

# Involuntary movement in infants during vitamin B12 treatment

*Süt çocuklarında vitamin B12 tedavisi sırasında gelişen istemsiz hareketler*

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## Abstract

Megaloblastic anemia is rare in infants and is generally due to vitamin B12 (cobalamin) deficiency in the mother. Neurologic symptoms of vitamin B12 deficiency include irritability, failure to thrive, hypotonia, and developmental regression/delay. Herein we present 2 infants with vitamin B12 that developed movement disorder 5 d after initiation of vitamin B12 treatment. Symptoms included tremor and myoclonus, involving in particular the face, tongue, and hands. Clinical findings in infants associated with vitamin B12 deficiency vary, and temporary involuntary movement can be observed during vitamin B12 therapy. (*Turk J Hematol 2011; 28: 317-22*)

**Key words:** Involuntary movement, vitamin B12 deficiency, infant

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## Özet

Süt çocuklarında megaloblastik anemi nadirdir ve genellikle annelerdeki vitamin B12 eksikliğinin bir sonucudur. Kobalamin eksikliğinin nörolojik semptomları huzursuzluk, büyüme geriliği, hipotoni ve nöro-gelişimsel becerilerde gerileme/gecikmeyi içerir. Bu makalede kobalamin tedavisinin 5. gününde özellikle dil, yüz, elleri içine alan tremor ve miyoklonus gibi istemsiz hareketler gelişen, kobalamin eksikliği olan, iki süt çocuğu sunuldu. Süt çocuklarında kobalamin eksikliği farklı klinik bulgularla karşımıza gelebilir ve tedavisi sırasında geçici istemsiz hareketler görülebilir. (*Turk J Hematol 2011; 28: 317-22*)

**Anahtar kelimeler:** İstemsiz hareketler, B12 vitamini eksikliği, süt çocuğu

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## Introduction

Nutritional megaloblastic anemia is a rare disorder in infants and is generally due to vitamin B12 (cobalamin) deficiency in the mother. Vitamin B12 is an essential vitamin and must be obtained from animal-derived nutrients, such as meat, fish, eggs, milk, and meat. During pregnancy, vitamin B12 passes from the placenta to the fetus via active transport and is stored in the fetus' liver. In infants born with a sufficient quantity of stored vitamin B12, vitamin B12 deficiency is rare; however, in developing countries vitamin B12 deficiency is common in infants born to mothers with pernicious anemia, those on a strict vegetarian diet, and those that are malnourished [1-3].

Although clinical findings show that vitamin B12 deficiency can be tolerated by adults for many years due to their endogenous reserve, in infants it may produce symptoms 2-12 months following birth due to an inadequate hepatic reserve [1-6]. Patients with vitamin B12 deficiency present with hematological, neurological, and psychiatric symptoms, which are more commonly observed in adults. Nevertheless, severe neurological problems, in addition to anemia, may be observed in infants that are fed no animal-derived nutrients, but only breast milk [1,6].

Vitamin B12 deficiency causes fatigue, restlessness, vomiting, difficulty swallowing solid food, and delay or regression of growth and development. Severe neurological findings, such as hypotonia, apathy, decreased eye contact, involuntary movement, seizure, lethargy, and coma, have been reported [1,3,4,7,8]. A delay in the diagnosis and treatment of vitamin B12 deficiency can lead to irreversible psychomotor retardation and neurological damage. Herein we present 2 male infants with severe vitamin B12 deficiency that presented with hematologic, neurologic, and typical cranial magnetic resonance imaging (MRI) findings, as well as involuntary movement during vitamin B12 therapy.

