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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Retrospective Analysis of Pediatric Patients with Vitamin B12 Deficiency

Vitamin B12 Eksikliği ile Takip Edilen Çocuk Hastaların Retrospektif İncelenmesi

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ABSTRACT

Aim: Vitamin B12 (cobalamin) is an important vitamin that plays a role in vital events. This study examines and analyzes patients with vitamin B12 deficiency in a specific region in a wide range of age groups, including infants.

Material and Method: 275 patients with vitamin B12 deficiency aged 0-18 years who were followed and treated in the Hematology outpatient clinic at a 3rd level training and research hospital during 3 years, were analyzed retrospectively.

Results: 120 (43.6%) patients were female of a total of 275 patients with vitamin B12 deficiency. The mean vitamin B12 level was 159.78±33.98 pg/ ml, the mean hemoglobin level was 11.47±2.27 g/dL, and the MCV was 81.51±10.37 fL. 100 patients were under one year of age. 22% of mothers of the infants had vitamin B12 deficiency, while 20.9% of mothers had levels of vitamin B12 that can be presumed border value. 32% of patients had iron deficiency. The 87% of causes that evoked vitamin B12 deficiency were nutritional. Another leading factor for vitamin B12 deficiency was *Helicobacter pylori* (HP) infection and the frequency was 10.2%. The expected increment in vitamin B12 and complete blood count values were observed after treatment.

Conclusion: Vitamin B12 deficiency becomes widespread in the first two years of life and infants are at risk. Another important factor is HP. Eradication of this infection could treat vitamin B12 deficiency.

Keywords: Vitamin B12, children, megaloblastic anemia, *Helicobacter pylori*, anemia

ÖZ

Amaç: Vitamin B12 (kobalamin yaşamsal olaylarda rol alan önemli bir vitamindir. Bu çalışma infantları da içeren geniş kapsamlı yaş grubunda belirli bir bölgedeki vitamin B12 eksikliği olan hastaları analiz etmektedir.

Gereç ve Yöntem: 3. basamak eğitim araştırma hastanesindeki hematoloji polikliniğinde 3 yıllık dönemde, vitamin B12 eksikliği tanısıyla takip ve tedavi edilen 0-18 yaş grubu 275 hastanın dosyası geriye dönük olarak incelendi.

Bulgular: 275 hastanın 120'si (%43,6) kız, 155'i (%56,4) erkekti. Hastaların serum vitamin B12 seviyesi ortalaması 159,78±33,98 pg/mL, hgb ortalaması 11,47±2,27 g/dL, MCV ortalaması 81,51±10,37 fL idi. 100 hasta bir yaşın altındaydı. Bebeklerin annelerinin %22'sinde B12 vitamini eksikliği bulunurken, annelerin %20,9'unda B12 vitamini düzeyi sınırdaydı. İnfantların, serum vitamin B12 seviyesi bakılabilen annelerinde %22 oranında eksiklik saptanırken, %20,9'unda ise sınırda değerler görüldü. Hastaların %32'sine demir eksikliği eşlik ediyordu. Emilimi bozarak B12 eksikliğine yol açan önemli faktörlerden biri olan ***Helicobacter pylori*** enfeksiyonu sıklığı %10,2 olarak saptandı. Hastaların %87'sinde vitamin B12 eksikliğinin nedeninin ön planda nutrisyonel olduğu tespit edildi. Tedavi ile birlikte kan sayımı ve serum vitamin B12 seviyelerinde yükselme gözlendi.

Sonuç: B12 vitamini eksikliği yaşamın ilk iki yılında yaygındır ve infantlar risk altındadır.Yine emilim bozukluğuna yol açan ***Helicobacter pylori*** enfeksiyonunun çocuklarda azımsanmayacak sıklıkta görüldüğü ve bu enfeksiyonun eradikasyonunun vitamin B12 eksikliği tedavisinde katkısı olduğu tespit edilmiştir.

