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ORIGINAL ARTICLE

Vitamin B12 Deficiency in Pediatric Neurology Practice

Çağatay Günay, Gamze Sarıkaya Uzan, Özlem Özsoy, Ayşe Semra Hız Kurul, Uluç Yiş

Department of Pediatric Neurology, Dokuz Eylul University Faculty of Medicine, Izmir, Türkiye

Abstract

Introduction: Vitamin B12 deficiency continues to be an important health problem in developing countries with a wide spectrum of neurological and other system findings. Early diagnosis and appropriate treatment are essential to prevent permanent damage. In our study, we aimed to evaluate the demographic, clinical, radiological, and electrophysiological characteristics of the cases who applied to pediatric neurology outpatient clinic and had Vitamin B12 deficiency.

Methods: Among the patients presenting to the pediatric neurology department between January 2020 and June 2020, patients with Vitamin B12 deficiency were included in the study. Vitamin B12 deficiency was classified as subclinical deficiency (200–300 pg/mL), deficiency (160–199 pg/mL), and severe deficiency (<160 pg/mL). Demographic, clinical, radiological, and electrophysiological findings were analyzed.

Results: Vitamin B12 deficiency was found in 210 (21.4%) of 978 patients. The mean age was 3.3±5.1 years (1 month–17 years). About 53.3% (n: 112) of the patients were male. The most common complaints were seizures (n:59, 26.8%), headache (n:41, 18.6%), and neuromotor retardation (n:14, 6.3%). Subclinical deficiency was observed in 98 (46.7%) of the patients, deficiency in 55 (26.2%), and severe deficiency in 57 (27.1%). Nine patients (4.2%) showed improvement in symptoms after Vitamin B12 treatment, of whom the complaints were headache (n:5, 2.3%), tremor (n:2, 0.9%), forgetfulness (n:1, 0.5%), and dizziness (n:1, 0.5%).

Discussion and Conclusion: While Vitamin B12 deficiency was observed at a high rate, the complaints regressed with Vitamin B12 treatment in 4.2% of the cases. These complaints, which completely regressed with treatment, were headache, tremor, forgetfulness, and dizziness.

Keywords: Cobalamin; headache; neurology; seizure; vitamin b12.

Vitamin B12, also known as cobalamin, is a water-soluble vitamin of which main source is animal products such as red meat, dairy products, and eggs. After absorption, Vitamin B12 acts as a cofactor for enzymes involved in the synthesis of deoxyribonucleic acid, fatty acids, and myelin. Excess Vitamin B12 is stored in the liver, reducing the likelihood of deficiency[1]. Depletion of liver stores leads deficiency mainly due to nutritional deficiency or malabsorption. A wide range of prevalence has been reported, ranging from 14 to 73.5% in children in developing countries[2-13]. The concept of broad spectrum also applies to signs and symptoms in Vitamin B12 deficiency. As well as, non-neurological symptoms such as growth retardation, vomiting, anorexia, fatigue, drowsiness, pale skin, rapid heartbeat and breathing, abdominal pain, weight loss, diarrhea or constipation, lack of motivation, neurological signs, and symptoms with or without hematological disorders are included in this spectrum. Muscle weakness, numbness, tingling, and other sensory disturbances such as vibration, proprioception, loss of taste or

Correspondence: Çağatay Günay, M.D. Department of Pediatric Neurology, Dokuz Eylul University Faculty of Medicine, Izmir, Türkiye
Phone: +90 554 430 82 46 **E-mail:** cagataygunaymd@gmail.com
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smell, ataxia, visual impairment, dizziness, urinary or fecal incontinence, personality changes, memory impairment, seizures, hypotonia, and developmental delay are only a few components of the long list of neurological presentations. A high level of awareness, especially in children with mild symptoms, is required to prevent permanent neurological damage due to Vitamin B12 deficiency[14]. In this study, we aimed to evaluate the demographic, clinical, radiological, and electrophysiological findings of the patients with Vitamin B12 deficiency followed in the pediatric neurology department of Dokuz Eylul University Faculty of Medicine with a particular focus on those who benefit from replacement therapy.

