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### Frequency of Vitamin B12 Deficiency and Associated Findings in Children

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#### ABSTRACT

**Objective:** The purpose of this study was to determine clinical findings associated with vitamin B12 deficiency in patients presenting to the pediatric neurology department with various different symptoms and to discuss these in the light of the current literature. **Materials and Methods:** Children aged between one month and 18 years presenting to the Balıkesir University Medical Faculty pediatric neurology clinic, Turkey, between 01.08.2019-01.08.2021 and with vitamin B12 levels lower than 250 ng/mL were included in this retrospective, cross-sectional study. **Results:** One hundred sixty-one cases were included in the study 63 (39.1%) female and 98 (60.9%) male. The patients' mean age was  $7.43 \pm 5.77$  (0-17) years. The majority of patients of both genders were in the 0-6 age group. Neurological findings were present in 81.98% of patients with Vitamin B12 deficiency, and non-neurological findings in 18.02%. The most frequent neurological finding was neuromotor retardation (N=73, 45.34%), followed by seizures (N=33, 20.50%). The mean Vitamin B12 level among all the patients was  $167.70 \pm 45.17$  (58-250) pg/ml. No statistically significant difference was determined between boys and girls in terms of Vitamin B12 and ferritin levels or complete blood count parameters [Hb, Htc, and MCV] (respectively p=0.428, p=0.646, p=0.110, p=0.128, p=0.864). **Conclusions:** This study provides a general evaluation for health professionals regarding clinical presentations encountered by us in association with the disease.

**Keywords:** Vitamin B12, Children, Treatment, Deficiency, Sign.

### Çocuklarda B12 Vitamini Eksikliği ve İlişkili Bulguların Sıklığı

#### ÖZ

**Amaç:** Bu çalışmanın amacı, çocuk nörolojisi polikliniğine çeşitli semptomlarla başvuran hastalarda vitamin B12 eksikliği ile ilişkili klinik bulguları belirlemek ve güncel literatür ışığında tartışmaktadır. **Gereç ve Yöntem:** Bu retrospektif kesitsel çalışmaya 01.08.2019-01.08.2021 tarihleri arasında Balıkesir Üniversitesi Tıp Fakültesi Çocuk Nöroloji Polikliniğine başvuran ve B12 vitamini düzeyi 250 ng/mL'nin altında olan 1 ay-18 yaş arası çocuklar dahil edildi. **Bulgular:** Çalışmaya 63 (%39.1) kadın ve 98 (%60.9) erkek 161 olgu dahil edildi. Hastaların yaş ortalaması  $7.43 \pm 5.77$  (0-17) yıl idi. Her iki cinsiyetteki hastaların büyük çoğunluğu 0-6 yaş grubundaydı. Vitamin B12 eksikliği olan hastaların %81.98'inde nörolojik bulgular, %18.02'sinde nörolojik olmayan bulgular mevcuttu. En sık görülen nörolojik bulgu nöromotor retardasyon (N=73, %45.34), ardından nöbetler (N=33, %20.50) idi. Tüm hastalarda ortalama B12 vitamini düzeyi  $167.70 \pm 45.17$  (58-250) pg/ml idi. B12 vitamini ve ferritin düzeyleri veya tam kan sayımı parametreleri [Hb, Htc ve MCV] açısından erkek ve kız çocukların arasında istatistiksel olarak anlamlı fark saptanmadı (sırasıyla p=0.428, p=0.646, p=0.110, p=0.128, p=0.864). **Sonuç:** Bu çalışma, sağlık çalışanları için hastalıkla ilişkili olarak karşılaştığımız klinik tablolar hakkında genel bir değerlendirme sunmaktadır.

