Neurologic findings of nutritional vitamin B_{12} deficiency in children

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We report herein our interesting case series of 15 infants admitting with neurological symptoms who were found to have vitamin B_{12} deficiency.

Infants who were admitted to our hospital between 2004 and 2007 with neurological symptoms and were found to have vitamin B_{12} deficiency were included in this study. Data regarding clinical and laboratory features were obtained.

Of 15 infants, 9 were boys (60%) and 6 were girls (40%). The mean age was 11.7 months. Anorexia, pallor, hypotonia, and neurodevelopmental retardation were present in all infants. Seizures and tremor were observed in 46.6% (7/15) and 33% (5/15) of patients, respectively. Seizures were generalized tonic-clonic in 4 patients, generalized tonic in 1 patient and focal in 2 patients. Four patients had tremor on admission and 1 patient had occurrence after vitamin B_{12} treatment. Vitamin B_{12} deficiency may lead to serious neurological deficits in addition to megaloblastic anemia. Persistent neurological damage can be prevented with early diagnosis and treatment. We believe that a thorough clinical and neurological assessment might prevent failure to notice rare but possible vitamin B_{12} deficiency in infants with neurological deficits and neurodevelopmental retardation.

Key words: vitamin B12 deficiency, neurologic findings, infants.

Vitamin B_{12} is found as cobalamin in foods of animal origin and cannot be synthesized in humans. The most frequent cause of vitamin B_{12} deficiency is inadequate intake. However, intrinsic factor (IF) deficiency (congenital pernicious anemia), selective vitamin B_{12} malabsorption (Imerslund-Gräsbeck syndrome), gastric or distal ileal surgical interventions, and increase in vitamin B_{12} consumption (diphyllobothrium latum infections) may also lead to megaloblastic anemia by causing deficiency. The most important cause of vitamin B_{12} deficiency in infants is maternal dietary deficiency. It is generally observed in infants breast-fed by mothers who are strict vegetarians[1-3].

In addition to anemia, neurological symptoms and signs, such as irritability, apathy, developmental retardation, ataxia, paresthesia, hyporeflexia, hypotonia, tremor, seizures, loss of acquired motor abilities, and coma can be observed in vitamin B_{12} deficiency. Persistent neurological deficits may occur in late-diagnosed cases[4].

We report our interesting case series of 15 infants who were admitted with neurological symptoms and were found to have vitamin B_{12} deficiency.

Material and Methods

Infants admitted to our hospital between 2004 and 2007 with neurological symptoms and found to have vitamin B_{12} deficiency were included in this study. They were between 7 and 18 months old. All infants were assessed by clinical, physical and neurological examinations. Laboratory investigations included vitamin B_{12} and folic acid levels in both mother and infant, as well as whole blood count, peripheral blood smear, serum and urinary metabolic screening,

serum iron, and iron binding capacity in the infant. Diagnosis of megaloblastic anemia due to vitamin B_{12} deficiency was achieved through a combination of clinical and laboratory findings including clinical presentation, increased mean corpuscular volume (MCV) value (macrocytosis), hypersegmentation of neutrophils, and low vitamin B_{12} levels.

Cerebral magnetic resonance imaging (MRI) was performed on all infants. Infants having seizures were also evaluated by interictal electroencephalography (EEG).

Results

Of the 15 infants, 9 were boys (60%) and 6 were girls (40%). Their mean age was 11.78 ± 2.65 months (range: 7-18). While 9 infants were only breast-fed, 6 were both breast-fed and given cow's milk, but without any other supplemental food. All infants' families had low socioeconomic and cultural status. Maternal intake of animal products was also inadequate in the case of all infants. Body weight and length/height measurements of 10 infants (76.9%) were below the 3rd percentile for their age. Anorexia, pallor, hypotonia and neurodevelopmental retardation were present in all infants. Seven (46.6%) infants had seizures. Four of these had generalized tonic-clonic (GTC) seizures, 1 had generalized tonic and 2 had focal seizures. Tremor was present in 5 (33.3%) infants. Four of them had tremors prior to treatment and 1 had occurrence after treatment (Table I). Their mean serum vitamin B_{12} level was 69.50 ± 25.60 (30-129) pg/ml, and vitamin B_{12} level was <100 pg/ml in 10 (66.6%) infants. Mean maternal level of vitamin B_{12} was 150.4 ± 24.24 (102-178) pg/ml (normal reference: 180-914 pg/ml). All infants were evaluated for anemia, leukopenia and thrombocytopenia. Hemoglobin levels below 11 g/dl were regarded as anemia, leukocyte count below 6000/mm^3 as leukopenia, and thrombocyte count below 150,000/mm^3 as thrombocytopenia. Anemia was present in all infants. Seven infants (46.6%) had thrombocytopenia, 5 (33.3%) had leukopenia and 4 (26.6%) had pancytopenia. Mean MCV was 95.46 ±7.22 (90-110) fL. Hypersegmentation, macrocytosis and anisocytosis were observed in 5 infants (33.3%) (Table II). Proteinuria was not detected in any of the infants. While cortical atrophy was evident in 8 infants on cerebral MRI, the others had normal findings. Interictal EEG evaluation was performed on 7 infants with seizures; generalized epileptic activity was observed in 2 of them and focal epileptic activity in 1. Vitamin B12 treatment was started immediately in all the patients with a diagnosis of megaloblastic anemia. Blood values had improved by the second week of treatment.

