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MUSTAFA TAŞKESEN

AHMET YARAMIŞ

SELAHATTİN KATAR

AYFER GÖZÜ PİRİNÇÇİOĞLU

MURAT SÖKER

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## Neurological presentations of nutritional vitamin B12 deficiency in 42 breastfed infants in Southeast Turkey

Mustafa TAŞKESEN<sup>1</sup>, Ahmet YARAMIŞ<sup>2</sup>, Selahattin KATAR<sup>3</sup>, Ayfer GÖZÜ PİRİNÇÇİOĞLU<sup>1</sup>,  
Murat SÖKER<sup>4</sup>

**Aim:** Nutritional vitamin B12 deficiency is common in developing and underdeveloped countries and has a wide variety of neurological presentations. The aim of this study was to evaluate the neurological characteristics and laboratory results of infants with vitamin B12 deficiency.

**Materials and methods:** A total of 42 infants were included in this study. All patients were evaluated for clinical, physical, and neurological abnormalities, and an attempt was made to obtain short-term neurologic follow-up.

**Results:** Of 42 patients, 24 (57%) were boys and 18 (43%) were girls. The average age at diagnosis was 13.04 ± 5.68 months. Most of these infants were breastfed only and born from mothers with inadequate animal-derived protein consumption. Hypotonia (100%), anorexia (92.8%), neurodevelopmental (85.7%), and social (80.9%) retardation were the most present symptoms in all infants.

**Conclusion:** Severe neurological and hematological findings may be found in children with vitamin B12 deficiency. Early diagnosis and treatment is crucial in cases of hematological complications and neurologic impairment. Neurologic impairment may be irreversible if the diagnosis is delayed beyond 12 months. We think that dietary management, such as nutritional support with vitamin B12 for the mothers during pregnancy and complementary food for infants, may prevent the neurological deficits and neurodevelopmental retardation.

**Key words:** Neurological presentation, hypotonia, nutrition, vitamin B12 deficiency, infancy

### Güneydoğu Anadolu'da anne sütü ile beslenen ve vitamin B12 eksikliği saptanan çocuklarda nörolojik bulgular

**Amaç:** Beslenme yetersizliğine bağlı vitamin B12 eksikliği gelişmemiş ve gelişmekte olan ülkelerde yaygın olup, çeşitli nörolojik sorunlara neden olmaktadır. Bu çalışmanın amacı vitamin B12 eksikliği tanısı ile izlenen süt çocuklarının nörolojik bulgularını ve laboratuvar sonuçlarını değerlendirmektir.

**Yöntem ve gereç:** Çalışmaya 42 hasta alındı. Tüm hastaların klinik, fiziki ve nörolojik muayene sonuçları ve kısa süreli izlem sonuçları kaydedildi.

**Bulgular:** Hastaların 24'ü (% 57) erkek ve 18'i (% 43) kız ve tanı sırasında ortalama yaşları 13,04 ± 5,68 ay idi. Hastaların çoğunun sadece anne sütü ile beslendiği ve annelerinin hayvansal protein içeren gıdalardan yeterince tüketmedikleri saptandı. En sık başvuru semptomları hipotoni (% 100), iştahsızlık (% 92,8), nörogelişimsel (% 85,7) ve sosyal gerilik (% 80,9) idi.

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<sup>1</sup> Department of Pediatrics, Faculty of Medicine, Dicle University, Diyarbakır - TURKEY

<sup>2</sup> Department of Pediatric Neurology, Faculty of Medicine, Dicle University, Diyarbakır - TURKEY

<sup>3</sup> Department of Pediatrics, Veni Vidi Hospital, Diyarbakır - TURKEY

<sup>4</sup> Department of Pediatric Hematology, Faculty of Medicine, Dicle University, Diyarbakır - TURKEY

**Correspondence:** Mustafa TAŞKESEN, Department of Pediatrics, Faculty of Medicine, Dicle University, Diyarbakır - TURKEY  
E-mail: drmtaskesen@hotmail.com

**Sonuç:** Vitamin B12 eksikliği olan çocuklarda ciddi nörolojik ve hematolojik bulgular görülebilir. Erken tanı ve tedavi, hematolojik komplikasyonlar ve nörolojik etkilenme açısından önemlidir. Tanının gecikmesi (12 ay) durumunda nörolojik etkilenme geri dönüşümsüz olabilmektedir. Gebelik döneminde annelere vitamin B12 desteği ve süt çocuklarına tamamlayıcı besinlerin zamanında verilmesi nörolojik defisitlerin ve nörogelişimsel geriliğin oluşmasını önleyebileceğini düşünmekteyiz.