**Anahtar Kelimeler:** B12 Vitamini, Çocuk, Eksiklik, Bulgu, Tedavi.

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## INTRODUCTION

Vitamin B12 plays a role in several systems in the body, and in cell division and differentiation, by taking part, together with folic acid, in DNA synthesis (Dogan & Demirci, 2010). Vitamin B12 is not synthesized in the human body, and therefore needs to be absorbed with diet. As in the rest of the world, Vitamin B12 deficiency is also a frequently encountered problem in Turkey (Hafizoglu, 2020). The most frequent clinical symptoms in vitamin B12 deficiency are delayed growth and development, gastrointestinal motility disorders, hyperpigmentation, stomatitis, glossitis, lethargy, ataxia, hyporeflexia, tremor, seizures, movement disorders, retardation in acquired motor skills, abnormal mental states, and coma (Graham, Arvela & Wise, 1992). Vitamin B12 deficiency can also emerge with non-specific symptoms and findings. Neurological findings develop in 80-90% of patients with vitamin B12 deficiency. These may be peripheral or central in nature (Healton, Savage, Brust, Garrett, & Lindenbaum, 1991). The onset of peripheral symptoms typically takes the form of symmetrical paresthesia in the extremities and gait ataxia. Memory disorder, altered personality, and even psychosis have been described as central and psychiatric symptoms associated with vitamin B12 deficiency in the literature (McCaddon, 2013). No link has been reported between the presence of nervous system findings in patients with vitamin B12 deficiency and the extent of vitamin deficiency (McCaddon, 2013).

The purpose of this study was to determine neurological and non-neurological manifestations in patients presenting to the pediatric neurology department with various different symptoms and to discuss these in the light of the current literature.

## MATERIALS AND METHODS

### Study group

Children aged between one month and 18 years presenting to the Balikesir University Medical Faculty paediatric neurology clinic, Turkey, between

01.08.2019 and 01.08.2021 and with Vitamin B12 levels lower than 250 ng/mL were included in this retrospective, cross-sectional study. Demographic data and clinical and laboratory findings (vitamin B12, complete blood count, and ferritin) were recorded from the patient files.

Patients with structural anomalies, folic acid deficiency, a history of gastrointestinal surgery and drug use, or with acute infection findings, patients with autoimmune, metabolic, or genetic disorders, or chronic neurological disease, and patients whose clinical findings contracted with Vitamin B12 therapy were excluded from the study.

### Statistical analysis

Statistical analysis was performed by using SPSS 15 package program. Descriptive statistics were presented as mean, standard deviation, minimum, and maximum values for measurement variables, and as number (n) and percentage (%) for qualitative variables. Normality of distribution of numerical variables was evaluated using the Shapiro-Wilk test. The Mann-Whitney U test was applied in the comparison by gender of non-normally distributed numerical data, and Student's t test was used for independent groups exhibiting normal distribution. p values <0.05 were regarded as statistically significant.

### Ethical considerations

Ethical approval for this study was obtained from the local ethical committee before the start of the study (no. 2021/224 dated 06.10.2021).

## RESULTS

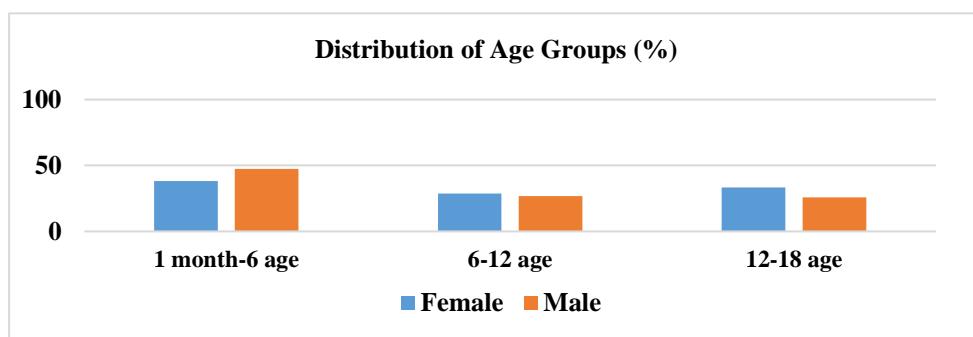
One hundred sixty-one cases were included in the study 63 (39.1%) female and 98 (60.9%) male. The patients' mean age was  $7.43 \pm 5.77$  (0-17) years. Seventy (43.5%) cases were in the 0-6-year age group, 44 (27.3%) in the 6-12 age group, and 47 (29.2%) in the 12-18 age group. Mean ages were  $7.36 \pm 5.58$  (0-17) years for boys and  $7.54 \pm 6.11$  (1-17) for girls. The majority of patients of both genders were in the 0-6 age group (Table 1, Graphic 1).