Table I. Examination and Clinical Findings in the Infants

	n	%
Anorexia	15	100
Pallor	15	100
Nausea	6	40
Glossitis	6	40
Diarrhea	5	33.3
Hyperpigmentation	5	33.3
Tremor	5	33.3
Seizure	7	46.6
Hypotonia	15	100
Neurodevelopmental retardation	15	100

Table II. Laboratory Results of the Infants

	Mean ± SD	Range
Hb (g/dl)	7.71±1.36	6-10
WBC (x10^3/mm^3)	6.54±3.79	2.5-13.0
Plt (x10^3/mm^3)	155.4±80.34	50-252
MCV (fL)	95.46 ±7.22	90-110
B_{12} (pg/mL)	69.50 ± 25.60	30-129
FA (ng/mL)	11.33±2.47	7-15

Hb: Hemoglobin. WBC: White blood cell. Plt: Platelet count. MCV: Mean corpuscular volume. FA: Folic acid.

Discussion

Nutritional vitamin B_{12} deficiency is the most frequent cause of megaloblastic anemia in low socioeconomic level groups. The most frequent origin of vitamin B_{12} deficiency in the infancy period is also nutritional deficiency, seen in breast-fed infants of vitamin B_{12}-deficient mothers.

During pregnancy, vitamin B_{12} is actively transferred to the fetus across the placenta and reaches twice the level of maternal serum[5]. Neonatal vitamin B_{12} store level is around 25-50 µg at birth. These stores are generally enough for about 6-12 months in a normal infant. Therefore, deficiency in the first 6-12

months only occurs in infants with maternal vitamin B_{12} deficiency[1].

Allen et al.[3] reported a megaloblastic anemia prevalence of 8% in a study involving 200 children between 18 and 36 months. Malnutrition was found to be a contributing risk factor. We also detected malnutrition in both the infants and their mothers.

In a Guatemala study, 46.7% of the mothers had low levels of plasma vitamin B_{12}, 32.3% had holotranscobalamin II deficiency, and 31% had low vitamin B_{12} breast-milk[6]. Vitamin B_{12} of breast-milk and serum as well as folic acid levels of 50 mothers between the ages of 18 and 38 years with low socioeconomic status were evaluated in India. Breast-milk and serum vitamin B_{12} levels were reported to be higher in non-vegetarians compared to lacto-vegetarians[7]. In another similar study conducted in the United States, low levels of vitamin B_{12} were demonstrated in the breast-milk of vegetarian mothers[8]. In this study, it was observed that, due to the low socioeconomic status, there was a lack of animal products and adequate vitamin supplementation in the mothers' diet during pregnancy and lactation. Observation of infants' vitamin B_{12} deficiency in the first 6-12-month period is also supportive of maternal deficiency. Koc et al.[9] reported that the frequencies of vitamin B_{12} deficiency were 72% and 41% in mother and babies, respectively, in the Sanlıurfa province of Turkey. In another study in Turkey, Katar et al.[10] studied 3368 children, of whom 33 had megaloblastic anemia. Thirty-two patients had vitamin B_{12} deficiency and one patient had folate deficiency.

Central nervous system symptoms such as nausea, lethargy and nutritional disorders that are related to vitamin B_{12} deficiency are often initiated between the ages of 2 to 12 months. Other significant symptoms and signs include irritability, apathy, hypotonia, microcephaly, seizures, optic atrophy, tremor, abnormal motions, and developmental retardation[4]. We similarly verified neurodevelopmental retardation and hypotonia in all infants in this study, in addition to seizures in 7 (46.6%) and tremors in 5 (33.3%).