Anahtar Kelimeler: B12 Vitamini, çocuk, megaloblastik anemi, helikobakter pilori, anemi

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INTRODUCTION

Vitamin B12 (cobalamin) is a water-soluble vitamin that is obtained mainly from animal foods, acts as a coenzyme in important reactions in the body, and is especially involved in the production of Deoxyribonucleic Acid (DNA), which is necessary for cell division and proliferation (1). People meet all their cobalamin needs nutritionally (1, 2).

In vitamin B12 deficiency, tissues that grow rapidly and have rapid cell renewal are especially affected. Deficiency in children causes physical and neuromotor developmental delay, as well as megaloblastic anemia (2-4). Causes of vitamin B12 deficiency in childhood include inadequate intake, vitamin B12 absorption defects that intrinsic factor deficiency, gastric mucosal disease, malabsorption in the small intestines, widespread gastrointestinal malabsorption including vitamin B12 malabsorption, competition with Vitamin B12, Vitamin B12 Transport Defect and metabolism disorders could be considered (5). *Helicobacter pylori* (HP) infection and associated malabsorption might occur in children (6, 7).

Vitamin B12 deficiency causes serious neurological damage and long-term intellectual disorders in children (8). Therefore, prevention, recognition, and treatment of deficiency are important for the healthy development of infants and children.

This study analyzes data from a specific region, including a comprehensive age group classification and different etiological data. It is special in that it simultaneously analyzes infants and those with malabsorption due to gastritis. Our study also aimed to examine the frequency, nutritional history, comorbidities, demographic, clinical, and laboratory characteristics of patients with vitamin B12 deficiency, evaluate the treatment results, and compare the results with the literature.

MATERIAL AND METHOD

The data of patients in the 0-18 age group who were diagnosed with vitamin B12 deficiency and followed up and treated during 3. years in the Hematology Polyclinic of the 3rd Level Training and Research Hospital, living far from the sea and in a certain inland region, were retrospectively examined. These patients were identified by filtering from the hospital information system database. The diagnosis ages of the patients were grouped as newborns, infants, toddlers between 13-24 months, and children over two years of age.

Age at presentation, demographic, clinic, laboratory, and other findings were recorded in the patient follow-up form. Ethical approval was not necessary as the data were collected as part of clinical management and any identifiable data were anonymised fully. Nevertheless, Study Approval was received for this study from the hospital committee. The Helsinki Declaration was taken into consideration. The study was conducted by the Declaration of Helsinki.

Complete blood count and vitamin B12 levels were checked again in some patients for control purposes in the third month after the start of treatment. When evaluating nutritional deficiency; The group consuming red meat once a week or more frequently was considered sufficient, while the others were considered nutritional deficiencies.

The normal range of serum vitamin B12 was considered to be 200-800 pg/mL (9-11). Complete blood count values and the normal range of serum folic acid, ferritin, and homocysteine levels were measured for each age group (12, 13).

HP infection screening was performed using invasive and/or non-invasive tests in patients with upper gastrointestinal symptoms such as epigastric pain, nausea, heartburn, and gastroesophageal reflux symptoms.

Vitamin B12 treatment was administered intramuscularly (IM) every day for 1 week, then 4 doses weekly, and finally 3 doses once a month, according to a standard protocol, after adjusting the vitamin B12 dose according to the age of the patients (1). Ferrous sulfate is given orally at 4 mg/kg/day to patients with iron deficiency; Amoxicillin, clarithromycin, and lansoprazole were also given orally as triple eradication therapy to those who were HP positive.

Biochemical Analysis

Vitamin B12, folic acid, and ferritin were studied with the electrochemiluminescence immunoassay (ECLIA) method on the ADVIA Centaur XP brand device. Serum iron and LDH were studied using the colorimetric method on a Unicel DXC 800 Beckman Coulter brand device. A complete blood count was performed on an ABX Pentra DF 120 automatic blood count device. Homocysteine was studied using the electrochemiluminescence immunoassay (ECLIA) method on the Immulite 2000 XP brand hormone analyzer. Normal serum levels were determined according to the devices used in the laboratory.