## Case 1

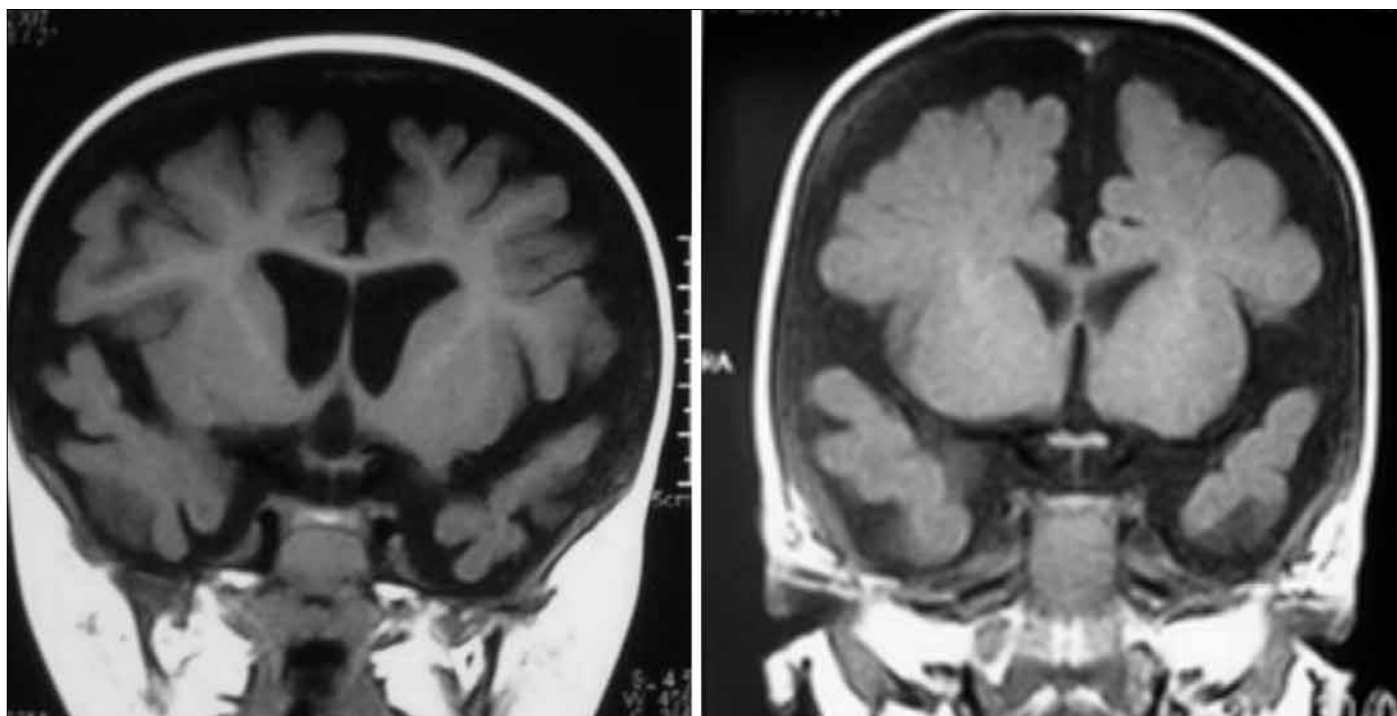
A 6-month-old male that was fed only breast milk presented to our hospital with a chronic cough and dyspnea. He was born full term, weighing 3770 gram after an uncomplicated pregnancy and delivery.

He was able to control his head at age 2 months. His mother had been treated for iron deficiency anemia during the pregnancy.

The patient's weight was in the 50<sup>th</sup>-75<sup>th</sup> percentile, and height and head circumference were in the 25<sup>th</sup>-50<sup>th</sup> percentile. At presentation he was pale and anxious, and had respiratory distress and hepatomegaly. He did not establish eye contact, lacked head control, and was not able to sit without support. Muscle strength was low and reflexes were brisk. Complete blood count results were as follows: macrocytic anemia; hemoglobin (Hb) level: 4.9 g/dL; white blood cell (WBC) count: 2800 mm<sup>3</sup>; platelet (PLT) count: 95,000 mm<sup>3</sup>; mean corpuscular volume (MCV): 102 fL; red blood cell distribution width (RDW): 21.6%. Peripheral blood smear showed anisocytosis, macrocytosis, poikilocytosis, single and double (few) sets of platelets, and hypersegmented neutrophils (few).