Materials and Methods

Archival records of all cases followed up by the pediatric neurology department of Dokuz Eylul University Faculty of Medicine between January 2020 and June 2020 were retrospectively analyzed of those with low Vitamin B12 levels were included in the study. Vitamin B12 deficiency was classified as subclinical deficiency (200–300 pg/mL), deficiency (160–199 pg/mL), and severe deficiency (<160 pg/mL)[15-18]. While patients with deficiency and severe deficiency were treated with intramuscular cyanocobalamin, oral cobalamin was used in patients with deficiency. Demographic, clinical, radiological, and electrophysiological findings of the patients were analyzed with the information obtained from patient files and system data. The accepted upper limits for neurodevelopmental stages were responsive social smile at 3 months, head control at 4 months, sitting with support at 6 months, sitting without support at 9 months, and independent walking at 18 months[19,20]. The age limits for language retardation were accepted as age of two for a single word, and age of three for the inability to form a two-word sentence. The study was approved by Dokuz Eylul University Faculty of Medicine Ethics Committee (approval number: 2021/26–41) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the distribution of numerical variables was evaluated using the Kolmogorov–Smirnov test. Numerical variables were expressed as median (minimum [min]-maximum [max]), and categorical variables were expressed as numbers and percentages (%).

Results

Demographic Features

Vitamin B12 level was below 300 pg/mL in 210 (21.4%) of 978 patients who were examined in the outpatient clinics of Dokuz Eylul University Faculty of Medicine pediatric neurology department between January 2020 and June 2020. In terms of severity, 98 patients (46.7%) had subclinical deficiency, 55 (26.2%) had a deficiency, and 57 (27.1%) had severe deficiency. The patients were between 1 month and 17 years of age (median 3.3 years). About 53.3% (n=112) of the patients were male. There was consanguineous marriage between the parents in 8.1% (n=17). A family history of neurological disease was found in 17.1% (n=36). Of these, 14 were epilepsy (6.6% in all cases, 38.8% in cases with a family history of neurological disease), nine were migraine (4.3% in all cases, 25% in cases with a family history of neurological disease), four unspecified neuromuscular diseases (1.9% in all cases, 11.1% in cases with a family history of neurological disease), two each with psychomotor retardation and pervasive developmental disorder (1% in all cases, 5% in cases with a family history of neurological disease), and one each of them was neurobehcet, tuberous sclerosis, Gullian-Barre syndrome, multiple sclerosis, and unspecified neurodegenerative disease (0.5% of all cases, 2.7% of cases with a family history of neurological disease). Three (1.4%) patients had a family history of febrile seizures.

Complaints of the Patients

A total of 220 complaints, including more than one in ten patients, were evaluated. The most common complaints were seizures (n=59, 26.8%), headache (n=41, 18.6%), presentation for routine control of epileptic patients (n=31, 14%), growth retardation (n=14, 6.3%, and weakness (n=10, 4.5%). There were 101 complaints in the female gender in three of whom had more than one complaint, including seizures (n=29, 13.2%), headache (n=27, 12.2%), and routine follow-up visits of patients with epilepsy (n=10, 4.5%), developmental delay (n=5, 2.3%), and fainting (n=5, 2.3%). On the other hand, in males, seven patients had more than one complaint, a total of 119 reasons were evaluated, and seizures (n=30, 13.6%), routine control of patients with epilepsy diagnosis (n=21, 9.5%), headache (n=14, 6.4%), developmental delay (n=9, 4%), and weakness (n=8, 3.6%) were the most common reasons for admission (Table 1).