Patients to be tested for C14 urea breath were required to have not used proton pump inhibitors, bismuth-containing compounds, and antibiotics in the last 1 month, H2 receptor antagonists in the last 1 week, and antacids in the last 24 hours. Each patient was given a 37 kBq (1µCi) 14C-urea-citric acid composition capsule (Helicap, Noster System AB Stockholm, Sweden) along with 25 ml of water after fasting for at least 4 hours. Breath samples were collected with the heliprobe method.

Patients whose test result was Grade 2 were considered infected with *Helicobacter pylori*.

Statistical Method

Statistical analysis of the data obtained from the research was carried out in the SPSS for Windows 15.0 package program. In evaluations, the Chi-Square test and Fisher-Exact test are used for comparisons of categorical data, and comparisons of quantitative data; Student's t-test was used for comparisons between two groups for normally distributed data, the Mann-Whitney U test was used for non-normally distributed data, One-way Analysis of Variance and Bonferroni test were used for normally distributed data for comparisons of more than two groups, and Kruskall-Wallis Analysis of Variance was used for non-distributed data. Relationships between quantitative variables were examined with Pearson Correlation analysis. Arithmetic mean, standard deviation was used as a descriptive value in quantitative data, and frequencies and percentages were used in qualitative data. The statistical significance limit was accepted as 0.05.

RESULTS

The median age of 275 patients was 7 years (20 days-17.5 years). 120 (43.6%) of these patients were girls and 155 (56.4%) were boys. While the median age of girls was 8 years, the median age of boys was 6 years. The age of girls was found to be significantly higher than that of boys (p<0.01). It was seen that the serum vitamin B12 level increased as the age at diagnosis increased (**Table 1**). However, no statistically significant difference was observed (p: 0.072).

Table 1. Relationship between Age Groups and Serum Vitamin B12 level mean levels.

Age group	N (%)	Vitamin B12 (pg/mL) mean ±SD	P
Newborn	5 (1.8%)	152.60±45.32	=0.072
Infant	95 (34.5%)	152.62±38.33	
>2 years old	146 (53%)	163.94±30.52	
13-24 months	29 (10.5%)	163.52±31.04	

N:numbers, %: percentage, SD: standard deviation.

Patients' History at Admission and Physical Examination Findings

In 204 of 275 patients (74.9%), there was a symptom at admission. The most common signs and symptoms were weakness, fatigue, and pallor. When we look at the most common symptoms of patients according to age groups, not being able to gain weight, growth and mental-motor retardation were at the top of the list in infants.

No pathological physical examination findings were detected in 161 of 275 patients (58.5%) at the time of diagnosis. The most frequently observed pathological physical examination findings in the remaining 114 patients (41.5%) were pallor of the skin and mucous membranes. Jaundice, hypotonia, and growth and mental-motor retardation were the most common findings in infants. Serum vitamin B12 levels of patients with pathological physical examination findings were found to be significantly lower than others (p<0.05).

At the time of admission, 74 out of 275 patients (26.9%) had neurological findings/symptoms. Numbness, tingling in the extremities and headache were the most common neurological findings and symptoms (30 patients), while seizures (16 patients), inability to walk, and hypotonia (10 patients) were more common in infants.

Laboratory and Hematological Data of Patients

The mean vitamin B12 level and other mean values are summarized in **Table 2**.

Table 2. Laboratory Data of the Patients.