**Table 1. Patients' symptoms and signs.**

Gender n (%)	
Girl	63 (39.1%)
Boy	98 (60.9%)
Average age	
	$7.43 \pm 5.77$ (0-17) year
Age groups n (%)	
0-6 years	70 (43.5%)
6-12 years	44 (27.3%)
12-18 years	47 (29.2%)
Vitamin B12 levels	
<150 pg/ml	64 (39.8%)
150-190 pg/ml	44 (27.3%)
>190 pg/ml	53 (32.9%)

**Table 1. (Continue) Patients' symptoms and signs.**

Symptoms n (%)	
Neuromotor retardation	73 (45.3%)
Hypotonia	7 (4.3%)
Skin hyperpigmentation	11 (6.8%)
Paleness	1 (0.6%)
Apathy	1 (0.6%)
Vomiting	15 (9.3%)
Irritability	3 (1.9%)
Athetoid head movements	4 (2.5%)
Seizure	33 (20.5%)
Loss of appetite	1 (0.6%)
Sparse and depigmented hair	1 (0.6%)
Tremor	3 (1.9%)
Syncope	5 (3.1%)
Headache	2 (1.2%)
Dizziness/Vertigo	1 (0.6%)

**Graphic 1. Distribution of age groups between gender.**

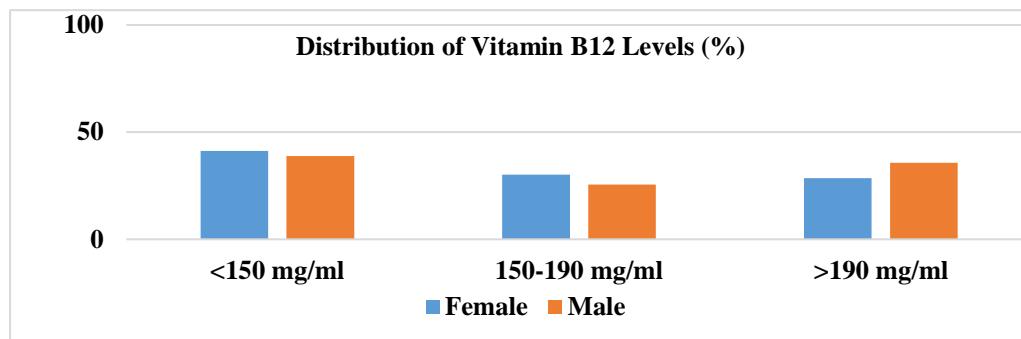
Neurological findings were present in 81.98% of patients with Vitamin B12 deficiency, and non-neurological findings in 18.02%. The most frequent neurological finding was neuromotor retardation (N=73, 45.34%), followed by seizures (N=33, 20.50%). Gastrointestinal motility disorders (N=15, 9.30%) were the most common non-neurological finding. The least frequent findings were vertigo, apathy, loss of appetite, and depigmented hair (N=1, 0.6%). The most frequent reason for presentation was neuromotor retardation in both boys and girls with Vitamin B12 deficiency (N=55, 56.1% and N=18, 28.57%). The mean vitamin B12 level among all the patients was  $167.70 \pm 45.17$  (58-250) pg/ml. Mean vitamin B12 levels were  $169.90 \pm 44.09$  (N=98) pg/ml

in boys and  $164.27 \pm 46.95$  (N=63) pg/ml in girls. Vitamin B12 levels were <150 ng/ml in 64 cases (39.8%), 150-190 pg/ml in 44 (27.3%), and >190 pg/ml in 53 (32.9%). Among boys, vitamin B12 levels were <150 pg/ml in 38 (38.8%) cases, 150-190 pg/ml in 25 cases (25.5%), and >190 pg/ml in 35 (35.7%). Among the girls, vitamin B12 levels were <150 pg/ml in 26 cases (41.3%), 150-190 pg/ml in 19 (30.20%), and >190 pg/ml in 18 (28.60%) (Graphic 2). The cases' mean hemoglobin (Hb) level was  $12.73 \pm 1.42$  (7.5-16.4) g/dl, mean hematocrit (Htc) level  $38.03 \pm 4.22$  (29.1-49.9), mean erythrocyte volume (MCV)  $79.79 \pm 6.32$  (58.2-97.4) fL, and mean ferritin level  $26.71 \pm 42.80$  (2.2-470.9) ml/ng (Table 2).

