Vitamin B12 deficiency as a treatable cause of severe brain atrophy

[1]Hamit OZYUREK, [2]Meltem CEYHAN, [3]Hulya INCE, [3]Omer Faruk AYDIN

[1]Pediatric Neurology Unit, Ankara City Hospital, Ministry of Health; [2]Department of Radiology, Faculty of Medicine, Ondokuz Mayis University; [3]Pediatric Neurology Unit, Faculty of Medicine, Ondokuz Mayis University, Ankara, Turkey

Abstract

We report here two infants with vitamin B12 deficiency who presented with delay in motor and mental development. Neuroimaging studies in our cases revealed diffuse severe cerebral atrophy. Follow-up MRI after vitamin B12 treatment showed significant regression of the brain atrophy. Early diagnosis and treatment in infantile vitamin B12 deficiency are important to prevent the irreversible neurological damage.

Keywords: Vitamin B12 deficiency, cerebral atrophy, magnetic resonance imaging, psychomotor development

INTRODUCTION

Infantile vitamin B12 (vit B12) deficiency is a rare clinical entity that results in hematological and neurological symptoms. Etiologic factors, clinical presentation, and radiological findings in infantile vit B12 deficiency are different from adult form. In contrast to mild neuropsychiatric symptoms in adolescents and adults; in infancy, irritability, apathy, progressive lethargy, developmental delay or regression, hypotonia, sensory deficits, involuntary movements, seizures and coma are frequently observed as neurological symptoms. These symptoms may be seen in some infants even without hematological findings. Instead of subacute combined degeneration of the cord that is detected in adults, cerebral atrophy and white matter lesions are seen in infants. [1-3]

Here we report two infants with vit B12 deficiency showing severe diffuse cerebral atrophy which was improved after vit B12 supplementation.

CASE REPORTS

Patient 1

A 12-month-old boy suffering from respiratory tract infection and dyspnea was referred to our hospital for further investigation and treatment. The family history was noninformative. The parents reported that the baby was developmentally delayed when compared to his peers. He had head control when 4 months old but never able to sit on his own.

On admission he was apathetic and hypotonic. His body temperature was 36.5°C, pulse rate was 134/min, breath rate was 42/min, and blood pressure was 85/50 mmHg. Both his weight (8.6 kg) and height (75 cm) were at 75th percentile. Head circumference was 46cm (10-25th percentile). He had crackles and rhonchi on distal zones of lungs and liver palpated 3cm below the costal margin. He had head control, but was not able to sit without support. Deep tendon reflexes were normoactive.

Chest radiograph showed right paracardiac infiltration. The MRI of brain revealed atrophy of frontal, frontotemporal, and anterior parietal regions on both hemispheres, and dilatation of lateral ventricles with mild retardation in myelination in the periventricular white matter (Figure 1a). Blood screening tests revealed mild pancytopenia (WBC:3×10^9/L, Hb:9.6g/dL, Htc:29.1%, PLT:147×10^9/L, MCV:87.8fL). Iron status was normal. There were hypersegmentated neutrophils, and anisocytosis in the peripheral blood smear. Further investigation for the etiology of pancytopenia revealed a low serum level of vit B_{12} (<150 pg/mL N:197-866), a high serum level of folate (>15 ng/dL N:3-14) and high urine level of methylmalonate. The serum level of homocysteine could not be measured on admission. The serum

level of vit B12 of his mother was also low (<150 pg/mL). The metabolic screening tests other than the organic acid screening test in urine, including venous blood gases, serum ammonium and lactate level, serum lipid analyses, tandem mass screening test, and the thyroid function test were normal. His dietary history revealed that he was exclusively breast-fed by his mother who could not consume enough animal source food due to very low-economic state.

The parental hydroxycobalamin was started at 1mg per day on the 6th day of admission. After 2 weeks of daily parenteral vit B12 therapy, the dosage was tapered to 1 mg per month. He became more interested in his surroundings at the follow-up visit one month after the start of treatment. The laboratory tests showed WBC 6.2×10^9/L, Hb 10.8 g/dL, Htc 33.9%, MCV 82fL, folate 9 ng/dL, and vit B12 level 1068pg/mL. The developmental skills especially gross motor functions gradually improved. He began to talk in reliable words at age of 17 months and he was able to sit on his own and to stand on his feet by support at age of 18 months. Repeat cranial MRI at the age of 20 months was reported as normal (Figure1b). When the Denver-II Developmental Screening Test was performed at the age of 3 years, he was retarded especially in language and fine motor abilities.

Patient 2

A 9-month-old girl with failure to thrive suffering from respiratory tract infection and congestive heart failure was referred to our hospital for further investigation and treatment. The baby had been receiving intravenous hydration therapy, antibiotics, and digoxin for four days on admission.

