Long-term outcome in children with nutritional vitamin B12 deficiency

Nutrisyonel vitamin B12 eksikliği olan çocuklarda uzun dönem sonuçlar

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Abstract

Objective: **Vitamin B12 deficiency is frequently observed in developing countries. Herein we report the long-term clinical and laboratory outcomes in 45 children presented with various symptoms of vitamin B12 deficiency.**

Materials and Methods: **Symptoms and physical findings, and percentiles for weight, height, and head circumference at presentation were recorded. The educational level of the patients' mothers, vitamin B12 deficiency-related diseases and family income data were collected. Complete blood count, serum vitamin B12, folate, iron, iron binding capacity and ferritin, and plasma homocysteine levels were recorded measured at presentation. The patients were treated with vitamin B12, as follows: 1 mg/d IM for 1 week, followed by 1 mg IM QWK for 2 weeks, and then monthly 1mg injections. Patients were neurologically and hematologically re-evaluated after treatment. The visual evoked potential (VEP) test was used to examine the integrity and function of the visual pathway. Brainstem evoked potential (BAEP) responses were used to analyze auditory function. Neuromotor development was assessed using Denver II Development Screening Test.**

Results: **The mean age of 20 male and 25 female patients was 5.6±5.9 years (range: 1.4 months-17 years). The most common symptoms at presentation were weakness, failure to thrive, and hematologic manifestations (pallor, petechiae, ecchymosis). Abnormal neurologic findings at presentation were observed in 20% of the patients, and were more commonly observed in those <2 years. VEP, BAEP, and Denver II Development tests were performed in 66% of the patients one year after vitamin B12 replacement was started. VEP and BAEP interval prolongation was observed in 37% and 17% of the cases, respectively. Denver II Development Test results showed developmental delay in 20% of the patients tested.**

Conclusion: **All the patients achieved full hematologic recovery within 1 month of treatment onset. Neurological symptoms resolved following B12 administration; however, during long-term follow-up ranged from 17% to 37% of the tested patients had persistent VEP; BERA, and Denver II abnormalities. Neurological symptoms resolved following B12 administration; however, during long-term follow-up 33% of the patients had persistent VEP, BERA, and Denver II abnormalities. As such, clinicians should continue to follow-up such patients even after hematologic and clinical improvement are obtained in order to assess their neurologic status.** *(Turk J Hematol 2011; 28: 286-93)*

Key words: Vitamin B12 deficiency, children, neurologic outcome

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Özet

Amaç: **Vitamin B12 eksikliği gelişmekte olan ülkelerde sık görülür. B12 eksikliğinin değişik yakınmaları ile gelen 45 çocuğun uzun dönem laboratuar ve klinik bulgularını bildirdik.**
Yöntemler ve Gereçler: **Başvuru anındaki yakınma ve muayene bulguları, kilo, boy ve baş çevresi persentilleri not edildi. Annenin eğitim düzeyi, eşlik eden hastalıklar ve aile geliri sorgulandı. Tanıdaki tam kan sayımı, serum vitamin B12, folat, demir, demir bağlama kapasitesi, ferritin ve plazma homosistein seviyeleri kaydedildi. Tedavi için B12 intramüsküler olarak ilk hafta her gün, sonra iki hafta boyunca haftada bir, takiben aylık verildi. Tedaviden sonra hastalar nörolojik ve hematolojik bulgular için tekrar değerlendirildi. Görsel uyarılmış potansiyel (VEP), görsel yolların fonksiyonlarını ve bütünlüğünü değerlendirmede kullanıldı. Beyin sapı uyarılmış işitsel cevapları (BAEP), işitsel fonksiyonları değerlendirmek için kullanıldı, Nöromotor gelişim, Denver II gelişim tarama testi ile değerlendirildi.**
Bulgular: **Ortalama yaş ve cinsiyet oranı sırasıyla 5.6±5.9 yıl (1.4 ay -17 yıl), 20 erkek/25 kız idi. En sık yakınmalar halsizlik, gelişme geriliği ve hematolojik yakınmalardı. Baş vuruda anormal nörolojik bulgular tüm vakaların %20'sinde görüldü. Bu bulgular iki yaştan küçük çocuklarda daha sıktı. B12 tedavisinden bir yıl sonra VEP, BERA ve Denver II gelişim testi vakaların %66'sına yapıldı. VEP ve BERA'da uzama sırasıyla vakaların %37 ve %17'sinde gösterildi. Denver II gelişim testi %20 hastada gecikmiş bulundu.**
Sonuç: **Tüm çocuklarda birinci ayda tam hematolojik düzelme sağlandı. Baş vuruda nörolojik bulgular iki yaş altında daha sık görüldü. Bu bulgular B12 tedavisi ile geriledi. Buna karşın uzun dönem sonuçlarda VEP, BERA ve Denver II testinde bozukluk test yapılan olguların %17'si ile %37'si arasında değişen oranda devam ediyordu. Bu nedenle klinisyenler bu çocukları hematolojik ve klinik düzelme olsa bile nörolojik prognoz açısından uzun vadeli izlemeli ve değerlendirmelidir.** *(Turk J Hematol 2011; 28: 286-93)*
Anahtar kelimeler: Vitamin B12 eksikliği, çocuk, nörolojik sonuçlar

