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Evaluation of Increased Vitamin B12 Levels in Children: Is it Clinically Significant?

Çocuklarda Artmış B12 Vitamini Düzeylerinin Değerlendirilmesi: Klinik Olarak Anlamlı mı?

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Abstract

Introduction: The underlying etiology of increased serum cobalamin (vitamin B12) levels in children is not fully documented. Despite it is commonly linked to autoimmune and malignant diseases in adults, there is no diagnostic algorithm in pediatric patients for increased vitamin B12 levels. In our study, we aimed to contribute to the diagnostic approach by investigating the etiology of high vitamin B12 levels in pediatric patients.

Materials and Methods: In this retrospective cohort study, 68 patients (47 women, 21 men) aged 0-18 years with a vitamin B12 level ≥600 pg/mL were evaluated. The patients were analyzed in three groups (group 1; 600-799 pg/mL, group 2; 800-999 pg/mL, group 3; ≥1000 pg/mL) according to their vitamin B12 levels and etiologies underlying increased vitamin B12 levels were documented.

Results: The median age of the patients was 39 (minimum: 4, maksimum: 214) months. When the complaints at admission, physical and laboratory findings were compared, there was no significant difference between the three groups. When we examined the etiological factors of increased vitamin B12 levels; It was determined as "idiopathic" in 70.6% of the patients, 'nutritional protein intake' in 11.8%, "autoimmune disease" in 10.3%, and "malignancy" in 7.4%.

Conclusion: These results indicate that although the most common etiology of elevated vitamin B12 levels is idiopathic; however, it may also be a reflection of autoimmunity or malignancy. Diagnostic approach algorithms for increased vitamin B12 levels in children should be developed in the light of further studies.

Keywords
Increased vitamin B12, malignancy, autoimmune, children, cobalamine

Öz

Giriş: Çocuklarda artmış serum kobalamin (B12 vitamini) düzeylerinin altında yatan etiyoloji tam olarak bilinmemektedir. Erişkinlerde yaygın olarak otoimmün ve malign hastalıklarla bağlantılı olmasına rağmen, pediatrik hastalarda artmış B12 vitamini düzeyleri için tanısal bir yaklaşım yoktur. Çalışmamızda çocuk hastalarda yüksek vitamin B12 düzeylerinin etiyolojisini araştırarak tanısal yaklaşıma katkı sağlamayı amaçladık.

Gereç ve Yöntem: Bu retrospektif kohort çalışmada, yaşları 0-18 yaş arasında değişen, vitamin B12 düzeyi ≥600 pg/mL olan 68 hasta (47 kadın, 21 erkek) değerlendirildi. Hastalar vitamin B12 düzeylerine göre üç grupta (grup 1; 600-799 pg/mL, grup 2; 800-999 pg/mL, grup 3; ≥1000 pg/mL) incelendi ve vitamin B12 düzeylerinin yükselmesinin altında yatan nedenler belgelendi.

Bulgular: Hastaların medyan yaşı 39 (minimum: 4, maksimum: 214) aydı. Başvuru şikayetleri, fizik ve laboratuvar bulguları karşılaştırıldığında 3 grup

Anahtar kelimeler
Artmış B12 vitamini, malignite, otoimmün, çocuklar, kobalamin

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arasında anlamlı fark yoktu. B12 vitamini düzeylerinin yükselmesinin etiyolojik faktörlerini incelediğimizde; hastaların %70,6'sında "idiyopati"', %11,8'inde "besinsel protein alımı", %10,3'ünde "otoimmün hastalık" ve %7,4'ünde "malignite" olarak belirlendi.
Sonuç: Bu sonuçlar, vitamin B12 düzeylerinin yükselmesinin en yaygın etiyolojisinin idiyopatik olmasına rağmen; bununla birlikte, otoimmünite veya malignitenin bir yansıması da olabilir. Çocuklarda artmış B12 vitamini düzeyleri için tanısal yaklaşım algoritmaları ileri çalışmalar ışığında geliştirilmelidir.