	Mean±SD	Min.-Max.
Vitamin B12 (pg/mL)	159.78±33.98	40-200
vitamin B12 in mothers of the infants (pg/ mL)	262.59±92.74	56-528
Hemoglobin (g/dL)	11.47±2.27	5-17
MCV (fL)	81.51±10.37	44-103
Homocysteine (µmol /L)	18.23±22.27	4-189
Ferritin (ng/mL)	64.87±106.88	0.2-880
Folic acid (ng/mL)	12.92±7.53	2.2-30
Control Vitamin B12 (pg/mL)	687.30±545.18	1-2500

SD: standard deviation, min.: minimum, max.: maximum

Low ferritin level was detected in 88 patients (32%) in total. Hgb mean of patients with iron deficiency were found to be significantly lower before treatment than those without iron deficiency (p<0.001). In 9 patients (3.3%), low folic acid was detected in addition to Vitamin B12 deficiency. Laboratory, whole blood, and peripheral smear results are summarized in **Tables 2**, **3**, and **4**. No significant difference was detected between the mean vitamin B12 of patients with and without anemia.

Table 3. Relationship Between Complete Blood Count and Serum Vitamin B12 Mean Level.

Complete blood count findings percentage(%)	No	Yes	P
	Vitamin B12 Mean level (pg/mL) mean±SD	Vitamin B12 Mean level (pg/mL) mean±SD	
Anemia (38.5%)	158.50±33.67	161.81±34.54	>0.05
Leukopenia (25.2%)	159.64±33.89	161.41±35.79	>0.05
Thrombocytopenia (2.9%)	161.18±32.33	113.00±54.09	<0.001
Neutropenia (8.7%)	162.32±31.41	133.17±47.18	<0.001
Bicytopenia(4.4%)/pancytopenia (0.7%)	161.33±32.42	130.86±48.66	<0.001

SD: standard deviation.

Tablo 4. Peripheral smear findings.		
Peripheral smear findings	**N**	**%**
No abnormal findings	206	74.9
Hypersegmentation	9	3.3
hypochromic microcytic erythrocytes	50	18.5
Hypersegmentation + hypochromic microcytic erythrocytes	5	1.8
Blast	1	0.4
N:numbers, %: percentage.		

The mean vitamin B12 of patients with high MCV was found to be significantly lower than those with low or normal MCV (p<0.01). When the mean vitamin B12 of the patients with bicytopenia or pancytopenia were examined, serum vitamin B12 levels were found to be statistically significantly lower in both groups compared to the others (p <0.01). Serum vitamin B12 levels were found to be lower in patients with pancytopenia than in patients with bicytopenia (p<0.01). Bone marrow examination was performed in 13 (4.8%) of 275 patients, and megaloblastic changes were detected in the bone marrow in 3 (23.7%).

Examination of Laboratory Variables of Infants and Their Mothers

There were 100/275 patients who were under the age of one. The mean serum vitamin B12 level of the infants was 152.97±38.48 pg/mL. The mean age of the infants was 5±3.48 months (0-12 months). It was determined that 53% of infants were exclusively breastfed. It was seen that 35% of infants started to consume complementary foods at 6 months or less, and 9% started to consume complementary foods after 6 months. 56% had not started supplementary food yet. It was determined that the time for patients to start complementary foods was delayed.

Serum vitamin B12 levels could be measured in the mothers of 86 (86%) of the patients under one year of age. While the serum vitamin B12 level of 19 (22%) of 86 mothers was <200 pg/ml, the serum vitamin B12 level of 18 (20.9%) was between 201-250 pg/mL, serum vitamin B12 levels of 49 mothers (56.9%) were normal. Nutritional history could be questioned in 80 of 86 mothers. 74 of them (92.5%) consumed red meat once a year or less. While 5 of them consumed meat once a month, 1 of them consumed meat once a week or more frequently.

Associated diseases detected along with Vitamin B12 Deficiency

In 240 (87%) of the patients, the cause of vitamin B12 deficiency was thought to be primarily nutritional. HP infection was present in 28 patients (10.2%), and celiac disease was detected in 5 patients (1.8%). 2 patients were being followed up with a diagnosis of chronic diarrhea. Cystic fibrosis was suspected in 1 patient. Anti-parietal antibody positivity was detected in 6 of 275 patients (2.1%).

