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Original Article

A common problem in infants: vitamin B_{12} deficiency

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ABSTRACT

Background. Nutritional vitamin B_{12} (VB_{12}) deficiency is characterized by anemia, the inability to gain weight, delay or decline in development. Children of mothers with VB_{12} deficiency have a risk of nutritional VB_{12} deficiency. Prevention and early treatment are necessary to prevent irreversible neurological damage. We aimed to conduct a retrospective study to understand the characteristics of patients with VB_{12} deficiency.

Methods. Our study included patients admitted to Başkent University Faculty of Medicine Pediatric Hematology outpatient clinic between January 2015 - February 2020 for VB_{12} deficiency. Their clinical and laboratory characteristics were retrospectively examined through the hospital automation system.

Results. Vitamin B_{12} deficiency was detected in 129 of the 3198 patients; 100 of them were followed regularly. The mean age at admission of our patients was 10 ± 12 months (1 month - 7.5 years); 98% of these children were aged 0-2 years. The mean VB_{12} level of our patients was 171.63 ± 51.2 pg/ml (83 - 273), mean hemoglobin 11.2 ± 1.37 g/dl (6.3 - 13.9), mean MCV 74.5± 9.1 fl (54-106.5) and mean iron level was 54 ±23 μg/dl (18 - 94). At the end of one month of loading therapy (oral or intramuscular, IM), the average VB_{12} level was 769 ± 537 pg/ml (post loading). One month after the loading therapy (pre-maintenance) the average VB_{12} level was 426 ±156 pg/ml. In seven cases who received IM therapy, the loading treatment was performed for the second time. The mean VB_{12} level of the mothers of 85 cases was 174±127 pg/ml (134 - 650). VB_{12} deficiency was detected in 55% of mothers, VB_{12} level being between 200 - 300 pg/ml in 76%, and below 200 pg/ml in the 24%. The family members of 35% of our patients (including parents) had VB_{12} deficiency.

Conclusions. In our country, routine screening of VB_{12} levels in infants is not performed; however, its early diagnosis and treatment can prevent many adverse effects mainly on the central nervous system. The fact that 98% of patients were 0-2 years old indicates that its deficiency may be quite high in the young age, and routine screening of this age group for VB_{12} deficiency and further studies for prophylaxis may be needed.

Key words: nutritional vitamin B_{12} deficiency, maternal vitamin B_{12} deficiency, vitamin B_{12} treatment, infancy.

Vitamin B_{12} (VB_{12}, cobalamin) is of particular importance for the development of the central nervous system (CNS). It is characterized by anemia, an inability to gain weight, and a delay or decline in development. Children of mothers with VB_{12} deficiency have a similar risk. Prevention and early treatment are necessary to prevent irreversible neurological damage, especially in infants.[1]

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VB_{12} deficiency, may be due to nonconsumption or inadequate consumption of animal foods such as dairy products/ insufficient consumption of meat, milk (because of vegetarianism, poverty) or malabsorption (e.g., pernicious anemia, achlorhydria, ileum damage or gastric bypass surgery).[2]

Mothers who are vegetarians have low levels of VB_{12} in both their serum and breast milk. Symptoms of deficiency can be detected in these infants from 4-6 months after birth.[2]

There is no routine screening of VB_{12} levels in infants, however, its deficiency has significant effects on systems, particularly the central nervous system. The purpose of our study was

to form an opinion regarding the prevalence and characteristics of patients diagnosed with VB_{12} deficiency in our clinic.

Material and Methods

Children between the ages of 0-7 years who were diagnosed with and treated for VB_{12} deficiency at Başkent University Pediatric Hematology outpatient clinic between January 2015 - February 2020 were retrospectively analyzed through the hospital automation system. The study was approved by the Başkent University, Medical and Health Sciences Research Ethics Committee (Project number: KA22/215, 02.06.2022) and informed consent was obtained from the families. Serum VB_{12} level below 300 pg/ml was defined as VB_{12} deficiency. Prior to treatment, other tests such as folic acid levels, urine protein, coeliac auto antibodies, maternal VB_{12} level (serum), parasite in the stool (3 times in a row), *Helicobacter pylori* antigen in the stool were also evaluated. The loading and maintenance therapies were administered either as parenteral (classical therapy) or oral cyanocobalamin therapies. The loading phase of the parenteral therapy protocol included cyanocobalamin administration 100 μg/day every day in the first week; 100 μg/every other day during the 2nd week; 100 μg/twice a week for 3rd and 4th weeks; through intramuscular (IM) route. Maintenance therapy included 100 μg of cyanocobalamin IM once a month, the duration to be determined individually the shortest being three months.[3]