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Introduction

Vitamin B12 deficiency is usually observed in developing countries and poor dietary intake is the most frequent cause. Vitamin B12 is important for DNA synthesis and neurologic functions.The vitamin B12 deficiency negatively affects bone marrow, gastrointestinal and central nervous systems [1,2]. Most children with vitamin B12 deficiency present with non-specific manifestations, such as pallor, failure to thrive, developmental delay, weakness, and irritability [2,3]. Hematological manifestations completely resolve following vitamin B12 supplementation, but neurologic findings may persist [4]; therefore, early diagnosis and treatment are important. Herein we present 45 children treated for various symptoms of vitamin B12 deficiency, and their long-term clinical and laboratory outcomes.

Materials and Methods

Clinical and laboratory findings in 45 children treated for vitamin B12 deficiency between January 1996 and December 2009 were retrospectively evaluated. Symptoms and physical findings, and percentiles for weight, height, and head circumference at presentation were recorded. The level of educational of the patients' mothers, vitamin B12 deficiency-related diseases, and family income data were collected. Daily intake of vitamin B12 and folate in the patients and their breast-feeding mothers were evaluated based on reports of their diets during the previous week [5]. Growth retardation (short height and low weight) were defined as below the third percentile.

Complete blood count, serum vitamin B12, folate, iron, iron binding capacity and ferritin, and plasma homocysteine levels were recorded measured at presentation. Vitamin B12 absorption testing could not be performed in any of the patients. Routine urinary analysis was performed to test for proteinuria. Anemia, thrombocytopenia, and leukopenia were defined as follows: hemoglobin level <12 g/dL, thrombocyte level <150,000 mm, and leukocyte count <4500 mm, respectively. Low-level vitamin B12, folate, and ferritin was accepted as 200 pg/mL, 3 ng/mL, and 20 pg/mL, respectively. Plasma homocysteine levels >12 g/dL were considered as high. Peripheral blood smear screening for macrocytosis and hypersegmentation was performed. Hemoglobin electrophoresis was used to rule out the thalassemia trait in children with an MCV <85 fL.

The patients were treated with vitamin B12, as follows: 1 mg /d IM for 1 week, followed by 1 mg IM QWK for 2 weeks, and then monthly 1 mg injec-

tions. Iron supplementation of 6 mg kg/d was given to the patients with iron deficiency. Complete blood count, serum vitamin B12, folate, and plasma homocysteine were measured after 1 and 6 months of treatment. Neuromotor development in the patients was re-evaluated using the Denver II Development Screening Test 1 year after treatment started. Visual evoked potential (VEP) and brain stem evoked potential (BAEP) response testing were performed to determine the integrity and function of the visual pathway, and auditory function, respectively.