There were 15 of our selected infant patients in whom had associated neurologic symptoms and syndromic sign, and they had been tested for inherited metabolic diseases by acylcarnitine analysis with Tandem MS, serum amino acids, urine organic acid analysis. While transcobalamin II deficiency was detected in one patient, cobalamin E disease was detected in one patient, and methylene tetrahydrofolate reductase enzyme defect was detected in another patient. One patient was also diagnosed with West syndrome. A patient was also being followed due to gastric intrinsic factor deficiency. There were no positive viral serology results in the patients. Cobalamin E deficiency is diagnosed by metabolic tests and final diagnosis was made by complementation analysis in cultured fibroblasts. The patient had homocysteine in the urine metabolic screen prompted further testing for metabolites indicative of defects in cobalamin metabolism. He had a high serum homocysteine, low methionine, high methyltetrahydrofolate and normal methylmalonic acid.

Homocysteine was checked in 82 of 275 patients. The mean homocysteine level was 18.23±22.27 µmol/L. A strong, significant, and negative correlation was detected between vitamin B12 and homocysteine (p:0.003 r:-0.344). When looking at age groups, homocysteine levels in infants were significantly higher than other groups (p<0.001).

Patients with Accompanying *Helicobacter pylori* Infection

A screening test for HP infection was performed in 43 patients. HP positivity was detected in 28 of 43 patients (65.11%) and treatment was started. Based on the entire population, the rate was 10.2%. The mean age of those with positive HP screening was 183±21.93 months, while the mean age of those with negative screening was 145.93±44.87 months. The mean age was significantly higher in HP-positive patients than in negative patients (p<0.001). The rate of concomitant iron deficiency in HP-positive patients was 60.7% (17 patients). Among those with negative HP, iron deficiency was accompanied in 10 patients (66.6%).

Post-treatment control complete blood count and control B12 values of these 28 patients with HP infection were re-examined, and a statistically significant increase was detected compared to before treatment (p<0.001).

Follow-up and Treatment Results

Treatment was applied regularly in 244 of the patients (88.7%). 20 patients (7.3%) appeared to have problems complying with treatment.

In 134 of 275 patients, complete blood count tests and serum vitamin B12 levels were re-examined at their third-month follow-up. In 5 of 134 patients, the

serum vitamin B12 level measured in the 3rd month of treatment was found to be below 250 pg/mL. In 3 of these 5 patients, the control serum vitamin B12 level was <200 pg/mL. While two out of 5 patients had HP Infection; one patient was receiving treatment for brucellosis. These patients did not use replacement therapy and other treatments regularly. Neurological findings improved after B12 replacement treatment except one patient with seizure. That patient had still seizure and hypotonia who is diagnosed as West syndrome later.

Among the patients who started vitamin B12 treatment, one patient had contractions such as fasciculation of the tongue and myoclonic movements in the arm on the 4th day of IM treatment. A transcobalamin II defect was detected in this patient. No patient developed hypokalemia or heart failure.

DISCUSSION

Prevention, recognition, and treatment of vitamin B12 deficiency are important for the healthy development of infants and children (10). Among the causes of vitamin B12 deficiency, there are primarily nutritional reasons (14). This study has shown that it can also be seen in breastfed infants and that deficiencies may also occur due to conditions related to absorption problems in the gastrointestinal tract, even when nutritional intake is good. This study is unique in that it covers a wide age range from infants to adolescents and elucidates the etiology in a specific child population with vitamin B12 deficiency. Starting from infancy, vitamin B12 deficiency depends on the mother's vitamin deficiencies. It has also been shown in the study that older children may have malabsorption and vitamin B12 deficiency due to HP infection. The study showed that deficiency was observed even in cases where nutritional intake was good, and it was necessary to consider the absorption problem.

There are many prevalence studies conducted in various countries around the world. A feature of vitamin B12 is that normal values vary between races and societies (2, 15, 16). Looking at prevalence studies conducted around the world, vitamin B12 deficiency has been detected in 22% of school children in some regions of Mexico (2). Although there is no large study conducted throughout Turkey, there are studies conducted regionally and it has been reported that B12 deficiency is seen at a high rate (4, 10, 17, 18). Açkurt et al. reported vitamin B12 deficiency in expectant mothers during pregnancy (19).