**Table 2. Laboratory characteristics of the patients.**

	All patients	Girls	Boys
<b>Hemoglobin (g/dL)</b>	$12.73 \pm 1.42$ (7.5-16.4)	$12.52 \pm 1.10$ (10.2-14.6)	$12.87 \pm 1.58$ (7.5-16.4)
<b>Hematocrit (%)</b>	$38.03 \pm 4.22$ (29.1-49.9)	$37.42 \pm 3.52$ (30.1-44.0)	$38.43 \pm 4.60$ (29.1-49.9)
<b>MCV (fL)</b>	$79.79 \pm 6.32$ (58.2-97.4)	$79.90 \pm 6.66$ (61.4-92.5)	$79.72 \pm 6.12$ (58.2-97.4)
<b>WBC /mm<sup>3</sup></b>	$8.57 \pm 3.18$ (3.8-28.9)	$8.48 \pm 2.45$ (3.8-15.8)	$8.63 \pm 3.59$ (4.0-28.9)
<b>Platelet/mm<sup>3</sup></b>	$340.41 \pm 101.67$ (166-761)	$347.03 \pm 110.50$ (166-761)	$336.02 \pm 95.74$ (177-653)
<b>Vitamin B12 (pg/mL)</b>	$167.70 \pm 45.17$ (58-250)	$164.27 \pm 46.95$ (58-248)	$169.90 \pm 44.09$ (76-250)
<b>Ferritin (ml/ng)</b>	$26.71 \pm 42.80$ (2.2-470.9)	$19.01 \pm 20.48$ (2.2-134.0)	$31.66 \pm 51.86$ (2.9-470.9)

WBC: White Blood Cell. MCV: Mean Corpuscular Volume.



Graphic 2. Distribution of vitamin B12 levels.

No statistically significant difference was determined between boys and girls in terms of vitamin B12 and ferritin levels or complete blood count parameters [Hb, Htc, and MCV] (respectively  $p=0.428$ ,  $p=0.646$ ,  $p=0.110$ ,  $p=0.128$ ,  $p=0.864$ ).

## DISCUSSION

Vitamin B12 deficiency is a widespread problem in Turkey and worldwide, the prevalence of which is known to vary from one country to another. While the prevalence increases in elderly patients, deficiency can also be seen in childhood (Koç, Kocyigit, Soran, Demir, Sevinc, Erel, & Mil, 2006). Findings associated with vitamin B12 deficiency are generally chronic and progressive, and clinical findings linked to dietary deficiency may take 3-18 months to emerge (Koç, Kocyigit, Soran, Demir, Sevinc, Erel, & Mil, 2006; Hector & Burton, 1988). Neurological symptoms such as neuromotor retardation and seizures were frequently detected in the children with vitamin B12 deficiency in the present study.

In previous studies of children with vitamin B12 deficiency, Arslan et al reported a mean age of 13.62 years (min: six months, max: 18 years), and Demir et al. a mean age of  $12.07 \pm 3.85$  months (Arslan, 2020; Demir, Koc, Ustyol, Peker, & Abuhandan, 2013). The mean age of the patients in the present study was  $7.43 \pm 5.77$  years (0-17). Vitamin B12 deficiency was frequently observed in the 0-6-year age group in both sexes.

Demir et al. reported that vitamin B12 deficiency was more common in male gender (male/female:1.56), while Arslan described it as more common in girls (male/female:0.62) (Arslan, 2020; Demir, Koc, Ustyol, Peker, & Abuhandan, 2013). The majority of cases of vitamin B12 deficiency in the present study were male ( $N=98$ , 60.9%).

Demir et al. reported a mean vitamin B12 level of  $139.7 \pm 64.5$  pg/ml, and Aslan one of  $160.409$  (min: 77 pg/mL, max: 263 pg/mL) (Arslan, 2020; Demir, Koc, Ustyol, Peker, & Abuhandan, 2013). The mean vitamin B12 level in the present study was  $167.70 \pm 45.17$  (58-250) pg/ml, with mean values of  $169.90 \pm 44.09$  (76-250) pg/ml in boys and

$164.27 \pm 46.95$  (58-248) pg/ml in girls. Vitamin B12 levels were  $<150$  ng/ml in the majority of cases in both sexes ( $N=64$ , 39.8%).

While B12 deficiency can affect several system functions, findings and symptoms such as feeding difficulties, seizures, delayed growth, megaloblastic anemia, developmental delay, hypotonia, microcephaly, lethargy, involuntary movements, irritability, and cerebral atrophy are frequently observed (Nawaz, Khattak, Khan, & Nangyal, 2020). Non-specific findings such as diarrhea, pallor, weakness, lack of appetite, vomiting, irritability, and tremor have also been determined in patients with vitamin B12 deficiency (Demir, Koc, Ustyol, Peker, & Abuhandan, 2013).

