabolic and hematologic processes, is a cofactor for DNA synthesis, carbohydrate-lipid metabolism, and purine synthesis (1). Insufficient vitamin B12 intake with foods, vitamin B12 deficiency of the mother, use of H2 receptor antagonists or proton pump inhibitors, malabsorption syndromes such as atrophic gastritis, pernicious anemia, and celiac disease, and disorder in intracellular cobalamin processing may cause vitamin B12 deficiency (2). The most common reason is the insufficient vitamin B12 intake due to malnutrition (3).

Vitamin B12 deficiency may not give a significant symptom at the beginning, however, it may cause discomfort, anorexia, anemia, thrombocytopenia, pancytopenia, growth retardation, developmental regression, apathy, weak growth, predisposition to infections, irreversible damage of the developing brain, gastrointestinal system findings, intrauterine deficiency, and congenital anomalies in time (1,2,4).

The recommended daily vitamin B12 intake is 0.4 μg for infants aged between 0 and 6 months, 0.5 μg for infants aged between 7 and 12 months, 0.9 μg for children aged between 1 and 3 years, 1.2 μg for children between 4 and 8 years, 1.8 μg for children between 9 and 13 years, and 2.4 μg for individuals older than 14 years (1). Vitamin B12 deficiency varies according to the age, diet, socioeconomic status, gender, and race of the child and it can be seen at every age (1,5-7).

While vitamin B12 deficiency is seen at the rate of 1-3% in developed countries, it can be seen at the rate of 40% in developing countries, and 22-66% in poor regions in terms of socioeconomic aspect (3). Vitamin B12 deficiency is present in 2.9-25.7% in the world and 0.03-48.8% in Turkey among all the patients and healthy individuals (7-9).

High vitamin B12 level related to high haptocorrin and transcobalamin levels that occur via different mechanisms such as excess vitamin B12 intake (for nutritional or treatment purposes), release of vitamin B12 from the sources in the cases such as liver injuries, transcobalamin synthesis defect, leukocytosis, hematological malignancies, liver diseases, renal diseases, autoimmune diseases, and solid tumors may develop (10).

There is limited data regarding the correlation between vitamin B12 deficiency and seasonal changes. In our study, vitamin B12 deficiency and seasonal changes were investigated.

The aim of this study is to retrospectively screen the vitamin B12 levels in children who do not have a known chronic disease and come to the outpatient clinic due to fatigue or loss of appetite. To determine the frequency of vitamin B12 deficiency, borderline deficiency, high and normal vitamin values in these children and to investigate the distribution of these values according to age, gender, season.

This study screened children without acute or chronic disease for vitamin B12, unlike previous studies in Turkey. The number of children whose B 12 level was investigated in this study is higher than in other studies. B12 levels are evaluated according to age groups of children aged 0-18 without acute or chronic diseases. In this way, it gives an idea about normal, deficient, insufficient, and high vitamin B12 levels. Because they live in the same city, it allows to compare the B12 levels of children of different age groups who have a similar diet. B12 levels are evaluated in children according to the seasons. In this way, it can be a guide for B12 supplementation with foods, if necessary, according to the seasons.

Materials and Methods

The hospital where the study was conducted is the only university hospital in the city. After the approval of the Erzincan Binali Yıldırım University Ethics Committee (decision no: 32, date: 16.10.2018), the files of the patients who applied to the general pediatric policlinic between 01.01.2012 and 31.12.2018 were retrospectively scanned through the hospital information system.

Firstly, patients aged 18 years and over, diagnosed with acute infection and diagnosed with chronic disease were excluded from the study. Secondly, patients who had routine blood tests and vitamin B12 levels were determined. Among these patients who were evaluated later, those with abnormal liver function tests, kidney function tests and electrolyte values were excluded from the study. While some of the patients had vitamin B12 levels measured at different times, only the first vitamin B12 levels of the children were considered from the values at their recurrent arrivals, and each patient was recorded once. After excluding chronic and acute diseases from the diagnosis part of the hospital system and laboratory results, the vitamin

B12 results of those who had application complaints, weakness, fatigue, loss of appetite or those who applied for a healthy child examination were recorded. According to the vitamin B12 needs of the patients, their ages were grouped as 0-6 months, 7-12 months, 1-3 years, 4-8 years, 9-13 years, and 14-18 years (1). Even though the sensitivity and specificity of serum or plasma vitamin B12 levels were low, vitamin B12 is the most commonly used status biomarker. It also reflects the amount of metabolically active cobalamin, haptocorrin-bound cobalamin, and vitamin B12 sources (11). Serum vitamin B12 level was studied on the Siemens Centaur XP Immunoassay System at the hospital. For vitamin B12, values less than 200 pg/mL were accepted as deficiency, those at 200-300 pg/mL limit as low (insufficiency), those at 301-900 pg/mL as normal, and more than 900 pg/mL as high (10,12,13).