Table 1. Presentation complaints of the patients

Complaints	Female, n (%)	Male, n (%)	Total, n (%)
Seizure	29 (13.2)	30 (13.6)	59 (26.8)
Headache	27 (12.2)	14 (6.4)	41 (18.6)
Routine follow-up	10 (4.5)	21 (9.5)	31 (14)
Developmental delay	5 (2.3)	9 (4)	14 (6.3)
Weakness	2 (0.9)	8 (3.6)	10 (4.5)
Fainting	5 (2.3)	3 (1.3)	8 (3.6)
Language developmental delay	2 (0.9)	5 (2.3)	7 (3.2)
Dizziness	2 (0.9)	5 (2.3)	7 (3.2)
Behavioral problems	2 (0.9)	3 (1.3)	5 (2.2)
Tremor	3 (1.3)	2 (0.9)	5 (2.2)
Prematurity follow-up	1 (0.5)	3 (1.3)	4 (1.8)
Pain in the limbs	3 (1.3)	-	3 (1.3)
Premature closing of fontanelle	2 (0.9)	1 (0.5)	3 (1.3)
Numbness	2 (0.9)	1 (0.5)	3 (1.3)
Tic	-	3 (1.3)	3 (1.3)
Forgetfulness	-	2 (0.9)	2 (0.9)
Large head circumference	-	2 (0.9)	2 (0.9)
Blurred vision	1 (0.5)	-	1 (0.5)
Hallucination	-	1 (0.5)	1 (0.5)
Frequent falling	1 (0.5)	-	1 (0.5)
High creatine kinase	-	1 (0.5)	1 (0.5)
Stereotypy	-	1 (0.5)	1 (0.5)
Hyperpigmented lesion	1 (0.5)	-	1 (0.5)
Speech disorder	-	1 (0.5)	1 (0.5)
Facial asymmetry	1 (0.5)	-	1 (0.5)
Strabismus	1 (0.5)	-	1 (0.5)
Loss of vision	1 (0.5)	-	1 (0.5)
Control after neonatal jaundice	-	1 (0.5)	1 (0.5)
Head deformity	-	1 (0.5)	1 (0.5)
İncontinence	-	1 (0.5)	1 (0.5)

Neurodevelopment and Neurologic Examination

Since one patient was adopted, information about neuromotor developmental stages could not be obtained. The responsive social smile of the patients was median of 2.2 months (min-max: 1–6 months). The ages of two (0.9%) patients were too young to perform this particular neuromotor developmental step. However, in 7 (3.3%), despite appropriate age, this neuromotor milestone could not be performed. Head control was achieved at a median age of 2.6 months (min-max: 1–9 months). Two (0.9%) patients were too young to perform this neuromotor developmental step and 8 (3.8%) patients could not do this step, despite being age-appropriate. The median time of sitting with support was 5.5 months (min-max: 4–24 months), while 7 (3.3%) patients were too young to perform this step. Eight (3.8%) patients had never performed this step, although they were age appropriate. Sitting without support was performed between 5 and 18 months (median: 7.2 months). The number of both those who were too young to perform this step and those who could not perform this step despite appropriate age was 12 (5.7%). While the patients started to walk independently at a median of 13.8 months (min-max: 9–48 months), the patients who were too young to perform this step and could not do this step despite their age were 21 (10%) and 14 (6.6%) in number, respectively. The onset of single-word use was between 8 and 84 months (median 15). While the number of patients who were too young to speak yet was 19 (9%), 14 (6.6%) were those who could not perform this step despite their age appropriateness. Formation of two-word sentences started between 15 and 60 months (median 23.1). While 25 (11.9%) of the patients were too young to form a two-word

sentence, 27 (12.8%) did not perform this developmental step despite being appropriate for their age. Responsive social smile, head control, sitting with support, sitting without support, independent walking, single-word use, and forming two-word sentences were detected above the defined upper limit in 23 (10.9%), 19 (9%), 18 (8.5%), 20 (9.5%), 17 (8.1%), 9 (4.3%), and 3 (1.4%) patients, respectively.

Regression in acquired abilities was observed in 5 (2.4%) patients in whom the diagnoses were epilepsy (n=2, 0.9%), Limb-Girdle muscular dystrophy Type 2a (n=1, 0.5%), pervasive developmental disorder (n=1, 0.5%), and demyelinating disease (n=1, 0.5%). The number of patients with normal neurological examination was 171 (81.4%). More than one abnormal examination finding was detected in 14 of the patients. The most common abnormal findings were very brisk deep tendon reflexes (n=18, 8.6%), muscle weakness (n=9, 4.3%), and spasticity (n=6, 2.8%) (Table 2).