She was born after an uncomplicated and a full term pregnancy. She had been exclusively breastfed since birth. At the age of 8 months, she was introduced to solid foods but she refused. She had a poor appetite and vomited regularly. Her parents first observed hypoactivity and weakness around two months of age. It was more remarkable in the last one month. Her mother was not a vegetarian, but animal product consumption was very low in her diet.

On admission she was apathetic, hypotonic, hypoactive, pale and malnourished. Her body temperature was 36.5°C, pulse rate was 138/min, breath rate was 38/min, and blood pressure was 80/50 mmHg. Both her weight (5.6 kg), height (60cm) and head circumference (40.5 cm) were below the 3th percentile. Her pulmonary findings included crackles and rhonchi on superior and middle zones of both lungs. She had palpable liver 4cm below the costal margin. Her head control was poor and she was not able to sit on her own. Deep tendon reflexes were normoactive.

The blood screening tests revealed anemia and thrombocytopenia (WBC: 7.9×10^9/L, Hb:6.7g/dL, Htc: 19.5%, PLT: 41×10^9L, MCV:83.1fL). The absolute neutrophil count was 1.2×10^9/L. There were hypersegmentated neutrophils, macrocytosis and anisocytosis in the peripheral blood smear. The bone marrow aspiration findings were also compatible with megaloblastic anemia. Further investigation of the etiology of pancytopenia revealed a low serum level of vit B_{12} (<150 pg/dl) and a normal serum level of folate and ferritin. The serum level of vit B12 of her mother was also low. The metabolic screening tests including venous blood gases, serum ammonium and lactate level, serum lipid analyses, tandem mass screening test with normal C3 level, and the thyroid function test were normal. Urine methylmalonic acid and blood total homocysteine levels could not be performed. The MRI of brain revealed diffuse cortical atrophy especially on both frontotemporal regions with moderate myelination delay (Figure 2a). Parental hydroxycobalamin was started at 1mg per day on the 5th day of hospitalization. Coarse tremors were observed following vitamin B12 treatment on the 8th day of hospitalization. The electroencephalography was normal. Tremors subsided within 8 days. She received erythrocyte transfusion on the 9th day of hospitalization. After one week of daily parenteral vit B12 therapy, the dosage was tapered to 1 mg per 2 days for 2 weeks, then to 1mg per month. Oral prophylactic dose of iron (2 mg/kg) was added to the treatment. The vit B12 treatment was stopped on the 18 month of therapy.

After 10 days of treatment, her hemoglobin, leukocyte and platelet counts increased. Her developmental skills especially gross motor functions gradually improved. She was active and alert at her follow-up visit. She was able to sit on her own and stand on her feet by support at age of 15 months and 17 months, respectively. She could speak in words when she was 18 months old. The repeat MRI brain revealed disappearance of atrophy at the age of 21 months (Figure 2b). When the Denver-II Developmental Screening Test was performed at the age of 3.5 years, retardation in language, personal-social and fine motor abilities was shown.
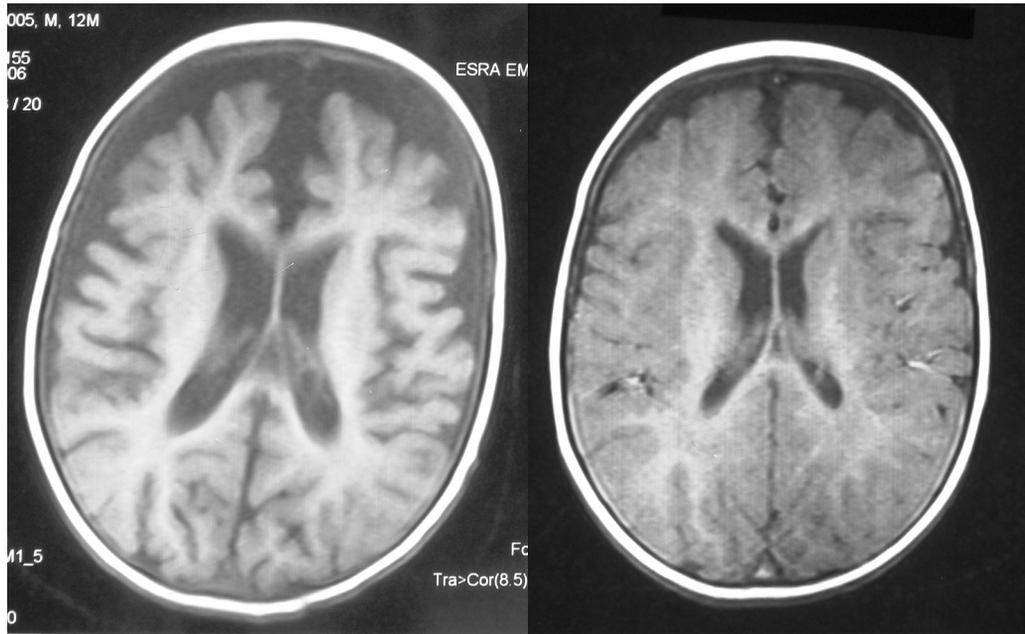
Figure 1. a. T-weighted image showed diffuse severe cortical atrophy at the age of 12 months and b. 8 months later, there was complete regression of cortical atrophy.