Statistical Analysis

SPSS 22.0 statistics package program was used for data assessment. The descriptive statistics of the analysis results were given as mean, minimum (min), maximum (max) values, and standard deviation for the measurement variables, and the percentage (%) and number (n) were given for the qualitative variables. The normal distribution of the numerical variables was assessed by Shapiro-Wilk test. Mann-Whitney U test was used if the data were not normally distributed in the comparison of both groups. Kruskal-Wallis test was used for comparing more than two independent groups. The chi-square test was used for the comparison of qualitative data. The value of $p<0.05$ was accepted as statistically significant.

Results

Of a total of 3163 children included in the study, 1634 (51.7%) were girls and 1529 (48.3%) were boys and the average age was 6.8±5.1 (min: 3 days - max: 17.9 years). The age average of girls was higher than the boys. More than half of the children (55.6%) were aged between 1 and 8 years and vitamin B12 was assessed in more children in the summer season. Table 1 and Table 2 show age data according to vitamin B12 needs and the application season.

Median value of vitamin B12 was 374 pg/mL (min. 65-max. 1747). Vitamin B12 deficiency was present in 173 (5.5%) children, borderline vitamin B12 deficiency was present in 748 (23.6%) individuals, normal vitamin B12 level was present in 2177 (68.8%)

Table 1. The number of patients and median B12 values of the patients according to gender, vitamin B12 needs, and their vitamin B12 levels

		Number of patients (%)	Age/month median (min-max)	Vitamin B12 level median (min-max)	p	Vitamin B12 level <200 (pg/mL) n (%)	Vitamin B12 level 201-300 (pg/mL) n (%)	Vitamin B12 level 301-900 (pg/mL) n (%)	Vitamin B12 level >900 (pg/mL) n (%)	p
	Total	3163 (100)	70.1 (0.1-214.9)	374 (65-1747)	-	173 (5.5)	748 (23.6)	2177 (68.8)	65 (2.1)	-
Gender	Girl	1634 (51.7)	76.2 (0.1-214.9)	378 (65-1392)	0.550	97 (3.1)	356 (11.3)	1040 (32.9)	36 (1.1)	0.118
	Boy	1529 (48.3)	64.3 (0.1-214.5)	371(93-1747)	-	76 (2.4)	392 (12.4)	1137 (35.9)	29 (0.9)	-
Age range according to vitamin B12 needs	0-6 m	90 (2.8)	4.9 (0.1-6.97)	358 (134 -1747)	-	11 (0.3)	21 (0.7)	53 (1.7)	5 (0.2)	-
	7-12 m	260 (8.2)	9.2 (7.1-11.9)	345.5 (123-1145)	<0.001	33 (1.0)	65 (2.1)	157 (5.0)	5 (0.2)	<0.001
	1-3 y	880 (27.8)	24.6 (12.0-47.8)	401.5 (93-1309)	-	41 (1.3)	170 (5.4)	638 (20.2)	31 (1.0)	-
	4-8 y	878 (27.8)	75.5 (48.0-107.9)	423 (65-1392)	-	19 (0.6)	144 (4.6)	700 (22.1)	15 (0.5)	-
	9-13 y	616 (19.5)	136.5 (107.9-167.9)	342 (128-1297)	-	32 (1.0)	168 (5.3)	410 (13.0)	6 (0.2)	-
	14-18 y	439 (13.9)	189.9 (168-214.9)	302 (97-1466)	-	37 (1.2)	180 (5.7)	219 (6.9)	3 (0.1)	-