The exact mechanism underlying neurological deficits in vitamin B_{12} deficiency is not clearly understood. However, vitamin B_{12} is known to play a role as a cofactor in the remethylation of homocysteine and methyl malonyl CoA degradation. Vitamin B_{12} deficiency is thought to cause disturbance of methionine synthesis and accumulation of guanidoacetate, leading to neurotoxicity. Increased levels of homocysteine and methylmalonic acid are also a result of vitamin B_{12} deficiency. These may lead to demyelination, axonal degeneration and neuronal death[4].

Occurrence of seizures is rare in vitamin B_{12} deficiency. Glutamate and other excitatory amino acids (i.e. sulfur-containing amino acids) are known to be effective in the origin and expansion of seizures[11]. It has been proven in deficiency-related rat studies that homocysteine, a sulfur-containing amino acid and its metabolic product, homocysteic acid, induce convulsions[12]. Several studies currently exist describing an association between vitamin B_{12} deficiency and EEG abnormalities and epilepsy[2,11]. Korenke et al.[2] reported GTC-type seizures in a four-month-old infant. Biancheri et al.[11] reported epilepsy in 9 patients with vitamin B_{12} deficiency. Of these 9 patients, 3 had simple partial, 4 had complex partial, and 2 had GTC-type seizures. Furthermore, on the EEG evaluations of 9 patients with epilepsy, Biancheri et al.[11] detected focal epileptic activity in 7 and multifocal epileptic activity in 2 patients. In our study, epilepsy was also present in 7 infants. Seizure types were GTC in 4, generalized tonic in 1 and partial in 2 infants. EEG evaluations of the 7 infants revealed generalized epileptic activity in 2 and focal epileptic activity in 1.

The type (tremor, chorea, myoclonus, etc.), severity and duration of involuntary movements related to vitamin B_{12} deficiency varies considerably. Whilst they may be the presenting symptom in vitamin B_{12} deficiency, they may also occur after the initiation of treatment. These movements, resulting from the combination of tremors and myoclonus, can be misinterpreted as convulsions[13]. Development of hyperglycinuria has been reported in some vitamin B_{12} deficiency cases. It has been stated that glycine not only has an inhibitory effect on the spinal cord and brainstem, but also an excitatory effect on the cerebral cortex via N-methyl-D-aspartate and glutamate receptors. Hyperglycinemia has been suggested to be responsible for abnormal movements such as tremors[14]. Chandra et al.[15] reported coarse tremor in 12%

(6/51) of patients with megaloblastic anemia following therapy with vitamin B_{12}. Tremors were present in 5 of our cases. While 4 of them had tremors prior to treatment, only 1 case had such occurrence after treatment. The mechanism underlying involuntary movements during treatment is unknown. However, it has been proposed that a transient imbalance of metabolic pathways due to folate and cobalamin pathway activation by a sudden cobalamin uptake following a longstanding deficiency period might be responsible[13].

The most frequent neuroradiological findings that have been reported in vitamin B_{12} deficiency include cortical atrophy, thinning of the corpus callosum and retardation in myelination[11,16]. Biancheri et al.[11] reported that, in 10 infants with vitamin B_{12} deficiency, cortical atrophy was present in 8 infants and hydrocephaly in 2. There have been studies describing improvement of these conditions after treatment[17,18]. We noted cortical atrophy in 8 of the infants by neuroimaging. The other infants had normal MRI findings.

While hematological findings show a rapid improvement after treatment, neurological deficits can be irreversible. Persistent neurological sequelae that are associated with the degree and duration of deficiency have been reported[19]. Therefore, early diagnosis and treatment of vitamin B_{12} deficiency is crucial for long-term prognosis. The risk for irreversible neurological deficits is high when the diagnosis is made later than 12 months. Pearson and Turner[19] found mental retardation in a 32-month-old patient at assessment after three years of treatment. Graham et al.[4] observed improvement in cognitive functions in 2 of 4 infants. Von Schenck et al.[17] described a normal mental status in their case that was diagnosed before 10 months of age. In our study, infants are still being clinically followed for long-term prognosis.

In conclusion, hypotonia and neurodevelopmental retardation were present in all our patients. The other findings were seizure and tremor. Severe neurological findings may develop in addition to megaloblastic anemia due to vitamin B_{12} deficiency, especially in breast-fed infants whose mothers consume insufficient animal products. Early diagnosis and treatment of these infants may be crucial for the prevention of persistent neurological damage. Thorough hematological evaluation of infants with neurodevelopmental retardation along with neurological findings may prevent overlooking a possible vitamin B_{12} deficiency. Moreover, in order to avert irreversible neurological damage in the infants of mothers on a vegetarian diet, with pernicious anemia, or even with low socioeconomic status, vitamin B_{12} supplementation should be performed during pregnancy.

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