

May solid food refusal and other non-specific neurological symptoms be an early symptoms of Vitamin B12 deficiency in complementary feeding period?

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Abstract

Aim: In this study, we showed an early symptoms of VB12 deficiency in infancy complementary feeding period (CFP) without hematologic findings. Vitamin B-12 (VB12) deficiency can result in severe neurological degeneration within the first year of life. In literature, symptoms of VB12 deficiency in infant were described with hematologic findings which were like a pernicious anemia.

Material and Methods: A 104 of 1,848 mother-infant pairs admitted for well-child visits between January 2018 and December 2018 were included in the study. All babies were diagnosed with vitamin B12 deficiency. All baby-mother pairs were monitored during the CFP were included in the study. Overall, 83 mother who met the inclusion criteria and who agreed to participate in the study and their babies, were included in the study.

Results: The cause of follow-up of these children was refusal to breastfeed and irritability in 21 infants (25.3%). There were 19 infants (22.9%) with solid food refusal, 16 infants (19.2%) with sleeping problems, and 16 infants (19.2%) with failure to thrive. In the remaining 11 infants (13.2%), there were mild hypotonia, microcephalia, vomiting, and growth retardation. The mean age for the development of these symptoms was 5.5 ± 1.7 months, while the mean age of being diagnosed with VB12 deficiency was 6.4 ± 1.2 months.

Conclusions: In this study, symptoms of VB12 deficiency without any hematological symptoms and not caused by other organic causes, and arising during the period of transition to complementary feeding, were demonstrated. Physician must be aware of early findings of VB12 deficiency before severe neurological findings and hematological symptoms.

Keywords: Breastfeeding; deficiency; vitamin B12

INTRODUCTION

Vitamin B-12 (VB12) is a fundamental nutrient required for DNA synthesis, erythropoiesis, brain development and neurological functions. VB12 deficiency can result in severe neurological degeneration within the first year of life (1). While VB12 deficiency is common in adulthood, it is very rarely seen in infancy and childhood. It is particularly more frequently reported in infants born to mothers with VB12 deficiency (2). Although folic acid supplement through nutrients and medication in early pregnancy reduces the incidence of folic acid deficiency, there is no reduction in the prevalence of VB12 deficiency (3). Causes of VB12 deficiency are listed as inadequate intake, insufficient absorption, autoimmune diseases, drug use and rare genetic diseases (4-5). Even though inadequate dietary intake is known as the most frequent cause of the development of VB12 deficiency, there are no definitive recommendations on the routine supplement of VB12 (6).

In the classical presentation of Vitamin B12 deficiency, severe macrocytic anemia, jaundice and neurological symptoms take the stage (1). Numerous hypotheses on the causes of neurological symptoms were discussed in the studies performed after the description of VB12 deficiency for the first time in 1962 (2). Many adults tolerate VB12 deficiency without any symptoms. However, infants born to mothers with VB12 deficiency are born with limited liver reserve and if they are fed breastmilk alone, VB12 deficiency may develop in the months immediately after birth. Although symptoms in infants are observed in the 2nd month the earliest, they typically become prominent between the 4th-10th months. These symptoms are described as irritability, failure to thrive, apathy, anorexia, solid food refusal, megaloblastic anemia and developmental regression (7). The studies in the literature are more focused on neurological symptoms in cases with hematological symptoms (2,8-9).

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The aim of this study is to evaluate to determine an early symptoms of vitamin B12 deficiency and the relationship between the VB12 levels and neurodevelopmental symptoms observed even before the hematological symptoms arise in babies fed with executive breastfeeding for the first 6 months, who were born to mothers who had unknown VB12 levels during pregnancy.

MATERIAL and METHODS

A 108 of 1848 (5.8%) mother-infant pairs admitted for well-child visits between January 2018-December 2018 were included in the study. These mothers are mothers who did not have any problems during their pregnancy, received folic acid supplement, attended routine controls, had their first and singleton pregnancy, and did not have VB12 deficiency history and was not diagnosed VB12 deficiency during pregnancy, and whose VB12 levels are not known. Presence of chronic disease, multiple pregnancy, risky pregnancy, known VB12 deficiency and being vegetarian were the exclusion criteria. Babies who were born term, born within the interbirth interval compatible with the gestational week, were not hospitalized after birth and do not have chronic diseases, were fed breastmilk alone within the first 6 months were included in the study. For the selected mother-infant pairs, all of the well-child visits within the first year after birth was done at a single center by the same pediatrician.