Introduction

Incidental finding of increased vitamin B12 (cobalamin) levels is a common condition. It is often neglected and ignored when very high levels are not detected. Over time, it has been observed that vitamin B12 levels are more frequently requested in clinics, as well as its deficiency, high levels are also observed. This situation has gained importance in terms of early diagnosis of serious conditions associated with vitamin B12 elevation (1). After oral intake of cobalamin of animal origin, binding occurs with haptocorrin (HC) in saliva, when it reaches the duodenum, HC is digested, and free cobalamin binds with intrinsic factor. Cobalamin absorbed from the ileal mucosa passes into the hepatic circulation via transcobalamin II (TCII). Its excretion from the circulation occurs by liver nonspecific protein intake (1,2). In addition to taking large amounts of cobalamin with food or medications; hematological diseases such as leukemias- polycythemia vera- hypereosinophilic syndrome (HES), solid tumors, autoimmune diseases, kidney and liver diseases, and infectious diseases may cause increased cobalamin levels. It is thought that the increase in cobalamin level is due to the increase in HC release in leukocytes and other cells. In liver diseases, it is thought to be due to decreased cobalamin clearance and/or cobalamin release during hepatic lysis (2-5). According to the results of many studies, it is recommended that patients should be investigated in terms of underlying malignant, inflammatory, and autoimmune diseases when high vitamin B12 levels are detected (6,7). Under conditions where the cobalamin level above 600 pmol/L is considered to be high: In 37% of the patients diagnosed with acute myeloid leukemia (AML) disease whose vitamin B12 measurement was performed; in 11% of patients diagnosed with acute lymphoblastic leukemia (ALL) disease and whose vitamin B12 measurement was performed; high levels were observed in 45% of patients with a diagnosis of liver cancer and 11% of patients with non-Hodgkin's lymphoma (8). Besides, the increased vitamin B12 levels were observed in patients with the autoimmune lymphoproliferative syndrome, and other T-cell-derived autoimmune diseases and were attributed to high HC in T-lymphocytes (8-10). However, all of these studies were conducted in adult patients. There is no clarity about the etiology and diagnostic algorithm in children with high vitamin B12 levels. For this reason, we retrospectively evaluated our pediatric and adolescent patients to shed light on the etiological evaluation of increased vitamin B12 levels.

Materials and Methods

Patient Data

Children and adolescents aged 0-18 years with vitamin B12 levels ≥600 pg/mL who applied to the general pediatrics and pediatric hematology outpatient clinics of Baskent University Hospital between 2015-2020 were evaluated retrospectively. This study was approved by Baskent University Institutional Review Board on 14.07.2020 (project no: KA20/289, date: 14.07.2020). Demographic information, laboratory results, and imaging results of the patients were obtained retrospectively. Evaluation of nutritional status was made according to the daily food consumption lists, which ranged from 3 to 7 days, previously recorded by the doctor in the file. If daily protein intake exceeded 20% of the diet, it was evaluated as "excess", between 15-20% as "normal" and below 15% as "low" protein intake (11). The patients were divided into 4 groups malignancy, autoimmunity, nutritional (nutritional protein intake), and idiopathic in terms of the etiology of vitamin B12 elevation. The etiology was recorded as "nutritional" if no other additional disease was detected and the protein intake was high. By evaluating the data of previous studies, patients were divided into 3 groups (group 1; 600-799 pg/mL, group 2; 800-999 pg/mL, group 3; ≥1000 pg/mL) according to their vitamin B12 levels (4,6,8).

Laboratory Analysis

Serum vitamin B12 concentrations were determined by a chemiluminescent microparticle immunoassay test with an Alinity analyzer (Abbott Diagnostics®, Chicago, Illinois).

Statistical Analysis

As descriptive statistics in the study, mean ± standard deviation or median (minimum-maximum) values are given depending on the assumptions for numerical variables, while numbers (n) and percentages (%) are given for categorical data. In the comparison of numerical data, Variance Analysis was used when parametric test assumptions were provided, and the Kruskal-Wallis test was used if not. The Fisher-Freeman-Haltone Exact test was used to compare categorical data. $P<0.05$ was considered statistically significant in the analysis. The analysis of the study was made in the IBM SPSS V25 program.