Statistical calculations were performed using SPSS for Windows v.16.0. Normal distribution was tested using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the iron deficient patients and those without iron deficiency. The Wilcoxon test was used to compare pre- and post-treatment findings. The chi-square test was used for categorical variables. Statistical significance was accepted as $p<0.05$. The study protocol was approved by the Uludağ University Ethics Committee.

Results

Mean age at presentation of the 20 male and 25 female patients was 5.6±5.9 years (range: 1.4 months-17 years). Mean follow-up was 46±36 months (range: 10-150 months). The most common symptoms were weakness, failure to thrive, and hematologic manifestations (pallor, petechiae, ecchymosis)., followed by gastrointestinal and neurologic symptoms (Table 1). Both the patients and their breast-feeding mothers had low dietary intake of vitamin B12. (Among the 22 patients aged <2 years, 19 were breastfed and/or had supplementary food. The rest (n=3) were on normal diet. Only one patient in our case series (older than 2 years) was on special diet for phenylketonuria. Proteinuria was associated in 4 (8.8%) out of 45 patients and their ages ranged from 1 to 6 years (mean: 3.6±2.4 years). In addition, 6 (13.3%) out of 45 patients had vitamin B12 deficiency-related diseases, including cerebral palsy (CP) (n=2), short gut syndrome (n=1), operated duodenal atresia (n=1), celiac disease (n=1), and phenylketonuria (n=1). They were older than 2 years.

Only 15% of the patients' mothers had a level of education above primary school. In all, 80% (n=36) of the patients' families had a monthly income providing the threshold, as defined in a recent report by the Turkish Statistical Institute [6].

In all, 10 (22%) of the patients had height and weight below the 3rd percentile at presentation, of which only 2 had a comorbid disease (CP); height and weight in the 8 children without a comorbid disease were normal (>3rd percentile) after receiving treatment for 1 year. Serum B12, folate, and plasma homocysteine levels are shown in the Figure 1. In all, 8 patients (19%) had serum B12 and folate levels

Table 1. Patients' Symptoms and Physical Findings at Presentation

	Symptoms (<2 years/ ≥2 years)	Physical Findings (<2 years/ ≥2 years)
General (Total)	31 (69%)	10 (22%)
Weakness	5/19	-
Failure to thrive	5/2	5/5
Hematologic (Total)	23 (51%)	42 (93%)
Pallor	10/6	20/18
Petechiae-Ecchymosis	4/3	3/1
Gastrointestinal (Total)	12 (27%)	9 (20%)
Oral ulcer	2/2	2/2
Vomiting	4/1	-
Pain on abdomen	1/2	-
Hepatosplenomegaly	-	3/2
Neurologic (Total)	8 (18%)	9 (20%)
Seizure	4/None	-
Paresthesia on legs	None/1	-
No head control/no walking	3/None	-
Neuromotor retardation	-	3/None*
Hypotonia	-	4/None
Microcephaly	-	1/1

*Patients with CP (n=2) were excluded

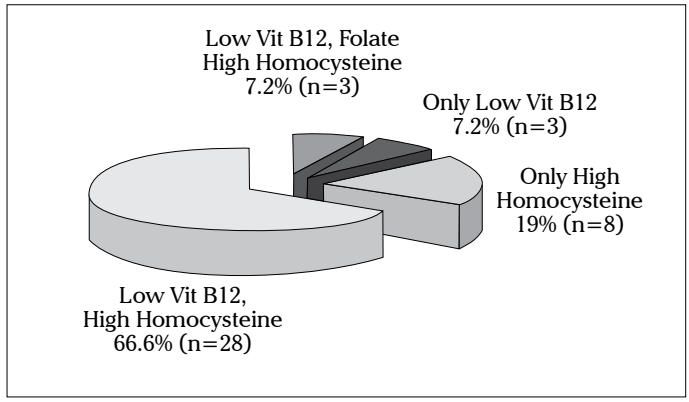

Figure 1. Distribution of Patients According to Serum B12, Folate, and Plasma Homocysteine Levels
*The results of transfused patients (n=3) were excluded

within the normal range; however, their plasma homocysteine levels were high. The serum vitamin B12 level was low in 15 (79%) of the 19 breast-feeding mothers.