Loading therapy of oral cyanocobalamin (oral therapy) was administered as 1000 μg/day VB_{12} (one ampoule), every day during the first week one ampoule every other day during the 2nd week; one ampoule twice a week during the 3rd and 4th weeks orally before meals. Maintenance therapy was given orally for the next three months, one ampoule per week, on an empty stomach.[3]

For monitoring the response to treatment in patients who received IM therapy, the VB_{12} level was examined immediately after the end of loading treatment (post- loading), 1 month later (before the first maintenance: pre-maintenance) and one month after the third maintenance (post-maintenance) and before the subsequent maintenance treatments if available.

In those who were given oral therapy, the VB_{12} level was examined immediately after the end of the loading therapy (post loading) and immediately after the end of the maintenance therapy (at the end of three months of maintenance therapy: post maintenance).

Serum iron, iron binding capacity, and ferritin were also evaluated in patients if available. In patients who received IM VB_{12} therapy, a second loading therapy was administered if their post-induction VB_{12} level was below 500 pg/ml. This protocol involved 250 μg/week cyanocobalamin by IM route, for four weeks. The aforementioned maintenance therapy was started one month after the end of the second loading therapy.

In the therapy protocol, no second loading therapy was recommended for those who received oral VB_{12} therapy since the maintenance of oral therapy involved more frequent administrations of drugs. The protocol was designed with the goal of keeping the lowest VB_{12} level during treatment at 350 pg/ml and filling up the stores as much as possible.

Statistical analysis

SPSS 21 software was used for statistical analysis. Descriptive statistics (including frequencies and percentages) were calculated for nominal variables. The mean ± standard deviation (SD), and median and range (minimum value-maximum value) were given for continuous variables. The significance of the difference between the groups was evaluated by Student's t-test. $P<0.05$ was considered statistically significant.

Results

VB_{12} deficiency was found in 129 of 3198 patients (4%) admitted to our outpatient clinic during this time period. The mean age at admission was 10 ± 12 months (1 month - 7.5 years); 98% of cases were between the ages of 0-2 years; 61 (47%) were girls and 68 (53%) were boys.

Admission complaints of patients are presented in Table I, and their characteristics and accompanying diseases in Table II. It was striking that a considerable number of patients in our cohort (44.3%) had no complaints or abnormalities on physical examination and were detected coincidentally. However, the majority (55.9%) had complaints or findings like irritability (17.8%), insomnia (11.6%), rejection of complementary foods (9.3%), delay in walking (8.5%), and microcephaly (8.5%) (Table I). Among the 126 patients between the ages of 0 and 2 years (n=126), 2 (1.5%) were receiving formula, 124 (96.1%) received breast milk and complementary food, and the 3 patients older than 2 years of age received only complementary food. Twelve patients (9.3%) refused complementary food.

No patient was solely breast fed. History of food allergy (cow's milk and multiple food) and prematurity were also striking in 10% and 3.2% of patients respectively (Table II). Thirty-five percent of patients (45/129) had a previously known history of VB_{12} deficiency in family members. Mean VB_{12} level of patients was 174 ± 49.6 (83 - 283) pg / ml (both oral and IM), mean hemoglobin (Hb) 11.2 ± 1.37 (6.3 - 13.9) g/dl, mean MCV 74.5 ± 9.1(54-106.5) fl and mean iron level was 54 ±23(18 - 94) μg/dl. Eighty-four mothers could be tested for serum VB_{12}; the mean VB_{12} of the mothers of our cases was 174 ±127 (134 - 650) pg/ml; 55% (46/84) had VB_{12} deficiency. VB_{12} level was between 200-300 pg/ml in 71.7% of the mothers (33/46) with VB_{12} deficiency, and ≤ 200 pg/ml in 28.3% (n: 13). Although none of the mothers were vegetarians, 20% of them consumed limited amounts of animal-based food because of economic conditions and dietary habits. The relationship between VB_{12} levels of the mothers and patients who were or were not breast feeding is presented in Table III. Among the mothers of patients with VB_{12} deficiency, 46 out of 84 mothers (54.7%) had VB_{12} deficiency (VB_{12} < 300 pg/ml). All except 1% of 129 patients were breast fed.

Table I. The symptoms and physical findings of the patients.