Routine urine analysis was normal. Serum immunoglobulin G (IgG) was 3.29 g/L (normal: 7-16 g/L), IgA was <0.24 g/L (normal: 0.7-4 g/L), and IgM was 0.405 g/L (normal: 0.4-2.3 g/L). Biochemical profile and thyroid function tests, and serum iron, ferritin, and folate levels were normal. Serum vitamin B12 was 56.51 pg/mL (normal: 197-866 pg/mL). Bone marrow examination was performed due to pancytopenia and megaloblastic changes were observed. Cranial MRI showed atrophy in the frontoparietal cortex and interhemispheric regions, with dilatation in the ventricles (Figure 1a and b). Plasma homocysteine and methylmalonic acid levels were not determined, as they are not routinely measured in our hospital. Additionally, the patient's mother has maintained a vegetarian diet. The mother's serum ferritin and vitamin B12 levels were low (6 ng/mL and 150 pg/mL, respectively); proteinuria was not observed.

The patient was diagnosed as nutritional megaloblastic anemia due to inadequate intake of vitamin B12, and parenteral vitamin B12 treatment (10 µg/d for 2 days, then 100 µg/d for 2 days, followed by 1000 µg/d for 1 week) was started. Following administration of 1 unit of erythrocyte suspension for tachycardia and severe anemia. On the 5<sup>th</sup> d of treatment generalized tremors and myoclonus were observed in the patient's hands, feet, tongue, and lips; therefore, the patient underwent electroencephalogram (EEG) examination and the results were normal.



**Figure 1.** Coronal T1-Weighted Cranial MRI Shows Bilateral Atrophy in the Frontoparietal Region and Dilatation in the Ventricles

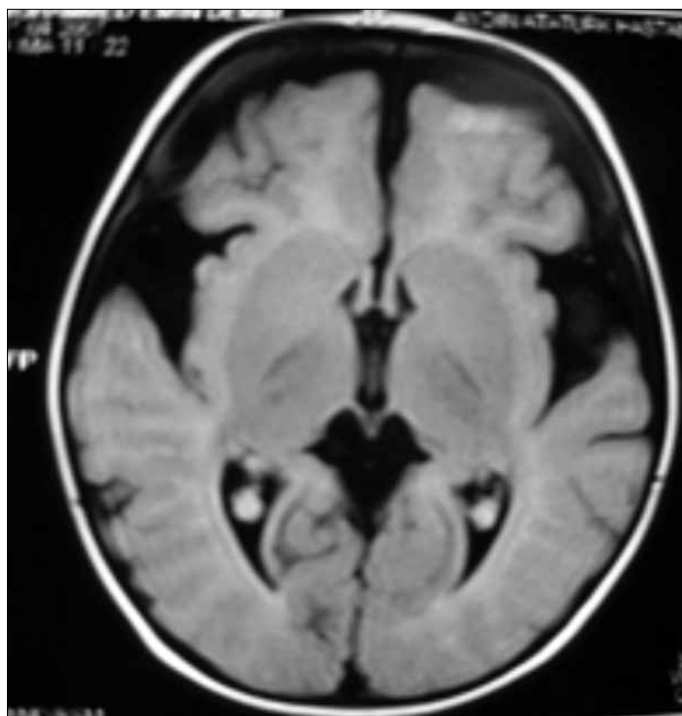
Oral piracetam therapy was initiated (40mg/kg/day) and on the 7<sup>th</sup> d of therapy, and myoclonus and tremor disappeared. Piracetam treatment was interrupted after 3 weeks. One month after the therapy began the patient's anemia improved, he could control his head and sit without support, and was more interested in his environment. At 18 months of age his neurologic development, Ig levels, serum vitamin B12 level, and complete blood count were normal.

## Case 2

A 13-month-old male presented to our hospital with fatigue, weakness, recurrent bronchiolitis, and megaloblastic anemia. He was born weighing 3300 g following an uneventful pregnancy. He was able to control his head at age 3 months. Upon presentation he was still primarily fed breast milk and was vomiting when fed animal-based nutrients, such as eggs, milk, and meat. Family history was unremarkable. The patient's weight and head circumference were in the 10<sup>th</sup>-25<sup>th</sup> percentile and his height was in the 25<sup>th</sup>-50<sup>th</sup> percentile.