m: Month, y: Year, max: Maximum, min: Minimum

Table 2. Vitamin B12 levels of patients in the application season

		Number of patients (%)	Age/month median (min-max)	Vitamin B12 level median (min-max)	p	Vitamin B12 level <200 (pg/mL) n (%)	Vitamin B12 level 201-300 (pg/mL) n (%)	Vitamin B12 level 301-900 (pg/mL) n (%)	Vitamin B12 level >900 (pg/mL) n (%)	p
	Total	3163 (100)	70.1 (0.1-214.9)	374 (65-1747)	-	173 (5.5)	748 (23.6)	2177 (68.8)	65 (2.1)	-
Season	Winter	788 (24.9)	73.8 (0.1-214.9)	401 (132-1747)	-	27 (0.9)	141 (4.5)	606 (19.2)	14 (0.4)	-
	Spring	730 (23.1)	66.6 (0.4-214.2)	396 (103-1392)	-	23 (0.7)	141 (4.5)	548 (17.3)	18 (0.6)	-
	Summer	920 (29.1)	71.7 (0.2-214.7)	343 (93-1321)	<0.001	76 (2.4)	271 (8.6)	559 (17.7)	14 (0.4)	<0.001
	Autumn	725 (22.9)	67.3 (0.1-214.8)	356 (65-1466)	-	47 (1.5)	195 (6.2)	464 (14.7)	19 (0.6)	-

max: Maximum min: Minimum

individuals, and high vitamin B12 level was present in 65 (2.1%) individuals. The age range with the lowest level of vitamin B12 was 14-18 years (p<0.001). Vitamin B12 deficiency was seen mostly between 1-3 years and borderline vitamin B12 deficiency was seen between 14-18 years. Vitamin B12 deficiency and borderline vitamin B12 deficiency were seen mostly in summer season according to the seasons. Excess vitamin B12 was observed mostly between 1 and 3 years. These findings were statistically significant. Table 1 and Table 2 show the frequency of vitamin B12 deficiency, borderline deficiency, excess and normal Vitamin B12 values according to gender, age group, and season, and the median (max-min) values of vitamin B12.

The age range with the lowest vitamin B12 levels in both female and male children was found to be between 14 and 18 years (p<0.001). Vitamin B12 deficiency and borderline deficiency were seen mostly between 1 and 3 years in girls and between 14 and 18 years in boys (p<0.001). Table 3 shows the frequency of vitamin B12 deficiency, borderline deficiency, excess and normal vitamin B12 values based on age group in girls and boys, and the median (max-min) values of vitamin B12.

Median value of vitamin B12 was at the lowest value with 332 pg/mL in August (min 93-max 1145) and vitamin B12 deficiency was seen mostly in August, and borderline vitamin B12 deficiency was seen mostly in July (p<0.001). Table 4 shows the frequency of vitamin B12 deficiency, borderline deficiency, excess and normal vitamin B12 values according to the months of application, and the median (max-min) values of vitamin B12.

Discussion

Vitamin B12 is important for all ages as of the intrauterine period and children are always at risk of vitamin B12 deficiency. The main cause of vitamin B12 deficiency in the first six months of life is the low level of vitamin B12 in breast milk. Infants get enough vitamin B12 only via breast milk in the first 6 months of life provided that the mother has no vitamin B12 deficiency. It has been shown that if vitamin B12 deficiency is present due to the vegan-vegetarian diet of the mother, insufficient vitamin B12 intake via foods, or other reasons, infants also have vitamin B12 deficiency (2,14-17).

Table 3. Vitamin B12 levels by gender and age

Gender	Age	B12 (pg/mL) median (min-max)	B12 <200 (pg/mL) n (%)	B12=201-300 (pg/mL) n (%)	B12=301-900 (pg/mL) n (%)	B12 >900 (pg/mL) n (%)	p
	0-6 m	357 (134-1038)	7 (0.5)	7 (0.5)	21 (1.4)	2 (0.1)	-
	7-12 m	330.5 (134-1145)	20 (1.3)	37 (2.4)	77 (5.0)	2 (0.1)	-
Girl	1-3 y	411 (100-1309)	24 (1.6)	96 (6.3)	331 (21.6)	20 (1.3)	<0.001
	4-8 y	422 (65-1392)	11 (0.7)	83 (5.4)	344 (22.5)	8 (0.5)	-
	9-13 y	344 (158-1297)	19 (1.2)	80 (5.2)	196 (12.8)	4 (0.3)	-
	14-18 y	303.5 (131-681)	16 (1.0)	53 (3.5)	71 (4.6)	0 (0.0)	-
	0-6 m	359 (155-1747)	4 (0.2)	14 (0.9)	32 (2.0)	3 (0.2)	-
	7-12 m	369.5 (123-1012)	13 (0.8)	28 (1.7)	80 (4.9)	3 (0.2)	-
Boy	1-3 y	396 (93-1205)	17 (1.0)	74 (4.5)	307 (18.8)	11 (0.7)	<0.001
	4-8 y	424 (136-1239)	8 (0.5)	61 (3.7)	356 (21.8)	7 (0.4)	-
	9-13 y	341 (128-999)	13 (0.8)	88 (5.4)	214 (13.1)	2 (0.1)	-
	14-18y	302 (97-1466)	21 (1.3)	127 (7.8)	148 (9.1)	3 (0.2)	-