Of all the patients (n=45), 20 (44%) had only anemia, whereas 12 (27%) had bicytopenia and 10 (22%) had pancytopenia. In all, 3 patients had a normal hemoglobin level due to recent erythrocyte transfusion and their hematologic and serologic findings were excluded from the study's analysis. In total, 8 out of 45 patient (19%) had iron deficiency anemia and normal hemoglobin electrophoresis findings; none of these 8 patients had another comorbid disease or neurologic symptoms at presentation. Hematologic findings in the patients are shown in Table 2.

Hematologic findings in all the patients improved significantly after the 1st and 6th months of treatment (Table 3); however, patients without iron deficiency had significantly greater hematologic recovery after the 1st month of treatment than the iron-deficient patients (Table 4).

Abnormal neurologic findings at presentation were observed in 9 (20%) of the patients. Cases with CP were excluded from this data since it is difficult to make a definitive distinction of their neurologic findings. None of the 9 patients had iron deficiency anemia. I Eight of these children were younger than 2 years old (Table 1). Additionally, 4 of these 8 children presented with convulsions and were successfully treated with vitamin B12 and anticonvulsants. Neuromotor retardation and hypotonia were observed in 7 patients and all had a good response to vitamin B12 treatment. All 8 patients aged <2 years with abnormal neurologic findings underwent cranial MRI; cerebral atrophy and secondary external hydrocephaly were observed in 5 of them.

Table 2. Patients' Hematologic Findings at the Time of Presentation, According to Iron Status

	Patients with Iron Deficiency n=8 (19%)	Patients without Iron Deficiency n=34 (81%)	p
Female/Male	3/5	18/16	>0.05
Age (years)	3.7 (0.33-17)	1.45 (0.12-16)	>0.05
Hemoglobin (g/dL)	7.2 (4.5-8.7)	7.7 (4.3-12)	>0.05
MCV (fL)	78.1 (59.5-80)	98.2 (83-114)	<0.001
Leukocyte (mm^3)	8650 (2400-17200)	5565 (1100-19000)	>0.05
Thrombocyte (mm^3)	111,000 (158.00-380.000)	195,000 (43.000-401.000)	>0.05
Vitamin B12 (pg/mL)	115 (34-1000)	150 (31-755)	>0.05
Folate (ng/mL)	6.2 (3.2-22.8)	15 (1.1-27)	<0.05
Homocysteine (g/dL)	12.3 (6.9-68.6)	19.5 (2-106)	>0.05
Ferritin (pg/mL)	7 (3-13)	39.5 (18-848)	<0.001
Growth Retardation	4 (50%)	6 (17.6%)	0.075

Values were given as median (range), *The results of transfused patients (n=3) were excluded

Table 3. Patients' Hematologic Findings at Diagnosis, and After 1 and 6 Months of Treatment

Time	Hb±S (range)	MCV±SD (range)	Vitamin B12±SD (range)	Folate±SD (range)	H±SD (range)
Admission	8.1±2.7 (4.3-15.5)	93.2±12.8 (59.5-115)	206.6±185.6 (31-1000)	13.1±7.6 (1.1-27)	26.4±23.3 (2-106)
1 month	12.3±2.4 (10.1-14.5)	90±5 (85-96)	400±150 (243-568)	15.2±6.1 (8-22)	10.4±6.3 (4-18)
6 month	14.6±2.2 (12.1-15.9)	88±4 (84-93)	800±100 (678-942)	16.3±4.2 (11-25)	6.1±2.3 (4-9)
Pa	<0.001	<0.001	<0.001	>0.05	<0.001
Pb	<0.001	<0.001	<0.001	>0.05	<0.001

Pa: Presentation and 1st month of treatment; Pb: presentation and 6th month of treatment, SD: Standard deviation; H: homocysteine