Diagnoses

No neurological disease was detected in 49 (23.3%) of the cases, while 22 (10.4%) had more than one diagnosis. The most common diagnoses were epilepsy (n=72, 34.2%), migraine (n=14, 6.6%), cerebral palsy (n=11, 5.2%), non-specific headache (n=111, %) 5.2), global developmental delay (n=11, 5.2%), syncope (n=9, 4.2%), and microcephaly (n=6, 2.8%). In the analysis by gender, in girls, the most common diagnoses were epilepsy (n=33, 15.7%), non-specific headache (n=9, 4.2%, and migraine (n=8, 3.8%). In boys, epilepsy (n=39, %). 18.5), cerebral palsy (n=8, 3.8%), and migraine (n=6, 2.8%) were the most common ones. Language development delay and autism spectrum disorder were reported in 5 (2.3%) patient each. Four patients (1.9%) had febrile seizure. Pseudotumor cerebri, hydrocephalus, multiple sclerosis, limb-girdle muscular dystrophy Type 2A, essential tremor, central vertigo, structural macrocephaly, Poland syndrome, intracranial mass, and undefined neuromuscular disease were identified in two patients each (0.9%). Furthermore, in one patient each (0.5%), acute psychotic attack, spina bifida, viral myositis, carpal tunnel syndrome, central facial paralysis, tic disorder, and breath-holding spells were described.

Table 2. Abnormal neurological examination findings of the patients

	Number	Percentage
Very brisk deep tendon reflexes	18	8.6
Muscle weakness	9	4.3
Spasticity	6	2.8
Hypoactive deep tendon reflexes	4	1.9
Hyperpigmented lesion	3	1.4
Facial asymmetry	2	0.9
Loss of deep tendon reflexes	2	0.9
Microcephaly	2	0.9
Dysmorphism	2	0.9
Strabismus	1	0.5
Nystagmus	1	0.5
Hypoesthesia	1	0.5
Macrocephaly	1	0.5
Muscle atrophy	1	0.5

Neuroimaging Findings

Forty-seven (22.3%) patients were evaluated with brain computed tomography in which 11 (5.2%) revealed abnormal results consisting of encephalomalacia, hydrocephalus, and intracranial mass in two patients each (0.9%) and Arnold-Chiari malformation, periventricular leukomalacia, cerebral atrophy, calcification, and intracranial hemorrhage in one patient (0.5%) each. Brain magnetic resonance imaging (MRI) was performed in 127 (60.4%) patients. A total of 58 abnormal results were obtained in 49 (24.2%) cases, with more than one abnormality in seven patients. The most common abnormal findings were non-specific T2 signal increase (n=10, 4.7%), gliosis (n=9, 4.2%), encephalomalacia (n=5, 2.3%), and cortical dysplasia (n=4, 1.9%). Periventricular leukomalacia, intracranial mass, hydrocephalus, thin corpus callosum, and arachnoid cysts were detected in three patients each (1.4%), while Arnold Chiari malformation, venous angioma, demyelinating disease-related findings, and pineal cyst were observed in two patients each (0.9%). In one patient each (0.5%), signs of increased intracranial pressure syndrome, cerebral atrophy, and intracranial hemorrhage were described. Magnetic resonance spectroscopy was performed and was normal in 2 (0.9%) patients. Spinal MRI was performed in 5 (2.3%) patients, and plaque and syringomyelia associated with demyelinating disease were detected in one patient each (0.5%).

Electrophysiological Study

Electroencephalography was performed in 106 (50.4%) patients in whom abnormal findings were identified in 51 (24.2%). The most common electroencephalographic abnormality was focal epileptic discharge (n=27, 12.8%). Generalized epileptic discharge (n=18) and dysrhythmia (n=6) were observed in 8.5% and 2.8%, respectively. Seven (3.3%) patients were evaluated with electromyography which demonstrated demyelinating polyneuropathy and mixed sensorimotor polyneuropathy were detected in one patient each (0.5%).