Symptoms such as failure to thrive, irritability, refusing to breastfeed, sleep problems, microcephalia, and growth retardation were considered as neurodevelopmental symptoms. When the clinician detected these symptoms for the first time in the infants' follow-ups, his/her first approach to the problem was to recommend making lifestyle and dietary changes and follow-up the family. When the follow-up started, the family was informed about the study and their consents were obtained. Diseases that might cause current complaints were eliminated. Since the problem persisted and no positive outcomes were attained after making the appropriate changes, blood tests were performed and VB12 levels were analyzed. In this study, serum VB12 levels less than 200 pg/mL (<148 pmol/L) was considered as VB12 deficiency (2). After the parents of the

infants with VB12 deficiency were informed about their children's deficiency, the blood level measurements of the parents themselves were requested. To evaluate VB12, complete blood count, ferritin levels, peripheral smear and proteinuria in infants, complete urinalysis was performed. Test were performed, and complete blood counts (Cell-Dym 1700, Abbott), urinalysis, vitamin B12 and folate levels (Electrochemiluminescence Immunoassay method with Access II), and iron and iron binding capacity in serum (Ferene complex method, Abbott C8000) were evaluated. Treatment for VB12 deficiency was performed according to the National Society of Hematology Guidelines.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Our University Institutional Review and Ethical Board (Project No: KA18/11). Written informed consent was obtained from all subjects/patients.

RESULTS

A total of 104 mother-infant pairs admitted for well-child visits between January 2018 and December 2018 were included in the study. Overall, 83 mothers who met the inclusion criteria and they agreed to participate in the study and their babies, were included in the study. Of the infants, 44.3% were males. The infants' the age of being diagnosed with VB12 deficiency, birth weights, gestational age, maternal age, hemoglobin, mean corpuscular volume (MCV), ferritin and VB12 levels are given in Table 1. When the data in the table were used to compare between the two genders, no significant difference was found between the genders in terms of the age of being diagnosed with VB12 deficiency, birth weight, gestational age, maternal age, hemoglobin, MCV, ferritin and VB12 levels. The mean VB12 levels of all infants was 162,33 pg/ml (SD \pm 29.93). It was found that the peripheral smears of all infants were normal. Moreover, urinalyses performed to check for Imlerslund-Gräsbeck syndrome in children, in whom VB12 deficiency was detected, were normal, and none of them had proteinuria.

Table 1. The infants' the age of being diagnosed with VB12 deficiency, birth weights, gestational age, maternal age, hemoglobin, mean corpuscular volume (MCV), ferritin and VB12 levels

	Male	Female	Total	P
n	39	44	83	
Age (month)	5.99 \pm 1.97	6.24 \pm 1.57	6.11 \pm 1.53	>0.05
Birth weight (gr)	3109 \pm 241	3258 \pm 112	3191 \pm 282	>0.05
Gest Age (week)	38.4 \pm 0.5	38.6 \pm 1.1	38.5 \pm 0.97	>0.05
Maternal Age (year)	30.9 \pm 3.27	30.8 \pm 2.7	30.8 \pm 2.97	>0.05
Hemoglobin (g/dl)	11.4 \pm 0.83	11.7 \pm 0.82	11.72 \pm 0.77	>0.05
MCV (fl)	76.64 \pm 5.54	78.86 \pm 4.15	77.55 \pm 5.23	>0.05
Ferritin (ng/ml)	28.2 \pm 10.5	34.14 \pm 12.95	32.14 \pm 14.5	>0.05
Vitamin B12 (pg/ml)	160.05 \pm 28.1	156.07 \pm 31.6	162.33 \pm 21.2	>0.05

The cause of follow-up of these children was refusal to breastfeed and irritability in 21 infants (25.3%). There were 19 infants (22.9%) with solid food refusal, 16 infants (19.2%) with sleeping problems, and 16 infants (19.2%) with failure to thrive. In the remaining 11 infants (13.2%), there were mild hypotonia, microcephalia, vomiting, and growth retardation. The mean age for the development of these symptoms was 5.5 ± 1.7 months, while the mean age of being diagnosed with VB12 deficiency was 6.4 ± 1.2 months. When the other causes (e.g. gastrointestinal disease, malabsorption, etc.) leading to these complaints were excluded, VB12 treatment was prescribed. The treatment was performed according to the National Society of Hematology Guidelines. Oral treatment was provided, with 1000 µg/day cyanocobalamin every day for 1 week, followed by two days a week for 2 weeks, then once a week for 1-2 weeks, and finally, monthly. Since severe hypocalcemia and/or sudden death in adults can be seen at the beginning of vitamin B12 treatment (first 48 hours), infants were closely monitored, and in cases of severe deficiency, the treatment was provided in small doses. Within an average of one month after starting the treatment, it was found that the complaints regressed. Control VB12 levels were restored to normal. It was found that the parents did not have VB12 deficiency. At the third month of treatment, symptoms disappeared completely. The mean vitamin B12 level after the treatment was 652.55 pg/ml (SD ± 98.22). The mean vitamin b12 level of mothers was 357,25 pg/ml (SD ± 32.52).