Table 4. Treatment Response of the Patients, According to İron Status*

	Patients with Iron Deficiency n=8			Patients without Iron Deficiency n=34		
	TP1	TP2	P	TP1	TP2	P
Hb (g/dL)	7.2	9.2	<0.05	7.7	11.1	<0.001
MCV(fL)	78.1	82	>0.05	98.2	87	<0.001
Vitamin B12 (pg/mL)	115	565	<0.05	150	482	<0.001
Folate (ng/mL)	6.2	14	>0.05	15	19.5	>0.05
Homocysteine (g/dL)	12.3	5.6	<0.05	19.5	5.5	<0.001

Values are given as median, TP1: At presentation; TP2: after 1 month of treatment, *The results of transfused patients (n=3) were excluded

During vitamin B12 treatment 4 patients developed myoclonus and tremors; these involuntary movements resolved in 2 patients with clonazepam, whereas piracetam was added to the treatment in the other 2 patients Involuntary movements in them resolved as well. VEP, BAEP, and Denver II Development tests were performed in 30 (66%) of the patients between treatment months 9 and 15 (mean: 11.9±1.88 months). VEP and BAEP intervals were prolonged in 11 (37%) and 5 (17%) of the patients, respectively. Denver II Development Test results showed developmental delay in 6 (20%) of the patients (Table 5).

Table 5. VEP, BAEP, and Denver II Findings

n=30	VEP	BAEP	Denver II
Abnormal	11 (37%)	5 (17%)	6 (20%)
Normal	19 (63%)	25 (83%)	24 (80%)

*Patients with CP (n=2) were excluded

Discussion

The most common manifestations of vitamin B12 deficiency observed in the present study were weakness and failure to thrive. Hematologic, gastrointestinal, and neurologic symptoms were observed in 51%, 27%, and 18% of the patients, respectively. Poor dietary intake is reported to be the most common cause of vitamin B12 deficiency [1]; however, Altay et al. had reported a series containing 36 children from Turkey with selective vitamin B12 malabsorption [7]. Unfortunately, we were unable to perform absorption tests in the present study. The necessity of using radioactively labeled compounds makes these tests extremely difficult to perform [8]. An alternative approach for evaluating vitamin B12 absorption is measurement of vitamin B12 saturated-transcobalamin (holo-TC) [9]. Bor et al. [10] reported that the diagnostic sensitivity and specificity of holo-TC measurement was 100% and 92%, respectively. In the present study only 4 (8.8%) patients <6 years of age had proteinuria; as vitamin B12 absorption testing was not available, we could only assume that these 4 patients might have had Imerslund-Gräsbeck syndrome. Altay et al. [7] observed proteinuria in 78% of children with Imerslund-Gräsbeck syndrome, all of who were younger than those without proteinuria. All of the patients with proteinuria in the present study were <6 years old. All of the patients in the present study and their breast-feeding mothers had low dietary intake of vitamin B12 and 79% of the breast-feeding mothers had low-level serum B12. Based on the present study's data, we think that poor dietary intake resulted in the observed vitamin B12 deficiency.

Consumption of meat and dairy products in Turkey has decreased during the last 2 decades due to economic crisis [11] and is lower than that in developed countries [12]. In fact, in the present study, 80% of the patients' families were in low socioeconomic status. The incidence of vitamin B12 deficiency in Turkish pregnant women ranges from 48.8% to 80.9% [13,14]. Koc et al. [15] reported that the incidence of vitamin B12 deficiency in Turkish infants and their mothers was 72% and 41%, respectively. Based on such data, vitamin B12 deficiency is an important problem in Turkey and infants born to deficient mothers are at high risk for developing manifestations of vitamin B12 deficiency. Therefore, nutritional and educational programs are required in Turkey, especially for pregnant and lactating women.

