Why Are Vitamin B12 Levels High in Children with Cerebral Palsy?

Serebral Palsili Çocuklarda B12 Vitamini Düzeyleri Neden Yüksek?

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Abstract

Background The purpose of the present study was to evaluate vitamin B12 levels in cases under follow-up with diagnoses of cerebral palsy (CP) compared to healthy controls..

Materials and Methods Fifty-three cases presenting to the Adiyaman University Education and Research Hospital pediatric neurology clinic, Turkey, and diagnosed with CP were included in this retrospective study. Sixty-four cases of similar age and weight presenting to the child health and diseases clinic were included in the control group. Demographic data, laboratory results [hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), platelet (plt), folate, ferritin, vitamin B12, and vitamin 25 OH D] findings were recorded from the patient files.

Results Complete blood count parameters [Hb (p=0.004), Hct (p=0.000), Mcv (p=0.000), and Plt (p=0.001)], vitamin B12 (p=0.031) and vitamin D levels (p=0.002) were significantly in the study group than in the control group.

Conclusion In contrast to previous studies in the literature, vitamin B12 levels were higher in patients with CP than in the healthy controls. The fact that the underlying pathophysiological mechanism is not fully understood clearly derives from the limited investigation of the subject in the literature to date.

Keywords Cerebral palsy, vitamin B12, vitamin D, folate

Özet

Amaç Bu çalışmanın amacı serebral palsi tanısı ile izlenen olguların sağlıklı kontrollere göre vitamin B12 düzeylerinin değerlendirilmesi hedeflenmiştir.

Gereç ve Yöntemle Çalışmaya Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi çocuk nöroloji polikliniğine başvuran ve serebral palsi tanısı konulan 53 olgu retrospektif olarak dahil edildi. Kontrol grubuna aynı dönemde çocuk sağlığı ve hastalıkları polikliniğine başvuran, sağlıklı çocuk muayenesi girilen ve yaş ve kilo açısından benzer 64 olgu alındı. Hasta dosyalarından demografik veriler, laboratuvar sonuçları [hemoglobin (Hb), hematokrit (Hct), ortalama korpüsküler hacim (MCV), platelet (plt), folat, ferritin, vitamin B12, 25 OH D vitamini], kranial görüntülemeleri ve elektroensefalografi (EEG) bulguları kayıt altına alındı.

Bulgular Çalışma ve kontrol grubunda hemogram parametreleri [Hb (p=0.004), Hct (p=0.000), MCV (p=0.000), plt (p=0.001)], vitamin B12 (p=0.031) ve vitamin D (p=0.002) düzeyleri arasında istatiksel olarak anlamlı saptandı.

Sonuç Çalışmamızda literaturde belirtilen çalışmaların aksine SP'li hastalarda sağlıklı kontrollere göre vitamin B12 düzeyinin daha yüksek olduğu saptanmıştır. Bu durumun altta yatan pato-fizyolojik mekanizması tam olarak bilinmemesini konunun literatürde sınırlı olarak çalışılmasından kaynaklandığı ortadadır.

Anahtar Kelimeler Serebral palsi, vitamin B12, vitamin D, folat

INTRODUCTION

Cerebral palsy (CP) is a heterogeneous group of early onset, non-progressive neuromotor disorders affecting the developing fetal or infant brain (1). In a systematic review published in 2013, CP was observed in 2.11 out of 1000 live births and as many as 59.18 out of 1000 live births in infants weighing below 1500 g (2).

Feeding is a serious problem in several childhood neurological diseases, and these children are at risk of nutritional deficiencies and growth retardation. A prevalence of feeding problems of 30-90% has been reported in children with CP, with an undernutrition rate of 90% (3). Vitamin and mineral deficiencies are also frequently seen in children with neurological disorders (4). According to data from the North American Growth in Cerebral Palsy Project, 58% of children with CP experience feeding difficulties, with severe difficulties occurring in 23% of these (5). Another study showed that at least 45-50% of children with CP were undernourished (6-8).