Symptoms and physical findings	N	%
Irritability	23	17.8
Insomnia	15	11.6
Rejection of complementary foods	12	9.3
Walking delay	11	8.5
Microcephaly	11	8.5
No symptoms or physical findings	57	44.3
Total	129	100

Table II. Patients' medical history and their comorbidities.

Comorbidities	n (%)
Cow milk allergy/multiple food allergy	13* (10%)
Prematurity/ small for gestational age (SGA) ***	4** (3.2%)

Maternal vitamin B_{12} deficiency in (maternal serum vitamin B_{12} levels <300 pg/ml) was detected in: 38 patients; food allergy (cow milk and multiple food) in 13; celiac disease in the one (both the child and the mother). Known etiology: 52/129 (40.4%); unknown etiology: 77/129 (59.6%).
*The mothers of the 9 out of 13 patients had low vitamin B_{12} level
** The mother of one pair of twins, out of 3, had low vitamin B_{12} level.
***The mean vitamin B_{12} levels of the mothers of premature/SGA babies were 340 pg/ml.

Table III. Vitamin B_{12} levels of patients according to maternal vitamin B_{12} level groups (N=84).

Maternal vitamin B_{12} level groups	N	Vitamin levels of patients (pg/ml)
100 - 150 pg/ml	3	157 + 41
150 – 200 pg/ml	10	160 + 45
200 – 250 pg/ml	16	182 + 49
250 – 300 pg/ml	17	178 + 57
>300 pg/ml	38	186 + 48

* 1 mother was not breastfeeding; her vitamin B_{12} level was 212 pg/ml, her child's vitamin B_{12} level was 189 pg/ml.

Coeliac disease was found in 1 (0.77%) as a coexisting disease with VB_{12} deficiency; the mother of that patient also had coeliac disease, as well. No patient had parasite ova, amoeba, or *Helicobacter pylori* in the stool. No patient had proteinuria suggestive of Imerslund-Grasbek syndrome, although 10% of patients with Imerslund-Grasbek syndrome may not have proteinuria.

Regular follow-up of VB_{12} levels after the loading therapy (oral or IM) could be performed in 85 out of 100 cases. IM therapy was used in 92 of the 100 cases, while oral therapy was used in eight. Detailed characteristics of the response to classical therapy (oral and IM) are presented in Table IV.

Seven cases, who had VB_{12} levels of 314±182 pg/ml (range: 121-402; <100 pg/ml, n=1; 100-150 pg/ml, n=4; 150-200 pg/ml, n=1; 200-250 pg/ml, n=1), were given a second ''loading'' therapy of 250 μg/week for four weeks, according to the therapy protocol. Those who received a second loading therapy attained a mean VB_{12} level of 880±767 pg/ml (range: 334-2000) at post 2nd loading and 452±126 pg/ml (range: 310- 646) at the pre-maintenance time-points (one month after the end of the ''second loading'' therapy, that is just before the ma''intenance therapy).

The VB_{12} levels of patients who had VB_{12} deficiency at admission and achieved a level of >300 pg/ml before first maintenance (n: 78) and <300 pg/ml (n: 7) are included in Table V. A comparison of IM and oral therapy is presented in Table VI.

Discussion

While most adults can tolerate malabsorption or a VB_{12}-insufficient diet without developing any clinical symptoms for several years, newborns may develop VB_{12} deficiency only a few months after birth due to limited liver storage; especially if maternal intake is restricted throughout pregnancy and if predominantly breast milk is given.[2]

Although most of the VB_{12}-deficient cases have only mild hematological findings, in approximately 10% of patients, life-threatening conditions such as symptomatic pancytopenia, severe anemia can be encountered.[4] Since VB_{12} deficiency is a common public health problem,

Table IV. Patients' response to parenteral therapy (before therapy, post-loading and pre-maintenance).

Time	Vitamin B_{12} level (pg/ml)
Before therapy (pre-loading) [n=100]	171.63 ± 51.2 (83-283)
After loading therapy (post-loading) [n=100]	769 ± 537 (147-2000)
Before first maintenance therapy [n=85] (pre-maintenance: 1 month after loading)	426 ± 156 (116-1100)
>350 pg/ml, n (%)	71/85 (83.6%)
<350 pg/ml, n (%)	14/85 (16.4%)

Data are presented as mean ± standard deviation (minimum - maximum) or n (%) as appropriate.

Table V. Distribution of patients according to initial vitamin B_{12} level groups and pre-maintenance level groups (1 month after loading).