Together with folic acid, vitamin B12 plays a very important role in fetal brain development and in the myelination process in children up until puberty (Nawaz, Khattak, Khan, & Nangyal, 2020). The neurological symptoms and findings of vitamin B12 deficiency are generally mild, although clinical presentations are quite variable. Severe nervous system pathologies are seen in 30% of patients (Lee, 1993). Arslan described dizziness and/or fainting as the most frequently seen symptoms (61.7%) in patients with vitamin B12 deficiency (Arslan, 2020). That study also reported a history of concentration difficulty and forgetfulness and decreased academic performance in 18.3% of patients, numbness and/or tingling or a stinging sensation in 10.8%, congenital hypotonicity in 3.3%, and symptoms involving more than one system in 5.8% (Arslan, 2020). Demir et al. determined motor retardation, hypotonia, and pallor in all (100%) infant patients, followed by apathy, anorexia, and skin pigmentation (78%), and lack of eye contact and social retardation (68.3%) (Demir, Koc, Ustyol, Peker, & Abuhandan, 2013). Similarly, Taşkesen et al. also reported hypotonia (100%) as the most common neurological finding. Other neurological findings encountered by Taşkesen et al. included lack of appetite (92.8%), and neurodevelopmental (85.7%) and social (80.9%) retardation Taşkesen, Yaramış, Katar, Pirinçlioğlu, & Söker, (2011). The most frequently observed

neurological findings in another study of 27 infants with vitamin B12 deficiency were apathy, hypotonia (66.7%), motor retardation (59.3%), social retardation (51.9%), tremors (14.8%), and athetoid movements (3.6%) (Zengin, Sarper, & Kilic, 2009). The most common finding in the present study was neuromotor retardation (n=73, 45.34%), followed by seizures (N=33, 20.50%), and gastrointestinal motility disorders (N=15, 9.30%). Neuromotor retardation was the most frequent finding in both girls and boys (N=55, 56.1% and N=18, 28.57%, respectively). The least common findings in our patients were dizziness, loss of appetite, and depigmented hair (N=1, 0.6% each).

Epilepsy is a rare condition in children with vitamin B12 deficiency (Lee, Chang, Wu, Weng, & Chen. 200, Kumar, 2004). Demir et al. reported a prevalence of seizures of 14.6% in patients with vitamin B12 deficiency (Demir, Koc, Ustyol, Peker, & Abuhandan, 2013).

The literature contains case studies of seizures associated with vitamin B12 deficiency. Kirik and Çatak that hypotonia was the neurological finding most frequently accompanying seizures (Kirik, & Çatak, 2021). The mechanism involved in vitamin B12-related epilepsy is still unclear. However, it is thought that myelin damage occurs in neurons in associated with deficiency, and that this may be associated with central neurons being more susceptible to the stimulating effects of glutamate central neurons (Kumar, 2004). The prevalence of seizures in the present study was 20.50% (N=33).

The treatment of vitamin B12 deficiency involves replacing the missing vitamin, and improvement in clinical and imaging findings occurs with treatment in the majority of patients. Keskin determined atrophy in the cerebral cortex at magnetic resonance (MR) imaging in a 12-month-old girl with psychomotor retardation diagnosed with severe vitamin B12 deficiency and reported improvement of both the psychomotor retardation and cranial MR finding with replacement therapy (Keskin, 2016). We also observed improvement of clinical findings in the majority of patients started on vitamin B12 therapy. However, if diagnosis is delayed, deficiency can lead to irreversible neurological damage, for which reason many researchers have emphasized the importance of early diagnosis and treatment (Demir, Koc, Ustyol, Peker, & Abuhandan, 2013).

In that context, studies have stated that clinicians must take particular care not to miss the diagnosis, especially in infants, since the signs and symptoms are not specific (Zengin, Sarper, & Kilic, 2009).

## CONCLUSION

The principal limitations of this study are its retrospective nature, the fact that development testing could not be performed due to the lack of a child development specialist, the inability to measure homocysteine in our center, and the fact that our is a

tertiary health institution in our region and that there is therefore a risk that the homogeneity of our patient population could not be established on account of the patients referred to us.

B12 deficiency is a health problem frequently encountered both in Turkey and worldwide, and early diagnosis and treatment are highly important. This study provides a general evaluation for health professionals regarding clinical presentations encountered by us in association with the disease. We think that our study will contribute to the literature both in Turkey and worldwide.

**Conflict of Interest:** The authors declare to have no conflicts of interest.

## Author Contributions

**Plan, design:** HA, OK; **Material, methods and data collection:** HA, OK, EO; **Data analysis and comments:** HA, OK, EO; **Writing and corrections:** HA, OK, DC.

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