DISCUSSION

In this study, in babies admitted with nonspecific symptoms such as refusal to breastfeed, solid food refusal, failure to thrive, sleep problems and constipation even before the hematological symptoms such as anemia and elevated MCV arose, serum VB12 levels were found to be low. Regression of symptoms after the treatment corroborated the diagnosis. In this study, symptoms of VB12 deficiency without any hematological symptoms and not caused by other organic causes, and arising during the period of transition to complementary feeding, were demonstrated. VB12 deficiency is more commonly diagnosed in adults than the infants and children (8). Since it causes permanent neurological damages particularly in infants, it must be diagnosed early and treated. Recently, there have been studies reporting that V12 deficiency rarely causes growth retardation, irritability, weakness (10-11). Katar et al. have described the neurological and psychiatric symptoms in children with vitamin B12 deficiency (9). However, it is very important that the clinicians who follow-up the infants consider the risk factors and recognize VB12 deficiency early when identifying the causes of certain problems that arise during this period.

Causes of VB12 deficiency are described as reduced intake, insufficient absorption, autoimmune diseases, drug use and rare genetic diseases (4-5). Since DNA synthesis is affected, rapidly proliferating hematopoietic

cells are affected early (12). Without any hematological changes, presence of neurological changes such as paresthesia, sensory deficits, loss of deep tendon reflexes, hypotonia, growth retardation, seizures, depression and mobility disorders has been reported in case studies (13-15). Moreover, failure to thrive, irritability, systolic murmur, glossitis, weakness, constipation, diarrhea and icterus were observed in these patients (16-17). The causes of almost all of these symptoms in the literature are reported as maternal vitamin B12 deficiency during pregnancy, the mother being vegetarian or postnatal inadequate intake (13-17). It was reported that these symptoms are mostly accompanied by hematological symptoms and the cases have multiple symptoms (9). In our study, while none of the infants had any VB12 deficiency-related hematological symptoms, the most common symptoms were refusal to breastfeed and irritability, solid food refusal, sleep problems and failure to thrive. There were rare cases of mild hypotonia, microcephalia, vomiting, and growth retardation. Before associating these symptoms with VB12 deficiency, the absence of other organic pathologies that can cause these symptoms was demonstrated. These symptoms were considered as neurodevelopmental symptoms and VB12 treatment was prescribed. It was found that the symptoms regressed at an average of one month after the initiation of treatment. At the third month, all of the symptoms disappeared.

While the mean age of symptom onset in these children was 5.5 ± 1.7 months, the mean age of diagnosis of VB12 deficiency was 6.4 ± 1.2 months. In the study by Katar et al., the mean age of diagnosis of psychomotor retardation in children diagnosed with nutritional megaloblastic anemia was 16.4 months (9). In a study performed in India, it was reported that the age of onset of anemia and neurodevelopmental retardation in children born to mothers with inadequate intake during pregnancy can vary between 3 to 8 months (18). While it was reported that hematological symptoms respond to treatment dramatically and recover without any complications, there are studies reporting that if diagnostic delay occurs after the 12th month of life, neurological damage can be irreversible. Thus, early diagnosis and treatment are very important (2,19-20). In this study, it was found that infants who only receive breastmilk during the first 6 months of their life show increased irritability and refusal to breastfeed towards the period of initiation of complementary feeding. Then, in the period of transition to complementary feeding, it was found that they show solid food refusal. It was found that a total of 40 infants (48.2%), with 21 infants (25.3%) showing refusal to breastfeed and irritability and 19 infants (22.9%) showing solid food refusal did not lose any weight but had difficulties during this transition period. These symptoms are symptoms that are observed particularly more frequently during the complementary feeding period. They can easily seem like nonspecific symptoms that can be prevented and monitored without performing any tests. If the complaints persist after the

appropriate changes in parents' attitudes and feeding attitude education, VB12 deficiency must be considered. If deficiency is detected, preventive measures can be taken. The results of this study emphasize that VB12 deficiency must be considered when there are nonspecific symptoms during the complementary feeding period.