Initial vitamin B_{12} level groups	Pre-maintenance level groups	
	>300 pg/ml (n=78)	<300 pg/ml (n=7)
<100 pg/ml (n: 6)	5 (83.3)	1 (16.7)
100-150 pg/ml (n: 28)	24 (85.7)	4 (14.3)
150 -200 pg/ml (n: 30)	29 (96.7)	1 (3.3)
200 - 250 pg/ml (n: 14)	13 (92.9)	1 (7.1)
250 - 300 pg/ml (n: 7)	7 (100.0)	

Data are presented as n (%).

Table VI. Comparison of intramuscular and oral therapy after loading therapy and after 3 months of maintenance therapy (second loading therapy is not included).

		VB_{12} levels (pg/ml)	
Initial VB_{12} level	Therapy	Post-loading level	Post-maintenance level 30 days after third monthly IM maintenance therapy OR 30 days after the end of oral maintenance therapy
200-250 pg/ml	IM cyanocobalamin (n: 12)	600 ±254	392 ± 32
	Oral cyanocobalamin (n: 3)	1085 ± 627	517± 22
	P value	0.083	0.043
250-300 pg/ml	IM cyanocobalamin (n: 7)	1079 ± 565	796 ± 58
	Oral cyanocobalamin (n:5)	1290 ± 598	585 ± 79
	P value	0.062	0.007

IM: intramuscular, VB_{12}: vitamin B_{12}
Data are presented as mean ± standard deviation.

vitamin B_{12} deficient newborns are detected by using markers for methylmalonic and propionic aciduria by tandem mass spectrometry.[5,6] The incidence of VB_{12} deficiency in these screening programs is 1/30000 in Germany, 1/113600 in U.S, 1/3000 in Estonia and 1/5000 in Italy.[7-10] Routine screening of VB_{12} levels in infants is not performed, however, many important consequences can be seen in its deficiency, especially those involving the central nervous system.

Nevertheless, in our cohort, the incidence of refusal of complementary foods was among the complaints of the mothers, in addition to insomnia and irritability. Those who refuse complementary foods, are irritable, and suffer from insomnia or sleep disturbances should be tested for VB_{12} deficiency, according to our findings. However, a large number of patients in our cohort did not have any complaints (44.3%) and found VB_{12} deficient by chance highlights the importance of routine VB_{12} screening of the infants.

Our careful etiological screening tests revealed maternal VB_{12} deficiency (maternal serum VB_{12} levels <300 pg/ml) in 38 patients, food allergy (cow milk and multiple foods) in 13 patients; and celiac disease in one patient (both the child and the mother). No patient had parasites, amoebas, or *Helicobacter pylori* in stool. No patient had proteinuria suggestive of Imerslund-Grasbek syndrome, although 10% of patients with Imerslund-Grasbek syndrome may not have proteinuria.[11] Consequently, no etiological factor could be identified in 59.6% (77/129) of the patients. This indicates that the etiology of many patients with VB_{12} deficiency cannot be determined in a general sense and that the available laboratory tests are insufficient.[2]

Planned long-term follow-up was in place for those who lacked a definitive etiologic factor.

That 10% of patients (who were on a diet at the time of evaluation) had cow's milk or multiple food allergies suggests that disturbance in the ileum probably involving the CUBAM receptor (cubilin/amnionless) was also present, or that the special diet they consume does not contain enough VB_{12}. Therefore, the risk of VB_{12} deficiency was reported to be high in breastfed infants on a diet excluding cow's milk, whereas complementary foods were associated with a higher B_{12} status.[12] These findings suggest that those with food allergies should be examined for VB_{12} deficiency and closely monitored.

Few studies have examined the association between maternal VB_{12} status in breast-fed infants.[13] Tanyildiz et al.[14] observed signs and symptoms of the central nervous system,

particularly in rapidly growing infants between the ages of 2 and 18 months. A remarkable finding was the simultaneous low levels of VB_{12} in the mothers in 55 of the 69 children who presented with neurological symptoms ($p < 0.05$). The fact that, 98% of patients in our cohort were children aged 0-2 years, indicates that the incidence of VB_{12} deficiency in this age group may be quite high in the pediatric population in our country, and therefore VB_{12} levels should be evaluated at an early stage.

The dramatic drop in post-loading VB_{12} levels 30 days later, at the pre-maintenance time-point, is thought to be due to VB_{12} settling into tissues and rebalancing with blood levels over time. Because of this, we believe that the serum VB_{12} level measured immediately after the loading therapy should be evaluated with caution.