Developmental Screening Tests

Patients with certain developmental delays were evaluated with developmental screening and intelligence tests such as Ankara Developmental Screening Inventory (AGTE), Denver II, and revised Wechsler's intelligence test for children (WISC-R). Denver II developmental screening inventory was performed in 23 (10.9%) patients. Twenty-two (10.4%) patients had developmental delay of which global developmental delay (n:19, 9%) was the most common one. Delays in the language and gross-fine motor skills were detected in 2 (0.9%) and in 1 (0.5%) patients, respectively. Moreover, AGTE was performed in 5 (2.3%) patients, 1 (0.5%) normal result and 4 (1.8%) global growth retardation were observed. In WISC-R, 1 (0.5%) normal result and 4 (1.8%) cognitive retardation were identified.

Vitamin B12 Levels

Of all patients in this cohort, Vitamin B12 levels were between 65 and 299 pg/mL (median: 198.1). While subclinical deficiency (200–300 pg/mL) was detected in most of the cases (n=98, 46.7%), deficiency (160–199 pg/mL), and severe deficiency (<160 pg/mL) were found in 55 (26.2%) and 57 (27.1%) patients, respectively. Of the patients with subclinical deficiency, 53 (25.2%) were female and the age range was fairly wide as 1 month–17 years (median 37 months). In cases with deficiency, male gender predominated (n=31, 14.7%), while the median age was 35 months (min-max: 1 month–17 years). While male gender was more common (n=36, 17.1%) in cases with severe deficiency, the median age was 49.7 months (1 month–17 years).

After the optimal treatment, the control Vitamin B12 levels were between 97 and 1500 pg/mL (median 353). In patients whose Vitamin B12 levels could not be increased with treatment (n=13, 6.1%), the median Vitamin B12 level was 195.7 (min-max: 97–269) pg/mL. The median Vitamin B12 levels were 229.3 (min-max: 172–288) pg/mL in patients (n=22, 10.4%) in whom, after treatment, Vitamin B12 levels improved, but not in sufficient amounts. Adequate improvement in Vitamin B12 levels after treatment was seen in 33 (15.7%) patients with a median Vitamin B12 level of 497.7 (min-max: 300–1500) pg/mL.

In this cohort, after adequate improvement in Vitamin B12 levels, nine patients had complete improvement of symptoms and/or signs consisting of headache (n=5, 2.3%), tremor in the hands (n=:2, 0.9%), forgetfulness (n=1, 0.5%), and dizziness (n=1, %). 0.5). While the median Vitamin B12 values of these cases were 209.1 (min-max: 130–293) pg/mL at the beginning, after treatment, the median value was found as 456.6 (min-max: 300–923) pg/mL.

Discussion

The prevalence studies of Vitamin B12 deficiency are mostly limited to regional reports. Despite the frequency in clinical practice of pediatric patients. Although a very low rate as 0.37% was reported in one study in Türkiye (0.37%), in another study, the prevalence in 0–3, 3–10, and 10–16 age groups was found to be 53.8%, 43.3%, and 75.7%, respectively[21,22]. In other countries, Vitamin B12 deficiency was reported at rates ranging from 14 to 73.5%[2-13,23-25]. Vitamin B12 deficiency was found in 21.4% of the patients in our study. This broad range of rates in the literature can be explained by the heterogeneity of age, gender, and sociodemographic characteristics in the study groups. Studies on Vitamin B12 deficiency have generally been conducted for certain age groups. Goyal et al.[2] reported that the mean age of cases with Vitamin B12 deficiency in children aged 6–60 months with malnutrition was 11.4±4.22 months. In a study investigating Vitamin B12 deficiency in 1–12 months-old patients aged 1–12 months in India, Vitamin B12 deficiency was reported in 22%. Under 4 months of age, this rate was 11%, but patients over 4 months of age had a higher incidence (27%) which has been attributed to increased metabolic need[8].