Adequate micronutrition is known to affect immune functions, inflammation modulation, wound healing, and growth in children (9). There is no single laboratory marker capable of indicating adequate or inadequate nutrition. Studies evaluating micronutrition in children with CP have reported widespread iron, zinc, copper, vitamin D, carnitine, folic acid, and vitamin B12 deficiencies, with incidences ranging between 10% and 55% (10, 11). The periodic monitoring of micronutrient levels as a component of nutritional status assessment in children with CP is therefore strongly recommended (12). Hillesund et al. determined that patients with CP had deficient levels of zinc, selenium, iron, folate, and vitamins E, B6, and B12 and emphasized the need to evaluate these children's micronutrient levels (13). Complete blood count and iron investigation for determining iron deficiency and anemia in patients with CP, and serum biochemistry investigation for the detection of underlying abnormalities in the liver, kidney, and bone turnover have been particularly reported in the literature (14).

The purpose of the present study was therefore to evaluate iron, folic acid, vitamin D, and vitamin B12 levels in cases under follow-up with diagnoses of CP compared to healthy controls.

MATERIAL and METHODS

Fifty-three cases presenting to the Adıyaman University Education and Research Hospital pediatric neurology clinic, Turkey, between 01 August, 2017, and 01 July, 2019, and diagnosed with CP were included in this retrospective study. Sixty-three cases of similar age and weight presenting to the child health and diseases clinic and undergoing healthy child examinations during the same period were enrolled in the control group.

Inclusion criteria were diagnosis of CP [based on the International Workshop on Definition and Classification of Cerebral Palsy definition) and the absence of any genetic, metabolic neurological disease or chronic disease other than CP capable of hindering growth (15).

Demographic data (age, sex, personal history, and family history), laboratory results (hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), platelet (plt), folate, ferritin, vitamin B12, and vitamin 25 OH D), and cranial imaging and electroencephalography (EEG) findings were recorded from the patient files. Approval for the study was granted by the local ethical committee (no. 2021/05-22).

Statistical Analysis

The study data were analyzed on Statistical Package for Social Sciences (SPSS) for Windows 23.0 software. The independent sample t test was applied in case of normally distributed parameters, and the chi-square test was used to evaluate categorical variables. P values <0.05 were regarded a statistically significant.

RESULTS

Fifty-three cases [28 female (52.8%) and 25 (47.2%) male] were included in the study group and 64 [35 female (54.7%) and 29 (45.3%) male] in the control group. Mean ages were 10.08±4.33 years (2.50-18) in the study group and 9.81±4.42 (2-18) in the control group. No significant difference was observed between the two groups in terms of age or gender.

Thirty (56.6%) of the cases with CP were in the <3 percentile, and one (1.8%) was in the >97 percentile. Head circumference was in the <3 percentile in 33 cases. Three patients were born at <28 weeks, nine at 28-32 weeks, five at 33-37 weeks, and 32 at 38-41 weeks. Thirty-four patients were born by normal spontaneous vaginal delivery. Parental consanguinity was present in 29 (54.7%) cases.

The most common risk factors for the development of CP were idiopathic causes (40.4%), asphyxia (25%), and prematurity (19.2%). Fifteen (28.3%) cases consisted of diplegic CP, 34 (64.18%) of paraplegic CP, two (3.76%), of hemiplegic CP, and two (3.76%) of extrapyramidal CP. Seven cases (13.1%) experienced focal seizures, and 21 (39.6%) generalized seizures. Cranial magnetic resonance imaging (MRI) was normal in four (7.5%) cases and abnormal in 33 (62.2%). Periventricular leukomalacia was present in nine (16.98%) cases, cerebral development anomaly in 11 (20.75%), cerebral atrophy in six (11.32%), hypoxic ischemic encephalopathy in two (3.77%), periventricular leukomalacia and cerebral atrophy in three (5.66%), periventricular calcification and periventricular leukomalacia in one (1.8%), and basal ganglia hyperintensity in one (1.8%). The most common cerebral development anomaly was corpus callosum agenesis.