At presentation he was pale and anxious. Cardiac examination showed a 1/6 systolic murmur in the mesocardial area. Muscle strength and tonus were

normal, and deep tendon reflexes were normoactive. He could not sit without support. There was developmental delay, including rough motor (sitting, crawling, walking), fine motor (grasping objects), speech (no significant words), and social (apathetic, doesn't smile, poor eye contact). Complete blood count results were as follows: Hb level: 8.3 g/dL; WBC count: 23,500 mm<sup>3</sup>; PLT count: 146,000 mm<sup>3</sup>; MCV: 104 fL; RDW: 23.5%. Peripheral blood smear showed hypochromia, anisocytosis, and macrocytosis. Routine urinalysis was normal. Serum vitamin B12 was low (140 pg/mL) and other biochemical profiles (thyroid function tests, and serum electrolyte, iron, ferritin, and folate levels) were normal. Serum IgM was low (0.3 g/L) (normal: 0.4-2.3 g/L) and the others immunoglobulin were normal. Plasma homocysteine and methylmalonic acid levels were not determined, as they are not routinely measured in our hospital. Cranial MRI showed atrophy in the frontoparietal region and dilatation in the ventricles (Figure 2). Although the complete blood count parameters in the mother and father were normal, their serum vitamin B12 levels were 150 and 188 pg/mL, respectively. The parents did not have proteinuria. The patient's mother has maintained a vegetarian diet for many years.



**Figure 2.** Axial T1-Weighted Cranial MRI Shows Severe Bilateral Cortical Frontoparietal Atrophy and Ventricular Dilatation

The patient was diagnosed as megaloblastic anemia due to inadequate B12 intake, and subcutaneous vitamin B12 treatment (100  $\mu\text{g}/\text{d}$  for 1 week and then 100  $\mu\text{g}/\text{d}$  every other day for 2 weeks, then 100  $\mu\text{g}/\text{d}$  twice a week for 1 week, followed by 100  $\mu\text{g}$  once a week for 4 weeks) was started. On the 5th d of treatment tremors and myoclonus began in the patient's right wrist, and in both hands, arms, and legs. His EEG was normal. We thought that the involuntary movements were due to vitamin B12 therapy, and therefore added piracetam (40mg/kg/day) to the treatment regimen. During the first week of the new treatment regimen tremors and myoclonus disappeared by gradually decreasing and ended 6th day. Piracetam treatment was interrupted after 3 weeks. At the 6-month follow-up the patient's neurologic examination results and serum vitamin B12 level were normal. Informed consents were obtained from the patients.

## Discussion

Patients with vitamin B12 deficiency usually have clinical findings related to the central nervous system, such as developmental delay, microcephaly, hypotonia, lethargy, irritability, involuntary movement, and seizures, 2-12 months after birth.

Involuntary movements, such as tremor and myoclonus, can be the first clinical symptoms of vitamin B12 deficiency or can appear several days after the start of vitamin B12 therapy. The duration of movement disorder is 10-30 d. The severity, nature, and timing of movement disorder are highly variable [1,4,7].

Jadhav et al. [9] first described nutritional vitamin B12 deficiency in 6 Indian infants aged 6-12 months that presented with megaloblastic anemia, psychomotor regression, and hyper pigmentation of the skin. Grech et al. [10] were the first to describe temporary involuntary movements in a 3-month-old patient with congenital transcobalamin deficiency on the 4<sup>th</sup> day of parenteral vitamin B12 treatment. Chandra et al. [11] reported that coarse tremors that occurred initially in the hands and feet gradually became generalized in 6 of 51 megaloblastic anemia patients treated with vitamin B12. Ozer et al. [12] reported 2 vitamin B12-deficient Turkish infants that were fed only breast milk and presented with fatigue, anemia, and developmental delay. Involuntary movements of the tongue, face, hands, and legs, such as tremor and myoclonus, appeared in both patients a few days after treatment with intramuscular vitamin B12. Their neurologic symptoms improved after initiating clonazepam treatment. Özdemir et al. [13] and Avci et al. [14] reported involuntary movements, including tremor and irregular shaking movements, during vitamin B12 treatment. The movements disappeared following clonazepam/piracetam/biperiden hydrochloride therapy.