In a study evaluating the neurological findings related to Vitamin B12 deficiency, the age of the patients was reported to be approximately 8.51 years[14]. The mean age of patients with Vitamin B12 deficiency was 3.1±1.0 years in a study in Türkiye investigating the relationship between Vitamin B12 level and hematological parameters[16]. In a study in which the relationship between Vitamin B12 deficiency and clinical symptoms was investigated in Türkiye, the mean age of the patients was 9.4±4.8 years in patients with Vitamin B12 levels <200 pg/mL and 9.1±4.4 years in patients with <300 pg/mL[22]. The different mean ages in the study groups can be explained by the fact that the studies were conducted only in certain age groups, as well as the different dietary habits of the populations and the inclusion of only patients with clinical manifestations of B12 deficiency.

In our study, optimal replacement treatment has been shown to give rise to improve in the neurological conditions which were headache (n=5, 2.3%), tremor (n=2, 0.9%), forgetfulness (n=1, 0.5%), and dizziness (n=1, 0.5%), in 4.2% of patients overall. In a study evaluating Vitamin B12 deficiency in anemic children, neurological symptoms were narrated in 22.5% of the patients of whom 80%, approximately 18% of all cases, was particularized with Vitamin B12 deficiency. The most common neurological symptoms in the group with Vitamin B12 deficiency were muscle weak-

ness (46.8%), fatigue (45%), behavioral changes (7.2%), and developmental delay (6.3%). Headache, forgetfulness, and dizziness, which were symptoms that improved with treatment in our study, were not reported, but tremor (0.9% in our study) was present in 3.6% of the patients[26]. However, the lack of data on whether the clinical findings regressed with the Vitamin B12 treatment of the patients in that particular study makes the certainty that the clinical pictures were caused by Vitamin B12 deficiency was questionable. Furthermore, the fact that the patients included in the study suffered anemia in most of which etiologies other than Vitamin B12 deficiency were identified indicates that the neurological manifestations could be rationalized by diverse reasons. Chhabra et al.[3] showed that neurological symptoms were present with a rate of 11.1% in pediatric patients with megaloblastic anemia secondary to Vitamin B12 deficiency. Aaron et al.[27] and Cui et al.[28] found neuropsychiatric and cognitive dysfunctions associated with Vitamin B12 deficiency in 3% of the study population. In a study conducted in our country in which the neurological findings in pediatric patients with Vitamin B12 deficiency were investigated, Vitamin B12 treatment has been shown to improve neurological conditions including hypotonia (23.7%), fatigue (21%), syncope (15.8%), dizziness (10.5%), seizure (10.5%), numbness (7.9%), unable to sit/walk without support/gait ataxia (5.2%), tremor (2.6%), and blurred vision (2.6%). In the same study, the median Vitamin B12 levels of the patients were 137.18 and 680.63 pg/ml before and after treatment, respectively[14]. In our study, while the median Vitamin B12 values were 209.1 pg/mL at the beginning, it was found to be 456.6 pg/mL after the treatment. Differences in dietary habits, timing of follow-up examinations, and compliance with treatment may be the reasons for the difference in vitamin levels before and after treatment. The fact that there are quite different clinical conditions and rates in the literature compared to our study may be due to the dissimilarity in study durations, disparate levels of pre-treatment Vitamin B12 deficiency, and heterogeneous study groups.

Conclusion

In our study, Vitamin B12 deficiency was found at a high rate in patients in the pediatric neurology outpatient clinics. Complaints consisting of headache, tremor in the hands, forgetfulness, and dizziness improved in 4.2% of the patients with Vitamin B12 treatment. Although neuroimaging and electrophysiological examinations do not give a specific result, the usefulness in the differential diagnosis process is indisputable. In Vitamin B12 deficiency, the level of which can be measured in many centers and the progression of the disease can be prevented with rapid and correct treatment, we believe that a careful and conscious approach is essential.

Ethics Committee Approval: The study was approved by Dokuz Eylul University Faculty of Medicine Ethics Committee (approval number: 2021/26–41) and conducted in accordance with the Declaration of Helsinki.

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