Sabuncuoglu Serefeddin Health Science (SSHS)

ISSN: 2667-6338, 2023/Vol.5:1/34-43

VITAMIN B12 DEFICIENCY IN CHILDOOD: A SINGLE CENTRE EXPERIENCE

[*1]Gökce CELEP, [2]Sümeyye EVSİLE

[1]Amasya University, Faculty of Medicine, Department of Pediatrics, Amasya, Türkiye

[2]Sabuncuoğlu Şerefeddin Training and Research Hospital, Department of Pediatrics, Amasya, Türkiye

Clinical Research

Received: 02.01.2022, Accepted: 27.03.2023

*Corresponding author: gokce4celep@yahoo.com

Abstract

Vitamin B12 is an essential micronutrient for neurodevelopment, growth, and erythropoiesis of the human body. Deficiency is a common public health problem affecting young children, leading to neuropsychiatric and hematologic disorders. The aim of this study was to determine the rate and clinical findings of B12 deficiency among a sample of well children in a city located of middle northern Turkiye. The study was carried out in the pediatric outpatient clinics of a tertiary health-care center in middle-northern Turkey between November 1, 2019, and May 31, 2022. The medical records about age, gender, clinical history, and laboratory data were retrieved from the hospital information system, retrospectively. Results were presented as percentages and fractional data after the analyses based on software. The study group consisted of 240 participants aged between 1-6 years old, 42.9% (n=103) of them were boys. The rate of vitamin B12 deficiency (<250 pg/ml) was 18.3% (n=44). Anemia was detected in 50 (20.8%) and macrocytosis was present in 31 (12.9%) of the participants. Constitutional symptoms were the most common reason of hospital administration (n=89; 37.1%) and vitamin B12 deficiency was mostly presented by constitutional symptoms (n=17; 38.6%). Vitamin B12 is a public health problem in children which can be prevented. Clinical suspicions should lead clinicians for ordering blood tests because accompanying problems may veil vitamin B12 deficiency. Screening programs can be carried out to prevent permanent neurologic complications in vulnerable populations.

Key Words: Childhood, Deficiency, Vitamin B12

Özet

B12 vitamini insan vücudunda nörolojik gelişim, büyüme ve eritropoez için gerekli bir mikro besindir. Eksikliği, özellikle küçük çocuklarda nöropsikiyatrik ve hematolojik problemlere neden olan önemli bir halk sağlığı sorunudur. Bu çalışmanın amacı Türkiye'nin orta kuzeyinde yer alan küçük bir il merkezinde sağlıklı çocuk popülasyonunda B12 vitamini eksikliği sıklığını ve klinik özelliklerini saptamaktır. Çalışma 1 Kasım 2019-31 Mayıs 2022 tarihleri arasında Türkiye'nin orta kuzey bölgesinde yer alan bir üçüncü basamak sağlık kuruluşunun pediatri polikliniklerinde yürütülmüştür. Yaş, cinsiyet, klinik yakınmalar ve laboratuvar sonuçlarına ait veriler hastane bilgi sisteminden geriye dönük olarak elde edilmiştir. Sonuçlar yazılım tabanlı sistemler üzerinden sunulmuştur. Çalışma grubu yaşları 1-6 arasında değişen, %42,9'u (n=103) erkek olan 240 çocuktan oluşmaktadır. B12 vitamini eksikliği (<250 pg/ml) hızı %18,3 (n=44) bulunmuştur. Katılımcıların 50 tanesinde (%20.8) anemi, 31'inde (%12,9) makrositoz saptanmıştır. Yapısal yakınmalar en sık başvuru nedeni (n=89; %37,1) ve B12 vitamini eksikliği ile ilişkisi en sık saptanan yakınma başlığıdır (n=17; %38,6).B12 vitamini eksikliği önlenebilir bir halk sağlığı sorunudur. Klinik şüphe durumunda klinisyenlerin tetkik istemesi gereklidir; çünkü eşlik eden sorunlar B12 vitamini eksikliğini maskeleyebilir. Hassas popülasyonlarda kalıcı nörolojik komplikasyonların önlenmesi için tarama programları yürütülmelidir.