**Anahtar sözcükler:** Nörolojik bulgu, hipotoni, beslenme, vitamin B12 eksikliği, süt çocukluğu

## Introduction

Vitamin B12 is essential for development of the central nervous system, and vitamin B12 deficiency may cause severe impairment in only a few weeks (1). Nutritional vitamin B12 deficiency occurs between 3 to 18 months of age, usually in children fed exclusively with breast milk, due to undernutrition of the mothers in underdeveloped or developing countries. (2,3). The reason for maternal vitamin B12 deficiency in these countries is low socioeconomic status, and infants presenting with severe hematological and neurological manifestations of vitamin B12 deficiency are more common than formerly appreciated (4,5).

Nutritional vitamin B12 deficiency in infancy may cause several neurological findings. Neurological symptoms of vitamin B12 deficiency are heterogeneous and include muscular hypotonia, irritability, lethargy, apathy, regression of psychomotor development, tremor, ataxia, and seizures (6,7).

Nutritional vitamin B12 deficiency is common in our region and has been reported on in previous studies (8-10). Late diagnosis of vitamin B12 deficiency and subsequent progression to severe neurological damage are common. The aim of the present study was to evaluate the neurological presentations and treatment outcomes of hypotonic infants with vitamin B12 deficiency.

## Materials and methods

Between 2007 and 2010, a total of 42 patients with neurological symptoms who had been diagnosed with nutritional B12 vitamin deficiency were enrolled in this study. All patients were evaluated by clinical, physical, and neurological examinations. Age, gender, nutritional history, initial symptoms, socio-economical background of the family, physical

examination findings; laboratory investigations, including vitamin B12, homocysteine, and folic acid levels of patients and their mothers, as well as whole blood count, peripheral blood smear, serum iron and iron binding capacity, serum and urinary metabolic screening; and the results of the follow-up examinations were recorded. All infants were assessed for anemia, leukopenia, and thrombocytopenia. All infants' families had low socio-economic and cultural status. The lower socio-cultural and economic status of participants was established based on their low education levels (uneducated) and household income levels (under 300 US dollars per month). The mothers of the patients were consuming insufficient amounts of animal proteins. None of them had followed-up regularly or received multivitamin supplements during pregnancy. While 32 infants were breast-fed only, 10 were both breast-fed and given cow's milk, but without any other supplemental food. For all patients, a physical examination and a Denver-II Developmental Screening Test were performed. Peripheral blood smears were evaluated by a pediatrician, whereas all other analyses were performed by biochemists.

Hemoglobin concentration and leukocyte counts vary by age. For this reason, in our patients, anemia and leukopenia were defined as hemoglobin and leukocyte counts of less than 11 g/dL, 6000/mm<sup>3</sup> and a thrombocyte count below 150 × 10<sup>3</sup>/mm<sup>3</sup>, as thrombocytopenia. Vitamin B12 and folate levels were measured by electrochemiluminescence immunoassay method (Cobas E601), and total homocysteine level was measured by the competitive chemiluminescent enzyme immunoassay method (Immulyte 2500). Serum vitamin B12 levels lower than 200 pg/mL and folate levels lower than 4 ng/mL were accepted as deficiency, and a homocysteine level higher than 12 mmol/L was accepted as deficiency in infants (1,9,10).

The patients were treated with intramuscular vitamin B12: 50-100 µg every other day for 1 week, twice weekly for 2 weeks, and once weekly for another 2 weeks. Vitamin B12 was also administered to mothers. The patients were followed-up and outcomes of treatment were recorded. Vitamin B12 deficiency associated with Immerslund-Grasbeck syndrome was eliminated by analysis of protein in urine. Yet proteinuria was not detected in any patient. Moreover, infants suffering from congenital, metabolic or chronic disease or iron deficiency were excluded from the study.