Results

The files of 68 patients were reviewed; 69.1% (n=47) were boys and 30.9% (n=21) were girls, with a median age of 39 months (4-214 months). When the three groups (groups 1-2-3) were compared according to vitamin B12 levels, no statistically significant difference was found in terms of the complaints at admission, past medical history, physical examination, and laboratory findings (Table 1). High vitamin B12 levels were detected in 48.5% (n=33) of the patients while being checked for routine follow-up. Among the symptomatic patients; 20.6% (n=14) had fatigue, 14.7% (n=10) had respiratory symptoms, 8.8% (n=6) had allergic complaints, 5.9% (n=4) had a loss of appetite, 1.5% (n=1) had weight gain. Underlying chronic diseases were detected in 22.1% of patients such as celiac disease, food allergy, leukemia, agranulocytosis, neuroblastoma, Glucose 6-phosphate dehydrogenase deficiency (G6PD), vasculitis, trisomy 21, transient abnormal myelopoiesis (TAM). Family history was positive in 5.9% (n=4) of patients whose parents had allergies, type II diabetes mellitus (type II DM), hypothyroidism, and thalassemia. Protein intake was 'normal' in 82.4% (n=56) patients and 'excess' in 17.6% (n=12) patients. None of our patients had a significant protein intake deficiency. There was concomitant medicine usage in 8.8% (n=6) of the patients. These were chemotherapy for malignancy and iron treatment in iron deficiency patients. The physical examination was normal in most of the patients except the patients with underlying malignancy (5.9%). Blood smears were evaluated in 68 patients of which 5.85% (n=4) had hypochromia and microcytosis, blasts, and neutropenia as pathological findings. Routine complete blood count and biochemical values were measured in almost every patient. For the etiological approach, sedimentation rate in 7 patients, rheumatoid factor in 4 patients, alpha-fetoprotein level in 7 patients (positive result was obtained in only one), thyroid function tests [thyroid stimulating hormone (TSH) and Thyroxine (T4) were normal, thyroid autoantibodies were high] in 1 patient, homocysteine in 5 patients, perinuclear anti-neutrophil cytoplasmic antibody (pANCA) (positive result) and cytoplasmic anti-neutrophil cytoplasmic antibody (cANCA) (negative result) in 1 patient, anti-double stranded deoxyribo nucleic acid (anti-dsDNA) in 8 patients, anti-nuclear antibody (ANA) in 6 patients (positive result were found in four of them), celiac antibodies in 18 patients (with two positive results) were performed. The etiology was determined as 'idiopathic' in 70.6%, "nutritional" in 11.8%, "autoimmune disease" in 10.3%, and "malignancy" in 7.4% of the patients. Etiological factors and the vitamin B12 level clusters are given in Figure 1. There was no difference in etiology between all 3 groups (p=0.485).

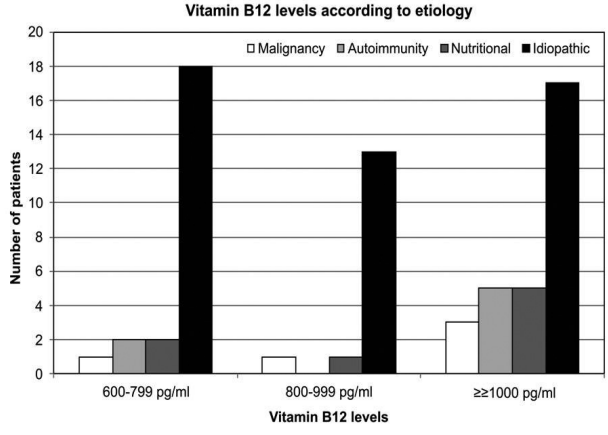

Figure 1. Patient groups according to etiology with vitamin B12 clusters.