Anahtar Kelimeler: B12 vitamini, Çocukluk çağı, Eksiklik

1. Introduction

Micronutrients' deficiencies are the important reasons and results of malnutrition, anemia, and neuropathy in children. Vitamin B12; Cobalamin in other words; is a water-soluble vitamin essential for cellular functions of the human body. It is necessary in metabolic pathways of one carbon metabolism. It is important for deoxyribonucleic acid (DNA) and protein synthesis, which plays an important role in cell growth and differentiation. Erythropoiesis, synthesis, and maintenance of the myelin sheet are vitamin B12 dependent processes. Deficiency of vitamin B12 results in anemia and neuropsychiatric problems throughout life (Finkelstein, Layden, & Stover, 2015; Nyaradi, Li, Hickling, Foster, & Oddy, 2013) .Pregnancy, fetal period, infancy and childhood

are the most vulnerable periods of life since growth and development take place predominantly (Finkelstein et al., 2015; Nyaradi et al., 2013) . Hematological, mucocutaneous, gastrointestinal, or neurological problems are the clinical manifestations of Vitamin B12 deficiency. Fatigue, weakness, constipation, loss of appetite, growth and developmental delay, numbness and tingling in hands and feet, ataxia, depression, confusion, dementia, poor memory, soreness of the mouth or tongue are the clinical symptoms whereas anemia, leukopenia, hypersegmentation in neutrophils, neutropenia and hyperhomocysteinemia are the laboratory findings (Akcaboy, 2015; Escott-Stump, 2008; Lanzkowsky, 2005; Pawlak, Lester, & Babatunde, 2014) .

Human cells cannot synthesize this vitamin. It is animal derived and meat, eggs, dairy products are the rich sources(NIH, 2020) . It is the only water-soluble vitamin that is stored in the liver of animals. A typical balanced diet is able to prevent deficiency, except vegan diets. National Institute of Health Office of Dietary Supplements recommends supplementation due to age and physiological development (NIH, 2020; Pawlak et al., 2014) . Low protein intake due to wrong nutritional habits and low socioeconomic status increase prevalence of Vitamin B12deficiency in all age groups (NIH, 2020; Pawlak et al., 2014).

Being a common public health problem vitamin B12 status has been reported frequently. The aim of this study was to determine the rate and clinical findings of vitamin B12 deficiency among a sample of well-children in a city located in middle northern Turkey.

2. Material and Methods

The study was carried out in the pediatric outpatient clinics of a secondary health-care center in middle-northern Turkey between November 1, 2019 and May 31, 2022. The medical records were retrieved from the hospital information system, retrospectively. Patients who need healthcare including regular treatment and/or a special diet lasting for three months or longer were excluded. Data about the symptoms and clinical findings, age, gender, vitamin B12 levels, hematologic parameters (hemoglobin (Hb), mean corpuscular volume (MCV) were noted.

B12 levels were studied by Siemens Advia Centaur® XP immunoassay system by using chemiluminescence method. The vitamin B12 levels less than 250 pg/ml were diagnosed as “vitamin B12 deficiency” (Altuntaş, Soylu, Suskan, & Akar, 2004; NIH, 2020). CBC analyses were performed by Mindray BC-6800® Shenzhen Mindray Bio-Medical Electronics Co. Ltd, China), which is an auto hematologic analyzer device analyzing hematologic samples via a laser optic

system. Hemoglobin (Hb), mean erythrocyte volume (MCV) values were arranged according to reference ranges by age groups (Brugnara C, 2015).

The clinical features are categorized systematically due to the initial complaint which was the reason for seeking healthcare (Table 1).

Table 1. The categorization of patient complaints at admission to hospital

Neurologic symptoms	Neurodevelopmental delay, afebrile convulsion, headache, tremor, vertigo, headache
Constitutional symptoms	Poor appetite, fatigue, failure to thrive myalgia
Gastrointestinal symptoms	Nausea, abdominal pain, constipation, gastro esophageal reflux
Mucocutenous symptoms	Pruritus, stomatitis, hyperpigmentation
Cardiovascular symptoms	Palpitation, chest pain, syncope

Data were entered into Microsoft Excel and analyzed. Results were presented as percentages and fractional data. Statistical analyses were performed by using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). The data were presented by descriptive statistics when necessary. Cross tables, the Chi-square test or Fisher's exact test were also used to compare the variables in different groups. The p value less than 0.05 was considered to declare statistically significant results.