DISCUSSION

The clinical and laboratory findings and nutritional history of both infants and their mothers revealed vit B12 deficiency. The most common cause of vit B12 deficiency in infants is maternal deficiency as seen in our cases. Nutritional deficiency and malabsorption are two main causes of maternal vit B12 deficiency. Dietary source of vitamin B12 are mostly from animal products including meat, eggs, fish, and milk. Nutritional deficiency can occur if only small amount of animal product is consumed. Pernicious anemia is the most common cause of malabsorption resulting in maternal vit B12
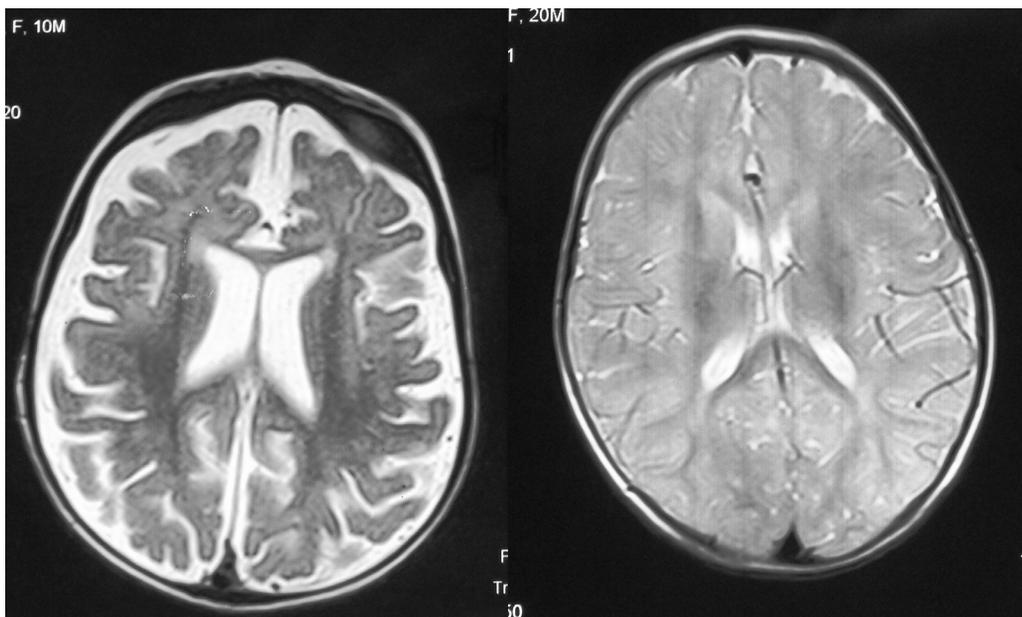

Figure 2. a. T-weighted image revealed severe cortical atrophy. b. Follow-up image performed 12 months later was normal.

deficiency. Malabsorption due to achlorhydria, ileal damage, and gastric bypass surgery are also rare causes of maternal vit B12 deficiency. If infants are exclusively breast-fed by mothers with vit B12 deficient, neurological manifestations usually appear between 2 and 12 months of age.[4,5] The mothers of our cases were not vegetarian, but animal product consumptions were very low in their diet due to the low socioeconomic status. We usually make a consultation with internal medicine department to exclude other causes of maternal vit B12 deficiency. The vit B12 supplementation is simultaneously prescribed to the mother in our clinical practice.

We observed coarse tremors on the 3th day of vit B12 treatment lasting 8 days in Patient 2. Following therapy with vit B12, involuntary movements consisting of tremor and myoclonus involving hand, feet, face, tongue and pharynx appear in some infants. The prevalence rate of involuntary movements was reported as between 12-33%. The movement disorders disappear within a few weeks.[6,7] Although the mechanisms underlying the movement disorder are not clear, it is hypothesized that sudden availability of vit B12 produced a temporary imbalance of cobalamin and folate pathways, with local deficiencies and excesses of metabolic intermediates that lead to tremors and myoclonus. Denervation supersensitivity, hyperglycinemia, cerebral thromboembolism, toxic effect of the cyanide moiety in cyanocobalamin are other explanations for mechanism of involuntary movement secondary to vit B 12 therapy.[8,9] We use hydroxocobalamin instead of cyanocobalamin to treat the infants with diagnosis of vit B12 deficiency in Turkey. Therefore the pathogenesis of involuntary movements seen in our cases is not due to toxic effect of cyanide moiety mentioned above.