Table 1. Characteristics and laboratory findings of vitamin B12 level groups				
	Vitamin B12 groups			
	Group 1 (n=23) 600-799 pg/mL	Group 2 (n=15) 800-999 pg/mL	Group 3 (n=30) ≥1000 pg/mL	p-value
Admission complaint				
Routine follow-up	13 (56.5)	7 (46.7)	13 (43.3)	0.999[a]
Weakness	4 (17.4)	4 (26.7)	6 (20)	-
Signs of respiratory tract infection	3 (13)	2 (13.3)	5 (16.7)	-
Allergic symptom	2 (8.7)	1(6.7)	3 (10)	-
Loss of appetite	1 (4.3)	1 (6.7)	2 (6.7)	-
Weight gain	0 (0)	0 (0)	1 (3.3)	-
Positive medical history	4 (17.4)	2 (13.3)	9 (30)	0.358[a]
Family medical history positivity	1 (4.3)	0 (0)	30 (10)	0.541[a]
Over protein intake	2 (8.7)	2 (13.3)	8 (26.7)	0.249[a]
Medicine use	2 (8.7)	1 (6.7)	5 (16.7)	0.701[a]
Physical examination pathological finding	1 (4.3)	1 (6.7)	2 (6.7)	1.000[a]
Positive blood smear finding	2 (8.7)	0 (0)	2 (6.9)	0.897[a]
Celiac disease positivity	1 (20)	0 (0)	1 (7.7)	0.589[a]
ANA positivity	1 (50)	0 (0)	3 (50)	0.714[a]
Positive abdominal ultrasonografi positivity	1 (4.3)	1 (6.7)	2 (6.9)	0.248[a]
Hemoglobin (g/dL) mean ± SD	12.8±1.59	12.7±1.3	12.5±0.85	0.703[b]
WBC (thousand/μL) median (min-max)	9.6 (4.5-12.0)	8.7 (5.7-14.9)	8.4 (4.0-314.0)	0.503[c]
Neutrophil (thousand/μL) median (min-max)	3.0 (0.3-6.2)	2.2 (0.3-5.3)	2.9 (0.4-166.3)	0.112[c]
Platelet (thousand/μL) median (min-max)	320 (232-597)	343 (117-605)	321 (921-1027)	0.643[c]
MCV (fL) median (min-max)	78.8 (54.1-96.0)	79.4 (76.0-82.5)	77.0 (59.2-89.8)	0.596[c]
AST (U/L) median (min-max)	28.5 (18-96)	30.0 (21.0-42.0)	29.0 (21.0-47.0)	0.909[c]
ALT (U/L) median (min-max)	15.0 (10.0-56.0)	16.0 (8.0-41.0)	15.5 (8.0-249.0)	0.827[c]
CRP (mg/L) median (min-max)	0.4 (0.18-6.10)	0.6 (0.1-10.5)	0.35 (0.1-37.0)	0.960[c]
AFP (IU/mL) median (min-max)	-	6115.3 (6.6-12224.0)	0.97 (0.78-1.35)	0.053[c]

[a]Fisher-Freeman-Halton exact test; n (%), [b]Variance analysis; mean ± standard deviation, [c]Kruskal-Wallis test; median (minimum-maximum), ANA: Anti-nuclear antibody, WBC: White blood cell, MCV: Mean corpuscular volume, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, AFP: Alpha feto protein

Discussion

In the current literature, it is emphasized that increased vitamin B12 level is important in the diagnosis and follow-up of some diseases. It is recommended that hematological diseases, solid tumors, autoimmune diseases, and kidney and liver diseases that may cause this increase should be investigated in etiology (3-5,12). In our study, which is consistent with the literature, it is noteworthy that the neoplastic diseases diagnosed in patients with high vitamin B12 levels at the time of diagnosis in our pediatric hematology outpatient clinic were not known beforehand. The relationship between high vitamin B12 and solid tumors was first reported by Carmel and Eisenberg (13) and attracted attention (14). In the series of Frémont et al. (15), approximately half of the patients with hepatocellular carcinoma presented with high serum cobalamin levels. Chiche et al. (16) detected solid tumors in various parts of the body in 23% of patients with high serum cobalamin. In 73% of these patients, the diagnosis of the solid tumor was previously unknown, and 80% of the patients with tumor diagnosis were at the stage that had not yet metastasized (16). From a prognostic point of view,