This study was approved by the local committee of non-invasive scientific researchers with decision no. 27/02/2020-E.5675

3. Results and Discussion

The study group consisted of 240 participants aged between 1-6 years old, 42.9% (n=103) of them were boys. The rate of vitamin B12 deficiency (<250 pg/ml) was 18.3% (n=44). Anemia was detected in 50 (20.8%) and macrocytosis was present in 31 (12.9%) of the participants. Only one participant had macrocytic anemia accompanying vitamin B12 deficiency. Constitutional symptoms were the most common reason of hospital administration (n=89; 37.1%) and vitamin B12 deficiency was mostly presented by constitutional symptoms (n=17; 38.6%). The rate of deficiency was in boys 16.5% (n=17) and 19.7% (n=27) in girls; there was no statistical difference (p=0.52)

Participants were divided into two age groups considering neurodevelopmental stages. Children aged 1-3 were the members of Group 1 and the group consisted of 152 (63.3%)

participants. Seventy (46.1%) of the members were boys. Vitamin B12 was detected in 16.4% (n=25) patients and 60% (n=15) of them were girls, there was no statistical significance between genders (p= 0,50). The rate of anemia was 15.1% (n=23) and 52.2% (n=12) of the patients were girls; but the difference between the genders were not statistically significant (p=0.85). Twenty-three (15.1%) of the group members had macrocytosis and five (21.7%) of them had vitamin B12 deficiency. Only one patient had macrocytic anemia. Constitutional symptoms and neurologic symptoms were the most common reasons for healthcare seeking (n=52; 34.2%; n=50; 32.9%, respectively). Neurologic symptoms were the most common clinical problems accompanying vitamin B12 deficiency in this age group (n=11; 44%; p=0.006). None of the participants had cardiovascular problems at admission.

Group 2 consisted of 88 patients (36.7%) aged between 4-6 years old. Fifty-five (62.5%) of them were girls. The rates of vitamin B12 deficiency, anemia and macrocytosis were 21.6% (n=19), 30.7% (n=27), 9.1% (n=8) respectively. Twelve (21.8%) of the girls had B12 deficiency, 13 (23.6%) had anemia and five (9.3%) had macrocytosis. The statistical difference within these variables were not significant (p=0.95; p=0.06; p=1.00; respectively). Constitutional symptoms and gastrointestinal symptoms were the most common reasons for hospital administration (n=37; 42%; n=30; 34.1%, respectively). The rates of all laboratory disorders and clinical findings are summarized in Table 2 and Table 3.

Table 2. The sociodemographic, clinical and laboratory features of the study group

	Group 1(n=152; 63.3%)		**Group 2 (n=88; 36.7%)**	
Age (years old)	1-3		4-6	
Gender (boys/ girls)	n=70; 46.1%	n=82;53.9%	n=33; 37.5%	n=55; 62.5%
Anemia	n= 23; 15.1%		n= 27; 30.7%	
Macrocytosis	n=23; 15.1%		n= 8; 9.1%	
Vitamin B12 deficiency	n=25; 16.4%		n= 19; 21.6%	
Constitutional symptoms	n=52; 34.2%		n=37; 42%	
Neurologic symptoms	n=50; 32.9%		n=12; 13.6%	
Gastrointestinal symptoms	n=45; 29.6%		n=30; 34.1%	
Mucocutenous symptoms	n=5; 3.3%		n=2; 2,3%	
Cardiovascular symptoms	n=0; 0%		n=7; 8%	

Table 3. The relationship of vitamin B12 deficiency and laboratory and clinical features

	B12 Deficiency group n; %	**Non-deficiency group n; %**
Anemia	6; 13.6	44; 22.4
Macrocytosis	10; 22.7	21; 10.7
Constitutional symptoms	17; 38.6	72; 36.7
Neurologic symptoms	13; 29.5	49; 25
Gastrointestinal symptoms	13;29.5	62; 31.6
Mucocutenous symptoms	0;0	7; 3.6
Cardiovascular symptoms	1; 2.3	6; 3.1

When comparing two groups there was no statistical significance within vitamin B12 deficiency and macrocytosis rate, but anemia rate was higher in the second group which was statistically significant (p=0.20; p=0.18; p=0.0004 respectively). Anemia was detected in six (13.6%) patients having vitamin B12 deficiency and macrocytosis was present in ten patients (22.7%) of the same group.

This study is the first report of our city's children about vitamin B12 deficiency. The rate of vitamin B12 deficiency (<250 pg/ml) in our study group was found to be 18.3%; meaning that approximately one of five children aged between 1-6 years old has vitamin B12 deficiency in our study group. The clinical presentation of vitamin B12 deficiency may change due to age. Constitutional symptoms were the most common reason of hospital administration (n=89; 37.1%) and vitamin B12 deficiency was mostly presented by constitutional symptoms; however neurologic symptoms were more common in the first three years of life. Anemia was detected in 50 (20.8%) and macrocytosis was present in 31 (12.9%) of the whole group. The rates of anemia and macrocytosis in the deficiency group were 13.6% and 10.7 respectively.