It was observed that after VB12 treatment, the remaining 11 infants recovered from sleeping problems, failure to thrive and mild hypotonia, microcephalia, vomiting and growth retardation. While hematologic symptoms such as macrocytic anemia are expected in these patients, none of the patients had any symptoms indicating pernicious anemia in their whole blood counts and peripheral smears. All infants in the study were babies receiving iron prophylaxis since the 4th month of their lives. There are studies in the literature in which pancytopenia is observed in addition to the symptoms of pernicious anemia (9, 21). Although sleep problems mostly arise due to behavioral problems, organic causes of disease must not be overlooked (2). In the study, family education was provided for 16 infants with sleep problems, and organic causes that can lead to sleep problems were investigated. It was found that after VB12 treatment, sleep problems of these infants disappeared.

One of the important points in this study is that mothers stated that they received folic acid supplement alone during pregnancy, but they did not know their VB12 levels before or during the pregnancy. Although there are no tests for VB12 levels in the current routine pregnancy follow-ups, the probability of VB12 deficiency must be considered if there are nonspecific neurodevelopmental symptoms. The requirement for controlling VB12 levels or dietary supplement during pregnancy follow-ups and breastfeeding period is open to debate. None of the mothers had their VB12 levels monitored during pregnancy. There were no known histories of VB12 deficiency or restrictive diet. It was found that mothers who required VB12 received iron supplement for approximately 1 month after the delivery, and received vitamin D supplement for up to 6 months after the delivery. It is known that there is inadequate VB12 intake in both of the adult and child groups. Since VB12 deficiency is mostly caused by reduced consumption of animal source foods such as meat, milk, egg and fish, it is reported more frequently among the lower-middle income group. Deficiency is clearly defined in individuals who are definitive vegans and vegetarians (2, 8, 22). Mothers included in the study had from middle-high socioeconomic status, were neither vegan nor vegetarian, and attended routine controls during their pregnancies. Early recognition of infants with unknown prenatal VB12 status but unexplained neurodevelopmental symptoms before hematological symptoms arise and irreversible neurological damage occurs is important. Infants who are fed breastmilk alone are under a bigger risk than those fed with formula. In addition, particularly the mother's failure to intake or inadequate intake of animal source

foods, foods fortified with VB12, and VB12 supplement during lactation period causes a pronounced VB12 deficiency (22-24). Moreover, in their study on Kenyan mothers, Williams et al. showed that VB12 levels in the breastmilk of mothers with unknown prenatal VB12 status are correlated with the serum VB12 levels of the infants. It was stated that even if their prenatal VB12 status is unknown, supplement for mothers with low socioeconomic status during lactation period is important (26). In our study, it was found that although the prenatal VB12 status of mothers with middle-high socioeconomic status is not known, it was normal during the lactation period. Although VB12 deficiency among these children can be attributed to prenatal deficiency, it can be said that these mothers can restore their VB12 levels to normal via their diets alone, without taking any VB12 supplement. With the emphasis on maternal diet particularly during the period of breastfeeding, it can be said that mothers pay more attention to their diets. Moreover, since the VB12 level in breastmilk is not known, it cannot be said whether the daily requirement of the infant is met. Although not significant, VB12 deficiency is particularly more frequent among infants that put on 30 gr/day and more, and therefore it can be concluded that VB12 requirement of these infants increase due to rapid weight gain but the VB12 level in breastmilk cannot meet this requirement. Moreover, even though the causes of malabsorption in these children are ruled out, their long-term follow ups are critical. They can have intestinal diseases with symptoms arising later in life. Furthermore, these babies can have polymorphisms that affect absorption. In their study, Finkelstein et al. showed that maternal folic acid levels pose a low risk for VB12 deficiency in the infant. It was reported that both folic acid and VB12 supplement in mothers are important (26). Similarly, in our study, it was found that VB12 supplement for mothers is very important because of its potential outcomes in the infants.

CONCLUSION

In conclusion, early recognition of infants with unknown prenatal VB12 status but unexplained neurodevelopmental symptoms before hematological symptoms arise and irreversible neurological damage occurs is important. Once the other organic causes are ruled out, neurodevelopmental complaints such as irritability, refusal to breastfeed, solid food refusal must be followed up closely. The requirement of VB12 supplement for mothers, particularly in the prenatal and postnatal period, must be taken into consideration.

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