Complete blood count parameters [Hb (p=0.004), Hct (p=0.000), MCV (p=0.000), and plt (p=0.001)], vitamin B12 (p=0.031) and vitamin D levels (p=0.002) were significantly lower in the study group than in the control group, while ferritin (p=0.621) and folate (p=0.154) levels were significantly higher in the study group (Table 1).

Table 1. *Comparison of the laboratory parameters of the study and control groups*

	Study group mean±SD (minimum-maximum)	**Control Group mean±SD (minimum-maximum)**	**p**
Age (years)	10.08±4.33 (2.5-18)	9.81±4.42 (2-18)	0.738
Hb (g/dl)	12.72±1.6 (9-16)	11.87±1.5 (8.72-16.7)	0.004
Hct (%)	38.92±4.65 (31-59)	36.04±4.01 (27.97-51.10)	0.000
MCV (fL)	79.92±7.21 (61-96)	73.98±6.7 (55.11-96.97)	0.000
Plt (/ml)	287±977.22 (109-607)	363.85±139.12 (117-865)	0.001
Vitamin B12 (pg/ml)	544±327.73 (136-1486)	405.6±187.86 (120-824)	0.031
Folate (ng/ml)	11.95±5.51 (5-25)	9.54±8.54 (2-37)	0.154
Ferritin (ml/ng)	18.68±13.37 (1.2-58)	17.48±11.11 (4-66)	0.621
Vitamin D (ng/ml)	19.51±12.57 (4.90-69)	30±17.62 (1-68)	0.002

Abbreviations: SD, Standard deviation; Hb, Hemoglobin; Hct, Hematocrit; MCV, mean corpuscular volume; plt, Platelet

DISCUSSION

Chewing and swallowing difficulties, inability to feed, and short meal durations have been described as among the factors exacerbating nutritional and growth risks in children with CP (8, 16). Involuntary muscle spasms and spasticity have been emphasized as contributory factors capable of affecting swallowing abilities in terms of feeding difficulties among children with CP (17). In a study of 100 cases of CP, Lopes et al. reported that 25% were low weight, 11% were slightly overweight, and 9% were severely overweight (18). Rogozinski et al. reported a prevalence of obesity in children with CP of 7.7% in 1994-1995, but that this had doubled to 16.5% by 2003-2004. At the same time, they also emphasized that the risk of obesity was higher in children with CP than in healthy children (19). In a thesis study, Ceylan determined malnutrition in 6.8% of patients based on Brooks et al.'s cerebral growth curves, and in 49.2% based on Neyzi standards (20). In a study of 74 children with CP, Almuneef et al. determined malnutrition in 56.4% of patients based on World Health Organization data (21). In the present study, malnutrition was present in 56.6% of cases, and obesity in 1.8%.