In accordance with the literature, the 2 presented cases were breastfed. In case 1 rough motor development regression, such as head control, and in case 2 developmental delay, such as sitting, crawling, grasping, and speaking, were observed. Although the 2 cases received different doses of vitamin B12, on the 5<sup>th</sup> d of treatment both patients had tremors and myoclonus, and both responded to piracetam treatment within 1 week.

It is not clear how vitamin B12 deficiency causes neurological symptoms. Some studies have shown that congenital anomalies in homocysteine remethylation or an abnormality in the methionine synthetase reaction leads to neurological symptoms [3,15]. Grattan-Smith et al. [4] suggested that movement disorder in such cases is due to hyper activation of

metabolic pathways that contain vitamin B12, and temporary vitamin B12 or folate metabolism imbalance. Changes in the plasma concentration of various amino acids were observed in response to vitamin B12 treatment. Although it has been proposed that hyperglycinemia is responsible for the involuntary movement observed in response to vitamin B12 treatment [7], it was also reported that glycine levels were normal [11].

It was reported that EEG results in patients with seizures due to vitamin B12 deficiency were abnormal, whereas normal EEG results were observed in patients with tremors and myoclonus [1,12,13,16]. As such, it was reported that use of antiepileptics was unnecessary and useless in patients with involuntary movements [1,10,16]. It is thought that involuntary movements is self-restricted and there is no consensus on the use of antiepileptic treatment [7,10].

Cerebral atrophy and retarded myelination based on cranial MRI have been reported in many cases of infantile vitamin B12 deficiency [1,4,5,12-14,17]. Cranial MRI in the 2 presented cases showed atrophy in the frontoparietal cortex and interhemispheric region, and dilatation in the ventricles secondary to the observed atrophy. Data concerning the long-term prognosis of neurological symptoms due to vitamin B12 deficiency are inadequate. Although hematological symptoms varying from megaloblastic anemia to pancytopenia can be cured, neurological symptoms may persist [4,16,18]. Some studies reported no improvement in verbal or psychomotor ability despite vitamin B12 treatment, which suggests that neurological impairment may be irreversible if the diagnosis is delayed beyond 12 months [18,19]. Monagle et al. [19] reported that 2 of 6 patients with vitamin B12 deficiency were followed-up for long-term neurological sequelae, and von Schenk et al. [2] reviewed 25 patients with vitamin B12 deficiency reported in the literature and observed that 6 of the patients diagnosed at a mean age of 10 months had normal development at follow-up, while 6 others diagnosed at a mean age of 13 months had persistent developmental delay. In a study performed in the southeastern region of Turkey, psychomotor retardation was observed in all 33 patients with nutritional vitamin B12 deficiency. Eleven patients have been followed. Whereas the repeated developmental screening test results

were normal in 6 patients who diagnosed <18 months, psychomotor retardation was persistent in 5 patients who diagnosed >18 months were continued the follow-up. [18]. Neurological development in a patient reported by Avci et al. [14] was near normal following vitamin B12 treatment, whereas in the 2 presented cases neurological development was normal.

C3, IgG, and IgM levels were low in mice with vitamin B12 deficiency [20]. Avci et al. [14] reported a patient with IgG and IgM deficiency that recovered following vitamin B12 treatment. Case 1, who presented due to frequently recurrent infections, had low IgG and IgA levels, and an IgM level at the lower limit of normal, whereas case 2 had low-level IgM. A clear decision could not be made whether low Ig levels are related to vitamin B12 deficiency or transient hypogammaglobulinemia of infancy. In our case, serum Ig levels normalized after vitamin B12 treatment, so within it was related with vitamin B12 deficiency.

In conclusion, children born with an insufficient vitamin B12 reserve can have vitamin B12 deficiency and such patients present with various clinical findings. Early diagnosis can prevent the occurrence of irreversible neurological damage in such patients.

#### 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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