vitamin B12 level is recommended as a possible tumor marker for poor prognosis (17,18). In liver tumors, the primary mechanisms involved in increased serum vitamin B12 formation are increased TC plasma levels due to the decrease in hepatic clearance of the HC-cobalamin complex and excessive degradation of hepatocytes (16-18). In addition, vitamin B12 elevation can be observed in myeloproliferative diseases, including chronic myelomonocytic leukemia and HES, myelodysplastic syndromes and acute leukemias, especially promyelocytic leukemia (3,16,19). In our study, we found that there were 5 (7.4%) malignancy patients with elevated vitamin B12 levels. These patients had diagnoses of neuroblastoma, ALL, AML, agranulocytosis, and TAM. These patients were pediatric hematology outpatients and had high vitamin B12 levels at the time of diagnosis. The presence of 2 cases of leukemia among our patients is also a finding that is consistent with previous studies showing that vitamin B12 is elevated in myeloproliferative diseases (3-5). A high serum vitamin B12 level in myeloid proliferation is primarily associated with the release of HC by tumor granulocytes and their precursors (20,21). Four of our patients evaluated for possible autoimmune disease were ANA positive, one of them was in group 1 and three of them were in group 3. Anti-dsDNA was analyzed in 8 patients and no positive value was found. Again, positive pANCA and negative cANCA results were found in only 1 patient. Only one of the patients was diagnosed with autoimmune disease, the other ANA + patients were followed up with the suspicion of autoimmune disease. Routine complete blood count and biochemical values were measured in almost every patient. For the etiological approach, sedimentation rate in 7 patients, rheumatoid factor in 4 patients, alpha-fetoprotein level in 7 patients (positive result was obtained in only one), thyroid function tests (TSH) and Thyroxine (T4) were normal, thyroid autoantibodies were high) in 1 patient, homocysteine in 5 patients. Celiac antibodies in 18 patients (with two positive results) were performed. We think that ANA positivity as a single marker does not suggest autoimmune disease, so we referred these patients to pediatric rheumatology, however according to financial problems they were not evaluated by rheumatology in our hospital so the final diagnosis of all these patients cannot be provided. So the title "autoimmunity" for these patients should be regarded as "possible autoimmunity". The etiology was determined as "idiopathic" in 70.6%, "nutritional" in 11.8%, "autoimmune disease" in 10.3%, and "malignancy" in 7.4% of the patients. There was no difference in etiology between all 3 groups (p=0.485). Cases of Gaucher disease, systemic lupus, rheumatoid arthritis, and Still's disease with high serum vitamin B12 levels have been reported in previous publications. It has been evaluated that high serum vitamin B12 levels in dysimmune and inflammatory diseases may be associated with an increase in TCII during the acute phase of inflammation (16,22,23). TCII levels were not measured in our patients, but we thought that the high levels of vitamin B12 in our patients may be due to the increase in TCII levels due to inflammation, as stated in the literature. In our study, 22.1% of the patients had celiac disease, food allergy, leukemia, agranulocytosis, neuroblastoma, Glucose 6-phosphate dehydrogenase deficiency (G6PD), vasculitis, trisomy 21, TAM. Since it may be the first sign of autoimmune diseases, we can conclude that autoimmune disease screening with history, physical examination, and laboratory may be useful in cases with high vitamin B12 levels. In addition, 5.9% of our patients had a family history of autoimmune and hematological diseases [allergy, type II diabetes mellitus (type II DM), hypothyroidism, and thalassemia], and this was evaluated as a positive family history in the study. This situation was not statistically significant and was accepted as a coincidence. Neuropsychiatric disorders (especially attention deficit and hyperactivity disorder) associated with B12 elevation are mentioned in the literature. There was no diagnosis of neuropsychiatric pathology in our patient group. Although publications are supporting the opposite, it is recommended that patients be evaluated for neuropsychiatric pathologies when vitamin B12 elevation is detected (3). A study by Albayrak and Albayrak (5) stated that a vitamin B12 level above 1000 pg/mL may be meaningful in the diagnosis and follow-up of the diseases we mentioned. In the study, the records of 40 children (23 boys/17 girls) with high B12 levels (>1000 pg/mL) were evaluated retrospectively. In addition, to elucidate the possible role of lymphocytes, vitamin B12 values of 13 patients with ALL were checked at the time of diagnosis. As a result, they stated that high vitamin B12 values are generally benign in children, but that leukemia may develop later in some patients. For this