Vitamin B12 levels are normally 160-1300 pg/mL in infants and 200-835 pg/mL in children (22). Folate levels in children are 4-20 ng/mL. Higher folate levels have been determined in children with CP fed by tube compared to those feeding normally. However, a high risk of folate deficiency, which may cause an increase in homocysteine levels, has been reported in children with CP using antiepileptic drugs (13, 23, 24). Vitamin D levels are determined by assessing 25 OH vitamin D levels in serum. Values of 30 ng/ml or above are regarded as sufficient (23). Duncan et al. reported vitamin D intake lower than 75% of daily requirements in 74% of children with CP (25). İspiroğlu et al. evaluated the complete blood counts, and iron, folic acid, and vitamin B12 levels of 50 cases with neurological disease. Those authors determined malnutrition in 78% of cases, iron deficiency anemia in 18%, iron deficiency in 8%, macrocytic anemia associated with folic acid deficiency in 10%, chronic disease anemia in 12%, vitamin B12 deficiency in 4%, iron deficiency anemia and folic acid deficiency in 8%, and iron deficiency, folic acid deficiency, and vitamin B12 deficiency alone or combined in 44%. In that study, nutritional insufficiencies and anemia were frequently observed in patients with neurological disorders. The authors emphasized the need for particular care on the subject of feeding among these patients, and that these should be periodically checked in terms of nutritional parameters (26). Hals et al. reported low hemoglobin and ferritin levels in children with neuromotor retardation (27). In a study of 40 patients with CP, Ayata et al. determined iron deficiency in 40% of cases, while in their study of 108 cases of CP, Papadopoulos et al. reported iron deficiency in 38%, and Hong et al. determined anemia in 50.2% of cases and iron deficiency anemia in 22.2% in their 229-case series (4, 28, 29). Kalra et al. reported lower serum iron, copper, and magnesium levels in children with CP compared to healthy individuals from the same age group with similar nutritional status. Those authors emphasized that patients with CP should receive vitamin and mineral supplementation (10). In a study of 36 pediatric patients with CP, Hillesund et al. reported that levels of vitamin E, vitamin D, folic acid, and niacin that need to be absorbed with diet were below daily requirements, and that ferritin levels were below normal in 14% of these children and folic acid levels in 8% (13). Henderson et al. determined that low calcium, magnesium, and vitamin D levels were highly significant in children with CP, and that pathological fractures may occur with even a minimal trauma in these children (30). Ceylan reported low levels of serum iron, ferritin, vitamin B12, and folate in patients with CP fed solely by mouth (20). Similarly in the present study, significant differences were determined between the groups in terms of complete blood count parameters (Hb, Hct, MCV, plt), and vitamin B12 and D levels. However, no difference was observed in folate or ferritin levels.

Some antiepileptic drugs reduce folate, vitamin B12, biotin, and thiamine levels (31). Although several studies have reported low vitamin B12 levels for various reasons, high vitamin B12 levels have also been observed. High vitamin B12 levels in plasma are generally regarded as harmless in clinical practice, and this may be underestimated and insufficiently understood (32, 33).

High serum vitamin B12 is defined as a level exceeding 950 pg/ml (701 pmol/l), corresponding to the upper threshold of biological normality according to biological standards, in the absence of any symptom and/or clinical anomaly (34).

Retrospective studies have reported prevalences of vitamin B12 elevation of 12-18% (33, 34). The most frequent causes of vitamin B12 elevation are high-dose vitamin intake, myeloproliferative, liver, and kidney diseases, cancer, polycythemia vera, cystic fibrosis, HIV, and infectious diseases such as malaria and typhus. High vitamin B12 levels have also been reported in Gaucher's disease, systemic lupus, rheumatoid arthritis, and Still's disease (34-37). Hintikka et al. found that adult patients with high vitamin B12 levels emerged more quickly from major depression (38). In contrast, Salles et al. reported that high cobalamin levels might represent a marker for evaluating a high mortality risk in geriatric patients (39). The majority of studies concerning high vitamin B12 levels have involved adults, although a few have focused on the effects of antiepileptic drugs on vitamin B12 metabolism in children, reporting conflicting results. Higher cobalamin levels have also been reported in children receiving valproic acid (40). In a study of celiac markers, Stenberg et al. reported increased vitamin B12 levels in 17 (19%) out of 91 children with CP, and that this elevation was more frequent in children using antiepileptic drugs (41). In another study representing a continuation of that research, the authors followed-up children with high vitamin B12 levels for one year, and determined that vitamin B12 elevation still persisted in these children (with six out of 11 patients with epilepsy using antiepileptic drugs, the most commonly employed being valproic acid) (42). Stenberg et al. reported being unable to account for the high vitamin B12 observed in 19% of patients in their first study and in patients followed-up over 12 years (10/19) (42). They emphasized that high plasma vitamin B12 generally consisted of metabolically inactive haptocorrin complexes (42). They also reported that vitamin B12 may be observed in association with autoantibody interference and that this can lead to misinterpretation of B12 values (42). Stenberg et al. also reported a slight correlation with immunoglobulin G antibodies against gliadin, indicating a possible link as a result of increased susceptibility to autoantibody formation in their first study (41).