The expected increase in MCV value may not occur when there is a thalassemia carrier, iron deficiency anemia, infection, or inflammatory disease along with megaloblastic anemia (13, 20). In a study conducted in the USA in 1994 on 406 adult patients, it was found that the probability of vitamin B12 deficiency was low (<25%) when MCV was normal (21). In the study conducted by Bay et al., the MCV value was below 90 fl in 1/3 of the cases (22). Consistent with the literature, 38.5% of our patients in our study were anemic and there was a significant negative correlation between vitamin B12 level and MCV. 32% of our patients were accompanied by iron deficiency. The mean MCV of those with iron deficiency was significantly lower than those without iron deficiency.

In cases born with low vitamin B12 stores and who receive insufficient vitamin B12 through breast milk, if vitamin B12 is not supplemented with external food, deficiency findings are expected to appear within the first few months of life. It has been reported in infant studies that vitamin B12 deficiency screening should also be added (17). The most important cause of deficiency in babies is due to deficiency in the mother (23).

Paleness, weakness, loss of appetite, inability to gain weight, vomiting, and diarrhea were the most common presenting symptoms in this study. When we look at the studies in the literature, the most common presenting symptoms were weakness, growth retardation, and hypotonia, especially in infants (24, 25). Our results were compatible with the literature.

The lower rates of anemia, thrombocytopenia, neutropenia, and pancytopenia in our study compared to other studies may be because the mean vitamin B12 level of our cases was higher than in other studies and that the vitamin B12 level of 70.5% of the patients was 150≤ pg/ml, which can be considered as mild deficiency. Our results showed that the incidence of neutropenia, bicytopenia, thrombocytopenia, and pancytopenia increased in proportion to the low vitamin B12 level.

Tests for neurological and neurometabolic diseases were made in fifteen infant patients.These patients had persistent symptoms despite adequate treatment and elevation of vitamin B12 level. It could be recommend to the physicians to test further for hematological diseases, for malignancies or for inherited metabolic diseases when there are associated severe systemic, hematological or neurological findings incompatible with vitamin B12 deficiency level or systemic, hematological, or neurological findings that persist despite the increase in levels with B12 treatment require us to suspect hematological, hereditary metabolic diseases and/or neurological diseases (26).

Bone marrow examination should be considered when clinical and laboratory findings like weight loss, fever and laboratory signs such as bicytopenia and pancytopenia. exist despite the elevation of vitamin B12. These

conditions should warn clinicians about hematological diseases or hereditary metabolic diseases in the routine follow-up of vitamin B12 deficiency (18).

HP infection, in which disorders related to the absorption of more than one micronutrient can be observed, could also be considered as another factor in the coexistence of Vitamin B12 deficiency with iron deficiency (6, 7). It has been suggested that HP may cause vitamin B12 deficiency and that treatment of this infection alone may correct anemia (27). Akçam et al. suggests that only achlorhydria caused by acute gastritis, without gastric atrophy, causes vitamin malabsorption (28). In our study, the HP rate was relatively high. It was observed that B12 levels of the patients increased after HP treatment.

Study Limitations

Since the data in our study were obtained by retrospectively examining patient files, our information was limited to what was recorded in the files.

CONCLUSION

This study showed that vitamin B12 deficiency is common in children in a particular region. The number of patients in the first 2 years of age indicates that this age group is at risk. Vitamin B12 levels should be checked in patients with iron deficiency, which indicates insufficient consumption of animal foods. Another risk group includes those with malabsorption diseases such as HP infection and chronic diarrhea. To prevent vitamin B12 deficiency in infants, vitamin B12 levels should be checked in pregnant women and mothers of infants and animal foods should be recommended.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Ankara Dr Sami Ulus Children Health and Diseases Training and Research Hospital Ethics Committee (Date: 23.8.2023, Decision No: E-73799008-799-222823473).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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