reason, they recommended that patients be followed for a while after testing for various hematological diseases. Akin et al. (4) also obtained results suggesting that vitamin B12 levels show racial differences and that using reference ranges of various populations may lead to inaccurate results. They evaluated 1109 healthy samples aged 0-24 years to determine normal serum vitamin B12 levels in children and adolescents in the Konya region of Turkey. They found normal reference levels for vitamin B12 in the 2.5-97.5 percentile range, 127-606 pg/mL for girls and 127-590 pg/mL for boys. Because of these results, they emphasized that normal levels should be obtained for each population. In our study, when creating 3 groups, the reason why vitamin B12 elevation was accepted as over 600 pg/mL as the limit value was to try to minimize the error. Different results have been obtained in studies conducted in many societies on vitamin B12 reference and it has been observed that it differs between countries. It was emphasized that the use of reference intervals of different populations may lead to incorrect results (24). The most common etiology was "idiopathic" in all 3 groups (groups 1-2-3). In many studies, patients with idiopathic etiology and vitamin B12 elevation have been evaluated, and it has been stated that these patients may be caused by differences in both their gut microbiota and genetic characteristics (3). In our study, no evaluation was made on this subject. The most common complaint in our patients who presented with vitamin B12 elevation was fatigue, consistent with the literature findings (3). These complaints were followed by pathological findings related to the respiratory system and allergic problems. These complaints are among the general findings of diseases that cause inflammation. This is also significantly compatible with our etiological results. However, this does not mean that vitamin B12 levels can be used as a marker of inflammation (3). Daily excess protein consumption was 8.7% in group 1, 13.3% in group 2, and 26.7% in group 3 (p=0.249). We evaluated the food consumption of our patients according to the nutritional lists of several days recorded in their files. Documented foods were evaluated according to their protein content. In addition, the foods written in this list were recorded according to the statements of the parents. The possibility of a biased evaluation can be considered as a limitation of our study. Protein intake rates of our patients with malignancy were normal. Only two of the patients who were followed up with the suspicion of autoimmune disease had a high protein intake according to the nutritional list of the last few days. These two patients were in group 3. Abdominal ultrasonography was performed in 23 patients in total, and positive findings were detected in only 4 patients; one patient with neuroblastoma with a mass in the liver, one with hepatomegaly and agranulocytosis with hyperechogenicity in the spleen parenchyma, one with ALL with hepatosplenomegaly, and the other with celiac disease with gas distention. The most common complaint in our patients who presented with vitamin B12 elevation was fatigue, consistent with the literature findings (3). These complaints were followed by pathological findings related to the respiratory system and allergic problems. These complaints are among the general findings of diseases that cause inflammation. This is also significantly compatible with our etiological results. However, this does not mean that vitamin B12 levels can be used as a marker of inflammation (3).

Study Limitations

The limitations of our study are the lack of a randomized controlled study, the small number of cases, and the evaluation of protein intake from file records rather than structured diet lists. In addition, most of the diseases in which vitamin B12 levels are used in diagnosis and follow-up are hematology and oncology diseases. In our study, pediatric hematology outpatients were also evaluated. Most of the patients admitted to pediatric hematology-oncology outpatient clinics already include these patients. Although this study has limitations, we think that it can be considered important because it supports the high level of vitamin B12 in these diseases from the etiological point of view. However, we think the study is still important as it provides a potentially useful algorithm for the assessment of increased vitamin B12 in children. Previous studies have often been done in adult patient groups. Our study is one of the few studies evaluating this issue in the pediatric group.

Conclusion

Elevated serum vitamin B12 is a common and underestimated finding. Although the most common etiology of increased vitamin B12 levels is idiopathic, we think that it should be evaluated in terms of

malignant and autoimmune diseases. Structured studies are needed to develop an approach algorithm for these patients.

Ethics

Ethics Committee Approval: This study was approved by Baskent University Institutional Review Board on 14.07.2020 (project no: KA20/289, date: 14.07.2020).

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

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