Those authors described total plasma B12 level elevation, a widespread finding in children with CP, as the most noteworthy characteristic. This finding may be caused by leakage over the gut mucosa as a result of increased intestinal permeability together with subclinical gut inflammation. The authors went on to suggest that this might be attributable to underweight or to vitamin B12-producing bacteria modifying the flora in such cases, possibly in association with valproic acid therapy (42).Vitamin B12 elevation has been reported in various disease groups. In a study from 2020, Hinkel et al. compared 44 cases with hepatic glycogen storage disease with 42 healthy controls of similar age and gender, and reported significantly higher vitamin B12 levels in the study group. Mean vitamin B12 levels were 379 ±182.93 (172-1015) pg/mL in the healthy control group compared to 667.28±408.83 (185–1876) pg/mL in the hepatic glycogen storage disease (p=0.0002) (43). Ergül et al. determined significantly higher mean vitamin B12 levels in a group with zinc deficiency [323 (238-440) pg/mL] compared to individuals with normal zinc levels [276 (208-382) pg/mL], and reported significant negative correlation between vitamin B12 and zinc levels. Those authors concluded that zinc exhibited a negative effect on vitamin B12 levels (44). Butala et al. detected vitamin B12 elevation in 26% of patients with neurological diseases, with high B12 levels in 3.1% of patients with CP among those diseases (45). They also emphasized that no pediatric guideline was available for patients with high vitamin B12 levels. The results of the present study might initially appear to be inconsistent with the previous literature. However, an examination of the physiology of vitamin B12 may help to explain this. An increase in plasma vitamin B12 levels is currently regarded as a potential indicator of a functional deficit whose clinical outcomes paradoxically resemble those of vitamin B12 deficiency (46). Greater binding of vitamin B12 to haptocorrins, secondary to plasma level elevation (particularly in the case of TCB I and III, representing the greater part of the haptocorrins), causes a potential decrease in its attachment to TCB II, thus producing an alteration in vitamin B12 delivery to cells. A functional deficit in vitamin B12 with a corresponding rise in homocysteine or methylmalonic acid values is therefore possible, although the initial anomaly involved is not a deficiency in vitamin B12 levels (47).

This in turn raises the question of whether elevated vitamin B12 levels are in fact secondary to their functional deficit, which Andres et al. described as capable of occurring at any serum value (46). Hope et al. determined significantly higher vitamin B12 levels in patients aged 2-53 years with various neurodevelopmental disorders compared to healthy controls and a schizophrenia group. Those authors concluded that vitamin B12 elevation was a specific characteristic of neurodevelopmental disorder (48). Surprisingly in the present study, vitamin B12 levels were significantly lower in the healthy controls [405.6±187.86 (120-824)] compared to the patients with CP [(544±327.73 (136-1486)] (p=0.031). We think that this may derive from absorbance abnormality in patients with CP.

In clinical practice, high levels of vitamin B12 may be encountered in patients using pediatric nutritional products for various reasons. The principal limitations of this study are the low case number, its retrospective nature, the fact that nutritional products were not evaluated, and that homocysteine levels could not be investigated.

CONCLUSION

In conclusion, in contrast to previous studies, vitamin B12 levels were higher in patients with CP in this research than in the healthy controls. The fact that the underlying pathophysiological mechanism is not fully understood clearly derives from the limited investigation of the subject in the literature to date. We think that further multicenter studies with larger patient populations are now needed to explain the vitamin B12 elevation in patients with CP.

Conflict of Interest:

The authors declare no competing interest.

Informed Consent:

Informed consent was not required due to the retrospective study design.

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