Vitamin B12 is one of the essential micronutrients related with neurodevelopment, growth and hematopoiesis and it is known to be a common public health problem (El-Khateeb et al., 2014). A study conducted in İzmir reported the rate of deficiency to be 23.3% in a pediatric population aged 1-5 years old (Çolak A, Anıl, Toprak, Köse, & Üstüner, 2012). The rate of vitamin B12 deficiency was reported to be 7.7% in Mexican children aged 1-6 years old (Cuevas-Nasu et al., 2012). There was no deficiency in a population of peer children attending at a healthcare center in Brazil (Barnabé et al., 2015) . Our deficiency rate was lower than other parts of Turkey, but higher than other parts of the world (Barnabé et al., 2015; Cuevas-Nasu et al., 2012; Çolak A

et al., 2012) . However, vitamin B12 deficiency was found to be more frequent in adolescence (Karabayir, Teber, Dursun, & Pehlivan, 2022; Sarna et al., 2020) .

The relationship between the prevalence of vitamin B12 deficiency and genders is not well-defined. In the reports of adult studies the results are controversial, in children gender seems not having significant effect in the prevalence of vitamin B12 deficiency, as in our study (El-Khateeb et al., 2014; Karabayir et al., 2022).

B12 plays a major role in energy production and synthesis of constructional molecules of human body during whole life (Ludwig & Matthews, 1997) . Complex transport and metabolism of vitamin B12 result in various clinical manifestations in case of deficiency including constitutional hematological, neurological, and gastrointestinal disturbances. Because myelination is very active during early life, neurological damage caused by reduced DNA synthesis is frequent in B12 deficiency in infancy. Vitamin B12deficiency in infants causes failure to thrive, lethargy, irritability, developmental delay, hyperpigmentation, tonus problems, convulsions, and cerebral atrophy (Akcaboy, 2015; Dror & Allen, 2008) . Constitutional symptoms were the most common complaint in our study group and frequency of neurologic symptoms were higher in the first group similar to the literature.

Vitamin B12 is one of the essential micronutrients related with hematopoiesis, but the clinical and laboratory findings are established later than neurologic symptoms. Deficiency results in megaloblastic anemia. Since DNA synthesis and cellular reactions need vitamin B12 co-factoring, other series in bone marrow are affected. Leukopenia and thrombocytopenia accompany megaloblastic anemia frequently (Kliegman RM, 2011). Megaloblastic anemia is presented by higher MCV values in complete blood count (CBC) tests. However, iron deficiency, which is the most common reason of nutritional anemias, may veil macrocytosis. Only the MCV value in the diagnosis of megaloblastic anemia may not always be guiding and it should not be used alone in the diagnosis vitamin B12 deficiency (Oosterhuis, Niessen, Bossuyt, Sanders, & Sturk, 2000). Iron deficiency accompanying vitamin B12 deficiency may lead to misdiagnose when only CBC is used for screening. Studies on vitamin B12 have established that CBC parameters may not always reflect the findings of deficiency (Kara İH, 2010). Similar to the literature, anemia prevalence and CBC parameters were not related to vitamin B12 levels when deficiency and non- deficiency groups were compared in our study. The prevalence of anemia and iron deficiency in our city was reported to be 29.6% and 26.2% respectively in another study (Celep & Durmaz, 2021). However,

the iron parameters of the participants of this study group were not mentioned in this report which is one of the limitations.

This study is the first one reporting the vitamin B12 status of our city's children aged 1-6 years old. However, it has great limitations: First of all, it was designed to be a retrospective study based on hospital records. Vitamin B12 levels were studied in patients who were thought to be deficient in the preliminary clinical evaluation which may cause a bias in sampling. The dietary habits, nutritional status of the patients was not reported. Clinical complaints were presented in general titles, not in details. Laboratory components of the B12 evaluation, plasma holo-transcobalamin, serum methylmalonic acid, serum homocysteine and urine methylmalonic acid are needed for correct evaluation, were not reported. Other CBC parameters related to deficiency such as leucocyte, thrombocyte counts, hipersegmented neutrophils were not mentioned. Although it has great limitations, this study had established that B12 deficiency was an important public health problem in this city's children.

4. Conclusion

In conclusion, vitamin B12 is a public health problem which can be prevented. Clinical suspicions lead clinicians for ordering blood tests, but screening programs can be carried out to prevent permanent neurologic complications.

Acknowledgement

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of interest

None

References

Akcaboy, M., Malbora, B., Zorlu, P., Altınel, E., Oguz, M. M., & Senel, S. . (2015). Vitamin B12 Deficiency in Infants. *Indian journal of pediatrics, 82(7)*, 619–624. doi: https://doi.org/10.1007/s12098-015-1725-3

Altuntaş, N., Soylu, K., Suskan, E., & Akar, N. (2004). Homocysteine levels in Turkish children. *Turkish Journal of Haematology: Official Journal of Turkish Society of Haematology, 21*(2), 79-82.