m: Month, y: Year, B12: Vitamin B12 levels, max: Maximum, min: Minimum

Table 4. Vitamin B12 levels by month

Season	Month	B12 median (min-max)	B12 <200 pg/mL n (%)	B12 201-300 pg/mL n (%)	B12 301-900 pg/mL n (%)	B12 >900 pg/mL n (%)	Total n (%)
Winter	December	454.5 (157-1747)	2 (0.1)	22 (0.7)	138 (4.4)	4 (0.1)	166 (5.2)
	January	381 (161-1044)	9 (0.3)	54 (1.7)	213 (6.7)	5 (0.2)	281 (8.9)
	February	398 (132-1037)	16 (0.5)	65 (2.1)	255 (8.1)	5 (0.2)	341 (10.8)
Spring	March	402.5 (163-1392)	9 (0.3)	51 (1.6)	236 (7.5)	8 (0.3)	304 (9.6)
	April	395 (103-1309)	6 (0.2)	45 (1.4)	167 (5.3)	5 (0.2)	223 (7.1)
	May	386 (144-1116)	8 (0.3)	45 (1.4)	145 (4.6)	5 (0.2)	203 (6.4)
Summer	June	354 (97-1321)	20 (0.6)	63 (2.0)	144 (4.6)	3 (0.1)	230 (7.3)
	July	345.5 (122-1211)	24 (0.8)	116 (3.7)	235 (7.4)	5 (0.2)	380 (12.0)
	August	332 (93-1145)	32 (1.0)	92 (2.9)	180 (5.7)	6 (0.2)	310 (9.8)
Autumn	September	333 (131-1249)	20 (0.6)	75 (2.4)	159 (5.0)	3 (0.1)	257 (8.1)
	October	354 (65-1053)	15 (0.5)	69 (2.2)	141 (4.5)	5 (0.2)	230 (7.3)
	November	374.5 (143-1466)	12 (0.4)	51 (1.6)	164 (5.2)	11 (0.3)	238 (7.5)

B12: Vitamin B12 level, max: Maximum, min: Minimum

The lowest vitamin B12 level is seen in the first six months of life; then, the level increases gradually, and peaks around seven years old. As myelinization is very rapid in the first two years of life, vitamin B12 deficiency in this period may lead to more serious neurological problems (2).

In the studies conducted in India, one of countries with high prevalence of vitamin B12 deficiency, it was found that vitamin B12 deficiency in India was present in 16% of children in age range of 1 and 6 months and 22-33.7% of children in age range of 1 and 12 months (15-17). The studies conducted in other

countries revealed that deficiency was found in 9.1-34.2% of children in age group of 0 and 1 year and in Turkey, this rate was 39.8% in infants between 6 and 12 months (6,18-21). In the present study, 12.2% of children aged between 0 and 6 months had deficiency, 23.3% had borderline deficiency, and in the period between 7 and 12 months when supplementary food and breast milk were given, 12.7% had deficiency and 25% had borderline deficiency.

In Colombia, Amazon, Brazil, and Nepal, the rate of vitamin B12 deficiency was 0-30.2% and insufficiency was 33-52% in children under 24 months (6,18,22); and in Mexico, Guatemala, and India, this rate was 3.3-36% in 0 and 3 year-old children (6,14,23), and deficiency of 0.64% was found in 4 and 24 month-old children (diagnosed with anemia) in Turkey (24). In the present study, 9.2% of children aged between 0-24 months had deficiency and 24.1% had insufficiency; 4.7% of children aged between 1 and 3 years had deficiency and 19.3% had borderline deficiency.