Neuroimaging findings in infantile vit B12 deficiency are different from adult form. Diffuse or focal cortical atrophy, thinning of corpus callosum, structural abnormalities and retardation in myelination are the most frequent neuroradiological findings in infantile vit B12 deficiency.[2,3,7,10,11] Acipayam *et al*. evaluated neuroradiological findings of 21 infants with vit B12 deficiency. Cerebral atrophy was observed in almost all patients. Ten infants had diffuse cortical atrophy, one had frontoparietal atrophy, two had frontotemporal atrophy and two had corpus callosum thinning.[7] In another study consisting of 15 infants with nutritional vit B12 deficiency, thinning of the corpus callosum was detected

more frequent than cortical atrophy.[11] In addition, coexistence of cortical atrophy and myelination disorder was reported in some cases.[10]

In the literature, there are limited reports of long-term MRI follow-up of infantile vitamin B12 deficiency. Korenke *et al*. reported a 4-month-old girl with vitamin B12 deficiency showing global cerebral atrophy on first MRI. When the second MRI was performed at the age of 7 years, moderate enlargement of the ventricles with a reduction of myelin was detected.[1] Kocaoglu *et al*. reported clinical and radiological follow-up of 12 -month-old infant with vit B12 deficiency. At the diagnosis, cranial MRI revealed severe cerebral atrophy with enlargement of cortical sulci and subarachnoid spaces. They performed cranial MRI three months after the initiation of therapy. Recovery of cerebral atrophy and normal subarachnoid space were detected.[12] In our cases, reversal of diffuse cortical atrophy were seen approximately 8 and 12 months after first neuroimaging, respectively. Although rapid clinical and radiological improvements are achieved by supplementation of vit B12, infants often suffer long-term neurological dysfunctions consisting of low IQ, psychomotor and linguistic delay. It appears that the duration of deficiency and severity of symptoms rather than serum vit B12 level affect the long-term prognosis. By reviewing 26 reported cases of cobalamin deficiency, Von Schenck *et al*. observed that patients diagnosed at the mean age of 10 months were associated with a normal outcome while patients diagnosed at the mean age of 13 months showed permanent neurological abnormalities.[3] However, Korenke *et al*. did not report any correlation between the diagnosis age and long-term prognosis when they reviewed the 30 infants reported in the literature with vit B12 deficiency due to maternal pernicious anemia and vegan diet.[1] Additionally, the initial improvement after the treatment may not result in favorable outcome in the long term. The neurological recovery was slow in our cases even though the diagnosis of Patient 2 was made at 9 month of age. We thought that the delay in improvement of developmental milestones in our patient after vit B12 supplementation was consistent with the brain atrophy being more diffuse and severe than cases reported in the literature.

The neurotoxicity mechanism of vit B12 deficiency is not well understood. Several theories have been proposed to explain the mechanisms by which vit B12 deficiency results in delayed myelination or demyelination of nerves. Firstly,

cobalamin is necessary in the breakdown of methylmalonyl CoA to succininyl CoA in fatty acid metabolism. Due to inappropriate conversion, the levels of methylmalonyl CoA and its precursor propionyl CoA are increased and may lead to odd chain fatty acid synthesis. Abnormal fatty acids disturb the myelin integrity by impairing the synthesis of ethanolamine, phospholipids, and sphingomyelin. Cobalamin is also a cofactor in the conversion of homocysteine to methionine. Methionine is converted to S-adenosylmethionine (SAM), which is converted to S-adenosylhomocysteine (SAH). Vit B12 deficiency results in elevation of SAH and homocysteine levels, and depression of SAM levels. SAM gives its methyl group for the conversion of phosphotidylethanolamine to phosphatidylcholine. These lipids make up about 14% and 11% of central nervous system myelin, respectively. So, vit B12 deficiency may lead to inefficient conversion of phosphotidylethanolamine to phosphatidylcholine that may impair myelination or result in demyelination.[4]

Imbalance of neurotrophic and neurotoxic cytokines, and accumulation of lactate in brain cells were mentioned as novel theories of neurotoxicity of vit B12 deficiency. Some cytokines like tumor necrosis factor-α (TNF-α) act as neurotoxins in CNS diseases that are characterized by demyelination, and others such as epidermal growth factor are neurotrophic. Higher serum and cerebrospinal fluid concentration of TNF-α and lower concentrations of EGF are found in adult patients with vit B12 deficiency. This imbalance of cytokines is corrected by vit B12 treatment.[4]

In conclusion, infantile vit B12 deficiency is a treatable cause of neurological disorders. Radiologic and clinic findings may be reversible with early diagnosis and adequate supplementation therapy in infants with infantile vit B12 deficiency. However mild or moderate neurological squeals may rarely persists long-term, even when infantile vit B12 deficiency is diagnosed early.

DISCLOSURE

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