The most common cause of cobalamin deficiency in nursing mothers is vegetarianism. In our series, some mothers stated that they consumed animal-based foods in limited amounts However, close to half (46%) of the mothers in our series had VB_{12} deficiency, which indicates the importance of close monitoring of mothers before and after pregnancy. In our study, 96.1% of patients with VB_{12} deficiency were fed with breast milk and additional food. Our findings are consistent with the fact that VB_{12} deficiency in breast milk is the most common cause of VB_{12} deficiency in infants. In addition to many other side effects, VB_{12} deficiency during pregnancy can also result in the birth of premature babies or babies with a low gestational weight.[15]

In order to prevent the development of VB_{12} deficiency, we believe that mothers should be closely monitored throughout and after pregnancy. It should be noted that the normal value of VB_{12} in adults is estimated to be 300 pg/ml. However, the normal range of VB_{12} in all laboratory kits indicates that the lowest normal level is between 160 and 180 pg/ml, which is significantly below the target level. This is the primary reason, in our opinion, for missing VB_{12} deficiency in previously tested patients. It was remarkable that the mothers of a significant proportion of children with VB_{12} deficiency in our cohort (26.3%) had VB_{12} levels between 200 and 300 pg/ml.

In order to avoid this situation, a general awareness of the lowest level of VB_{12} should be established as a level over 300 and even 350 pg/ml not only in children, but also adults and pregnant and nursing women should be given VB_{12} therapy to provide a VB_{12} level over 300-350 pg/ml. Additionally, women who give birth to SGA or premature babies should definitely be screened for VB_{12} deficiency. Breast milk intake alone restricts VB_{12} intake through additional food, interestingly, the duration of breast milk intake in VB_{12}-deficient infants may be longer when infants refuse complementary food. Although the cause of this behavior is unknown, it is thought to be due to hypotonia and difficulty of consuming solid food in VB_{12} deficient infants.[2]

Therapy for children with VB_{12} deficiency is not uniform. The most common therapy protocol used in our country and in our cohort does not involve a definite criteria of response at the end of the loading therapy, duration of therapy, maintenance therapy. In all protocols patient based follow-up is recommended, leaving the initiative to the doctor.

As a result of the studies in the world and our country over the years, it has been shown that oral VB_{12} treatment is as effective as intramuscular therapy in adults. Also sublingual methylcobalamin was determined as effective as oral and intramuscular cyanocobalamin improving vitamin B_{12} levels aged 0–3 years.[16] In order to administer a standard therapy, we administered the same loading therapy to all patients (a total of 1500 μg cyanocobalamin, as loading). However, for those who had not attained a post-loading level >500 pg/ml, we administered a second induction as it was mentioned before (additional 1000 μg of cyanocobalamin, yielding a total of 2500 μg of loading cyanocobalamine). Thus, the maintenance VB_{12} level could be attained over 300-350 pg/ml.

In the therapy protocol we have administered, a post-loading VB_{12} level below 500 pg/ml is arbitrarily deemed inadequate because the level of VB_{12} achieved at the end of the loading declined by nearly half in every patient; therefore, it is recommended that these patients receive a second loading therapy.

Routine therapy with 100 μg may have unfavorable outcomes in some patients. We think that there is no standard therapy but further investigations should be done. In our cohort, all patients benefited from the treatment. The period of maintenance is controversial and recommended for about one year. Our maintenance period was 1 year. Oral VB_{12} therapy, a novel mode of therapy was also administered in our clinic.[3] The results of eight children who received therapy for four months compared to the parenteral group showed contradictory results.

In conclusion, our study showed that the incidence of VB_{12} deficiency in children between the ages of 0-2 years may be high; therefore, evaluation of VB_{12} level in this age group may be necessary. We think that mothers, should be monitored during and after pregnancy for VB_{12} deficiency (their VB_{12} level should be >300 pg/ml) Babies with VB_{12} levels lower than 150 pg/ml - should be treated with a higher loading dose instead of the classical VB_{12} treatment dose (100 μg or less) These results indicate the need for further controlled studies to determine the ideal maintenance period, screening and prophylaxis for newborns.

Ethical approval

The study was approved by the Başkent University, Medical and Health Sciences Research Ethics Committee (Project number: KA22/215, 02.06.2022) and informed consent was obtained from the families.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation: CK, LO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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