## Results

Of the 42 patients 24 (57%) were boys, 18 (43%) were girls, and the mean age of infants was  $13.0 \pm 5.6$  months (range: 3-24). All infants were born from mothers with inadequate animal-derived protein consumption, and most of them were exclusively breastfed. The percentiles (weight and height measurements) of 29 infants (69%) were below the 3rd percentile for their age. All patients were from lower socio-economical and cultural areas.

Hypotonia, anorexia, and social and neurodevelopmental retardation were the most common symptoms present in patients. Seizures were observed in 12 (28.5%) infants. The seizures in 10 patients were generalized tonic-clonic, 1 was focal, and 1 was absence. These patients were treated with midazolam (0.1 mg/kg slow bolus intravenous), and then oral anticonvulsants were given; the seizures did not repeat. The presenting neurological symptoms and signs of the hypotonic babies are shown in Table 1.

Anemia was present in 35 (83.3%), thrombocytopenia in 12 (28.5%), leukopenia in 7 (16.6%), and pancytopenia in 5 (11.9%) infants. Hypersegmentation, macrocytosis, and anisocytosis were observed in 34 infants (80.9%). Mean MCV was  $87.2 \pm 8.8$  fL. Peripheral blood examinations of all patients were compatible with megaloblastic changes.

The mean serum vitamin B12 and homocysteine levels of infants were shown in Table 2. Hyperhomocysteinemia was detected in 33 (78.5%) patients. Of the 22 mothers for whom serum vitamin B12 measurement could be made, 21 had low serum vitamin B12 (Table 2). No folic acid deficiency or proteinuria was detected in our patients.

Vitamin B12 treatment was started immediately in all the patients with a diagnosis of megaloblastic anemia due to vitamin B12 deficiency. Blood values had improved by the second week of treatment. For the treatment, dietary management and parenteral vitamin B12 (50-100 µg/day IM for the first 2 weeks, then monthly) were given. In all patients rapid clinical improvement was observed after vitamin B12 administration. Follow-up visits were regularly attended by 73.8% (31/42) of patients. Normal scores on the Denver-II Development Screening Test were achieved by 14 patients 2 months after the treatment; however, 17 had delayed neurologic development. The measurement of serum vitamin B12 levels was required in 18 (18/31) patients, and the mean level was  $623.1 \pm 320.1$  pg/mL. Other patients achieved remission within 6 months. Long-term developmental assessment after treatment could not be done because some of the patients did not come to their follow-up regularly.

Table 1. Presenting neurological symptoms of the patients with nutritional vitamin B12 deficiency.

Neurological symptom	Number of patients (n)	%
Hypotonia	42	100
Anorexia	39	92.8
Neurodevelopmental retardation	36	85.7
Social retardation	34	80.9
Weakness	28	66.6
Seizure	12	28.5
Athetoid head movement	8	19.0
Apathy	6	14.2
Tremor	4	9.5
Fasciculation	2	4.7

Table 2. Laboratory results of patients with vitamin B12 deficiency.

Parameters	Mean $\pm$ SD	Range
WBC (/mm <sup>3</sup> )	10.5 $\pm$ 3.9	4.0-17.5
Hemoglobin (g/dL)	10.8 $\pm$ 1.1	9.4-12.0
Platelet ( $\times 10^3$ /mm <sup>3</sup> )	284.6 $\pm$ 154.8	89-551
MCV (fL)	87.2 $\pm$ 8.8	72-109
Homocysteine (mmol/L)	15.4 $\pm$ 4.7	6.9-24
B12 (infants) (pg/mL)	142.7 $\pm$ 46.3	30-190
B12 (mothers) (pg/mL)	159.6 $\pm$ 31.4	67-196

**Hb:** hemoglobin; **WBC:** white blood cell; **Plt:** platelet count; **MCV:** mean corpuscular volume.

## Discussion

The most important cause of vitamin B12 deficiency in infants is low intake of animal protein by the lactating mother together with complete dependence on breast milk. Vitamin B12 deficiency generally occurs in young children (<2 years of age) from groups with low socio-economic status, and the main cause is inadequate intake either from the diet or breast milk (11).