Hematologic findings in patients with vitamin B12 deficiency vary from anemia to pancytopenia [16]. Macrocytosis is not a common finding. MCV does

not increase when vitamin B12 deficiency is associated with iron deficiency or the thalassemia trait [16,17]. Although none of the patients in the present study had the thalassemia trait, Sayli et al. [18] reported Imerslund-Gräsbeck syndrome coexisting with the beta-thalassemia trait in a Turkish study population. In the present study 44% of the patients had only anemia, whereas 27% had bicytopenia, and 22% had pancytopenia, which resolved after 1 and 6 months of treatment, respectively ($p<0.001$). Additionally, 8 (19%) of the patients also had iron deficiency anemia, with an MCV <85 fL. The diagnosis of vitamin B12 deficiency is based on low-level serum vitamin B12 (usually <200 pg/mL), along with clinical evidence of disease [18]. In the present study 81% of the patients had low-level serum vitamin B12; however, it has been reported that patients with clinical signs of vitamin B12 deficiency can have a normal serum vitamin B12 level [19,20]. A study that included 406 patients with vitamin B12 deficiency reported that 98.4% had elevated serum methylmalonic acid (MMA) and 95.9% had elevated serum homocysteine [21]. Other reports suggest that the sensitivity and specificity of the serum B12 assay are significantly lower than previously thought [20, 22-25]. We were unable to measure serum MMA in the present study; however, plasma homocysteine was high in 91% of the patients. In addition, the diagnosis of vitamin B12 deficiency was confirmed in 8 (19%) of the patients based only on a high plasma homocysteine level.

In the present study more patients <2 years of age presented with neurologic symptoms than those aged ≥2 years ($p<0.05$). Numerous case reports have reported neurologic symptoms in patients with vitamin B12 deficiency in infants [26-30] and 2 large series from Turkey reported various neurologic symptoms in infants [31,32]. These findings might be due to the fact that myelinization of the central nervous system is incomplete and ongoing during the first 2 years of life. Although the mechanism of neurologic symptoms in B12 deficiency is not fully known, delayed myelination, neurotrophic and neurotoxic cytokine imbalance, and accumulation of lactate in brain cells have been proposed [33]. Seizure was the first symptom of vitamin B12 deficiency in 4 (9%) of the present study's patients; their EEGs were dysrhythmic with epileptic abnormalities. Several studies reported an association between vitamin B12 deficiency and EEG abnormalities [34]. Cranial MRI in 5 of the present study's 8 patients aged <2 years that presented with abnormal neurologic findings showed cerebral atrophy. Cortical atrophy, thinning of the corpus callosum, and retarded myelination have been reported as neuroradiological imaging findings in patients with vitamin B12 deficiency [35,36]. In the present study 4 patients developed involuntary movements during vitamin B12 treatment; it has been reported that such movements rarely occur during vitamin B12 treatment [37,38], although its mechanism is not fully known.

The patients in the present study recovered in response to vitamin B12 treatment from the following symptoms: pallor, petechiae, ecchymosis, failure to thrive, anorexia, vomiting, hypotonia, apathy, seizures, and neuromotor retardation. Hematologic indices and biochemical parameters returned to normal shortly after the start of vitamin B12 treatment; however, the patients with iron deficiency had slow improvement than those without iron deficiency ($p<0.05$, $p<0.001$ respectively), even though their initial hemoglobin and serum vitamin B12 levels were similar (Table 4). We think that well-designed controlled studies with large patient populations could yield valuable data concerning the relationship between vitamin B12 deficiency and iron deficiency.

In the present study VEP and BAEP intervals were prolonged and Denver II Development Test results showed developmental delay in 33% of the patients after 12 months of treatment. Although we were not able to perform these tests prior to treatment, we think these abnormalities were the result of vitamin B12 deficiency, as there were no other obvious disorders that could explain the findings. Abnormal VEP results were previously reported in cobalamin deficiency [39]. Despite dramatic hematologic and clinical improvement following vitamin B12 treatment, pediatric patients may suffer cognitive and developmental retardation [4]. The long-term prognosis of vitamin B12 deficiency depends on the severity and duration of deficiency. Delayed diagnosis (made after 1 year of age) is associated with permanent neurologic abnormality [40,41].

In conclusion, in the present study neurologic manifestations of vitamin B12 deficiency occurred in more of the patients aged <2 years than in those

aged ≥2 years. In the long-term outcome, patients ranged from 17% to 37% tested for neurologic abnormalities had persistent developmental and myelination delays. As such, clinicians must follow-up pediatric patients with vitamin B12 deficiency after hematologic and clinical improvements are observed in order to assess their neurologic status.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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