Vitamin B12 deficiency can be seen in 8-30% of children under 6 years and 1.6-32.5% in older children having a general reluctance to food and selective eating behaviors (23,25). In the studies on Vitamin B12 in children under 6 years; deficiency was found at a rate of 0- 67.2%, insufficiency at 10.7-24.2% in various countries of the world; and deficiency at a rate of 23.3% was observed in Turkey (6,17,20,22,23,26). In the current study, deficiency of 2.6% and borderline deficiency of 15.9% were found in the period between 24 and 60 months.

When examining level of vitamin B12 in school age during which dietary habits are affected from family and the circle, it was observed that vitamin B12 deficiency was 12-51% in school-age children in India (27) and 12.01% in Venezuela; vitamin B12 deficiency and insufficiency were 1.7% and 31.5%, respectively in Amazon and approximately 3% and 20% in Colombia (22); vitamin B12 deficiency was 1.3% in age group of 9-13 years in USA (28); and vitamin B12 deficiency was 10.8% in 203 children aged between 9-12 years in Şanlıurfa in Turkey (29). In the present study, it was determined that vitamin B12 deficiency was 3.9% in school-age children (7-14 years) and borderline vitamin B12 deficiency was 22.3%.

The pubertal and adolescent age group, covering the age group of 10-18 years, is the rapid growth and development period, and also, the development of the gray matter of the brain is at its fastest level during adolescence. Vitamin B12 deficiency, which develops for various reasons during this period, may lead to fatigue, nervousness, psychiatric problems, developmental problems, and mild to severe neurological and hematological problems. When vitamin B12 deficiency and insufficiency were investigated in the pubertal and adolescence periods, deficiency of 1.3-38% and insufficiency of 2.2-23% were shown in India, Colombia, and USA, and deficiency of 10.5% was shown in Turkey (26,28,30). In the current study, deficiency of 6.7 % and borderline deficiency of 35.5 % were found in the age period of 10 and 18 years. In the current study, it was observed that there was a higher rate of vitamin B12 deficiency in the first 12 months of life and in the adolescence period compared to other age groups, which was compatible with the literature.

In the studies conducted in Turkey, frequency of vitamin B12 deficiency was shown in 0.3-19% of children, and borderline deficiency was present in approximately 32% (8,9,21,24). In the current study, when all the children under 18 years were considered, there was deficiency of 5.5% and borderline deficiency of 23.6%.

In the study conducted by Margalit et al. (31), regarding gender differences, they stated that vitamin B12 deficiency was high in adult men and this may be related to the protective effect of estrogen in women, and the high level of homocysteine seen together low B12 could be a risk factor for cardiovascular diseases. In some studies, while the vitamin B12 level was lower in girls than in boys, statistical significance was not observed (30), and in some studies, B12 deficiency was observed more in males and this situation was associated with the rapid growth of the male gender (22,27). In the present study, vitamin B12 level was similar between female and male children. Prevalence of vitamin B12 deficiency or borderline vitamin B12 deficiency was similar between them ($p>0.05$).

There is limited data regarding the correlation between vitamin B12 deficiency and seasonal changes. In a study it was reported that seasonal change in vitamin B12 was uncertain. Vitamin B12 was taken less in winter, which was reflected as a deficiency in the spring. More vitamin B12 was taken in summer; therefore there was less vitamin B12 deficiency in

autumn. B12 turnover has been cited as the reason for its slowness (32). In the present study, vitamin B12 deficiency was mostly seen in the summer season and in August.

In three different single-centered studies, high vitamin B12 levels were found at the rates of 14.5%- 18.5%- 20%. Among the limited number of studies related to high vitamin B12 level, the prognosis of such elevations in terms of malignancies and diseases is investigated (33). High vitamin B12 level is present in a small number of patients (2.1%) in the current study.

Study Limitations

Because it was a retrospective study, detailed information about diet, neuromotor development, height and weight percentile of many patients could not be found. Therefore, there is no comparison with this information.

Conclusion

Vitamin B12 deficiency and borderline deficiency were seen in about one-third of patients. The most common groups with vitamin B12 deficiency are 1-year-old age group and the adolescent age group. Healthy nutrition with a relevant diet is important in childhood. Deficiency is seen more in summer season. This may be a supportive finding in terms of vitamin B12 supplementation in winter. Age and season are among important factors in vitamin B12 deficiency.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Erzincan Binali Yıldırım University (decision no: 32, date: 16.10.2018).

Conflict of Interest: No conflict of interest was declared by the authors.

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