Barnabé, A., Aléssio, A. C. M., Bittar, L. F., de Moraes Mazetto, B., Bicudo, A. M., de Paula, E. V., . . . Annichino-Bizzacchi, J. M. (2015). Folate, vitamin B12 and Homocysteine status in the post-folic acid fortification era in different subgroups of the Brazilian population attended to at a public health care center. *Nutrition journal, 14*(1), 1-10.

Brugnara C, O. F., Nathan DG (2015). *Diagnostic approach to the anemic patient* (8th ed ed.). Philadelphia: WB Saunders.

Celep, G., & Durmaz, Z. (2021). Çocuklarda Demir Eksikliği ve Demir Eksikliği Anemisi: Tek Merkez Deneyimi. *İstanbul Gelişim Üniversitesi Sağlık Bilimleri Dergisi*(13), 16-29.

Cuevas-Nasu, L., Mundo-Rosas, V., Shamah-Levy, T., Méndez-Gómez Humaran, I., Ávila-Arcos, M. A., Rebollar-Campos, M., & Villalpando, S. (2012). Prevalence of folate and vitamin B12 deficiency in Mexican children aged 1 to 6 years in a population-based survey. *salud pública de méxico, 54*, 116-124.

Çolak A, A., Anıl, M., Toprak, B., Köse, E., & Üstüner, F. (2012). The relationship between vitamin B12 level and peripheral complete blood count values in children. *Journal of Dr. Behcet Uz Children's Hospital, 2*(2).

Dror, D. K., & Allen, L. H. (2008). Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms. *Nutrition reviews, 66*(5), 250-255.

El-Khateeb, M., Khader, Y., Batieha, A., Jaddou, H., Hyassat, D., Belbisi, A., & Ajlouni, K. (2014). Vitamin B12 deficiency in Jordan: a population-based study. *Annals of Nutrition and Metabolism, 64*(2), 101-105.

Escott-Stump, S. (2008). *Nutrition and diagnosis-related care*: Lippincott Williams & Wilkins.

Finkelstein, J. L., Layden, A. J., & Stover, P. J. (2015). Vitamin B-12 and perinatal health. *Advances in Nutrition, 6*(5), 552-563.

Kara İH, K. H., Bahçebaşı T, Köylü OK, Sayın S, Demirin H, Memişoğulları R. (2010). Check-up polikliniğine başvuran 50 yaşüzeri bireylerin folat, B12 vitamini düzeyleri ve anemi yönünden değerlendirilmesi. *Turkish Journal of Biochemistry-Turk J Biochem, 35(4)*, 350-355.

Karabayir, N., Teber, B. G., Dursun, H. K., & Pehlivan, L. S. (2022). Is There An Association Between Vitamin B12 Level and Vitamin D Status in Children? *Journal of Pediatric Hematology/Oncology, 44*(3), e677-e681.

Kliegman RM, S. B., St Geme III JW, Schor NF, Behrman RE. . (2011). *The Anemias* (L. NB. Ed. 19th edition ed. Vol. Nelson Textbook of Pediatrics). Philadephia: Saunders Company.

Lanzkowsky, P. (2005). *Manual of pediatric hematology and oncology*: Elsevier.

Ludwig, M. L., & Matthews, R. G. (1997). Structure-based perspectives on B12-dependent enzymes. *Annual review of biochemistry, 66*(1), 269-313.

NIH, O. o. D. S. O.-. (2020). Dietary Supplement Fact Sheet: Vitamin B12. Retrieved http://ods.od.nih.gov/factsheets/ VitaminB12-HealthProfessional October 2022

Nyaradi, A., Li, J., Hickling, S., Foster, J., & Oddy, W. H. (2013). The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Frontiers in human neuroscience, 7*, 97.

Oosterhuis, W., Niessen, R., Bossuyt, P., Sanders, G., & Sturk, A. (2000). Diagnostic value of the mean corpuscular volume in the detection of vitamin B12 deficiency. *Scandinavian journal of clinical and laboratory investigation, 60*(1), 9-18.

Pawlak, R., Lester, S., & Babatunde, T. (2014). The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. *European journal of clinical nutrition, 68*(5), 541-548.

Sarna, A., Porwal, A., Ramesh, S., Agrawal, P. K., Acharya, R., Johnston, R., . . . Ramakrishnan, L. (2020). Characterisation of the types of anaemia prevalent among children and adolescents aged 1–19 years in India: a population-based study. *The Lancet Child & Adolescent Health, 4*(7), 515-525.