In the study by Chandra et al. (12) 51 subjects with megaloblastic anemia were evaluated. In that study the mean age was 18 months (6-132), and 60.8% of the subjects were below 2 years of age. In another study involving 200 children between 18 and 36 months by Allen et al., prevalence of megaloblastic anemia was reported as 8%, and poor nutrition was reported as a risk factor attributed to megaloblastic anemia (13). In our study all infants were below 2 years of age, and the mean age of infants was  $13.0 \pm 5.6$  months. Most of the infants were only breastfed and were of low socio-economical and cultural status. Twenty-nine infants (69%) were below the 3rd percentile for their age.

During pregnancy vitamin B12 is actively transported to the fetus by the placenta and reaches twice the level of maternal serum (14). Neonatal vitamin B12 stores are generally enough for about 6-12 months in a normal infant (15). If not diagnosed and treated, infants born with low vitamin B12 stores may show irreversible psychomotor retardation and severe neurological problems within the first years of life (9,16).

Koc et al., in a study conducted in our region, found vitamin B12 deficiency (<160 pg/mL) in 72% of the mothers and 41% of the babies, and severe deficiency (<120 pg/mL) in 48% of the mothers and 23% of the babies. In that study, folate deficiency was found in 12% of the mothers, but was not found in any of the babies (9). In our study, all of the infants had low vitamin B12 and no folate deficiency.

Neurological symptoms and signs of vitamin B12 deficiency such as nausea, lethargy, irritability, unhappiness, hypotonia, apathy, neuromotor developmental delay, nutritional disorders, and convulsions may be seen (10,15). Approximately half of the infants have abnormal movements including tremor, myoclonus, and choreoathetoid movements (17). In the study by Katar et al. (10) the most frequently reported clinical signs and symptoms were paleness, hypoactivity, attention deficit, and stomatitis. All of our patients had hypotonia, and anorexia, seizures, weakness, and social and neurodevelopmental retardation were the most common symptoms in all infants. Athetoid head movements were observed in 8 patients, and 4 had tremors that disappeared during sleep.

Vitamin B12 deficiency may lead to serious hematological problems in addition to anemia. Thrombocytopenia and neutropenia are also important problems. In a study involving 15 children between 7 and 18 months by Incecik et al. anemia was reported in all, thrombocytopenia in 7, leukopenia in 5, and pancytopenia in 4 (15). Among our patients 83.3% had anemia, 28.5% had thrombocytopenia, 16.6% had leukopenia, and 11.9% had pancytopenia.

Early diagnosis and treatment is very important in cases of hematological complications and neurologic impairment. Dietary treatment and intramuscular vitamin B12 (25-100 µg/day for young children and 250-1000 µg/day for older children; initially, every day for 3 or 7 days and then monthly) are important in cases of nutritional vitamin B12 deficiency (8,15). In our study vitamin B12 and/or dietary treatments were started immediately in all patients in whom blood values improved by the second week of treatment.

### Limitations of the study

Serum vitamin B12 levels could not be measured in all mothers, and not all patients could be followed-up regularly. The low number of participants and records from a single center may be the limitations of the present study, but data are still valuable and may be used by other centers for further investigations. The topic of this study is important as nutritional vitamin B12 deficiency is a public health problem in Southeast Turkey.

In conclusion, nutritional vitamin B12 deficiency continues to be an important health problem in our region, as suggested by previous studies. Inadequate intake of animal products, exclusive use of breast milk for feeding during the first 1 or 2 years of life, and low socio-economic background play an important role in the development of this condition. Low socio-cultural levels of the mothers, inadequate health advice, and misinformation about feeding—such as starting complementary food later—may be important reasons for vitamin B12 deficiency in infants. A delay in diagnosis and treatment may cause neurological and mental problems. Early diagnosis and treatment of vitamin B12 deficiency is crucial for long-term prognosis. Vitamin B12 supplementation of mother and child can prevent neurological symptoms in the baby. The neurological symptoms of infants with manifest vitamin B12 deficiency are reversible with early treatment.

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