Iran J Pediatr. 2017 October; 27(5):e12898. doi: 10.5812/ijp.12898.

Published online 2017 October 22. **Research Article**

How Does B_{12} Deficiency of Mothers Affect Their Infants?

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Received 2017 May 09; **Revised** 2017 July 26; **Accepted** 2017 August 14.

Abstract

Background: Vitamin B_{12} cannot be synthesized in the body and it is essential for growth and development in humans.
Objectives: To evaluate the vitamin B_{12} levels between the mothers and their infants who presented to the Pediatric Hematology outpatients department due to the symptoms of vitamin B_{12} deficiency. We also compared the effects of low B_{12} levels in both the mother and the child, compared to the effects of normal B_{12} levels in the mother and low levels in the child.
Methods: We enrolled 303 children aged 2 - 18 months between January 2013 and September 2015. Patients with a vitamin B_{12} level < 200 pg/mL in both the mother and the child and patients with a B_{12} level that was low in the child and normal in the mother were compared.
Results: The birth weight of the children was low in the group where the B_{12} level of both the mother and the child (n = 163) was low and presentation to the clinic with neurologic signs and symptoms such as tremor, restlessness, seizure, hypotonia, and macrocephaly not related to another etiologic reason was common ($P < 0.05$). A remarkable finding was the simultaneous low levels of vitamin B_{12} in the mother in 55 of the 69 children who presented with neurological symptoms ($P < 0.05$). A generalized or focal epileptic pathology was found in the EEGs and MR images including retardation in myelination, demyelination, atrophic findings or ventricular dilatation in children whose mothers have B_{12} deficiency simultaneously.
Conclusions: It is difficult to explain such complicated clinical pictures due to malnutrition especially in developing countries. Detecting and treating vitamin B_{12} deficiency early in mother and child is very important in prevention of potential irreversible neurological problems.

Keywords: Vitamin B_{12}, Infancy, Clinical aspects

1. Background

Vitamin B_{12} cannot be synthesized in the body and is essential for growth and development in humans; therefore, vitamin B_{12} must be supplied by diet. B_{12} deficiency that is related to insufficient red meat consumption or malabsorption can be seen in adults; however, this deficiency can be tolerated in adults and the symptoms take a long time to manifest. The most important reason for infant vitamin B_{12} deficiency is maternal B_{12} deficiency. For example, the babies of vegetarian mothers and those with intestinal malabsorption or a cobalamin transport defect will be born with deficient B_{12} storage, and the deficiency symptoms can therefore appear within the first 6 months of life (1-5). In older children, other factors may be associated with vitamin B_{12} deficiency, such as the absence of animal derived foods or fortified foods, a vegetarian diet, low socioeconomic level and infection by gastrointestinal parasites (6).

Vitamin B_{12} deficiency mainly affects the central nervous system (due to its rapid mitotic activity), the hematopoietic system, and the gastrointestinal system. Vitamin B_{12} is especially involved in essential functions of the central nervous system, such as DNA synthesis, the homocysteine methylation cycle, and neurotransmitter synthesis. B_{12} is therefore important for enabling central nervous system functions, and it is not surprising that central nervous system deficits appear in vitamin B_{12}-deficient infants. B_{12} deficiency can cause growth retardation, neutropenia, skin lesions, frequent infections, tremors, irritability, hypotonia, and seizure, among other symptoms (7-11). Simultaneous investigation of the mother and infant especially an infant breastfed by a mother with vitamin B_{12} deficiency is important for the early detection of vitamin B_{12} deficiency and initiation of nutritional support before significant neurological symptoms develop. We, therefore, first aimed to evaluate the vitamin B_{12} levels between the mothers and their infants who presented to the pediatric hematology outpatients department due to the symptoms of vitamin B_{12} deficiency. We also compared the effect of low B_{12} levels in both mother and child, compared to that of normal B_{12} levels in the mother and low levels in the child.

2. Methods

2.1. Study Population and Study Design

We enrolled 303 mother-infant pairs who presented to the pediatric hematology outpatients department from January 2013 to September 2015. The study design was cross sectional. A structured questionnaire was administered through face-to-face interview to the mothers. It included demographic characteristics (child's sex, age, etc), socio-economic status, history of breastfeeding, frequency of habitual food intake, and birth weight of the infant. Accompanying presenting symptoms and signs (growth retardation, loss of appetite, frequent infection, hypotonia, irritability, and seizures) were also queried. EEG and MR evaluations were performed for patients with neurological signs and symptoms and results registered. Those with a different underlying chronic disease such as a metabolic, hematologic or neurologic disorder were excluded. Group 1 represented low B_{12} levels in both the mother and child while Group 2 represented normal B_{12} levels in the mother and low levels in the child. We compared two groups in terms of presenting signs and symptoms. Approval from the ethics committee and consent from the families were obtained.

2.2. Anthropometric Assessment

Anthropometric measurements (presentation weight, height, head circumference) were performed by trained pediatric assistants following standardized procedures using calibrated equipment. Among children aged < 24 months, recumbent length was measured using a locally made infant measuring board; weight was measured with an electronic pediatric scale. Each measurement was repeated and the mean value was calculated.

2.3. Biochemical Measures

Peripheral smear, blood count, and serum vitamin B_{12}, folic acid, homocysteine, iron and LDH levels were evaluated for the diagnosis of B_{12} deficiency. Blood B_{12} levels of the mothers of the same patients were also determined at the time of diagnosis. Approximately 5 mL of fasting venous blood was collected from mother-infant pairs by nurses. Serum folate and vitamin B_{12} concentrations were measured using the method of direct chemiluminescence (ADVIA Centaur XP, SIEMENS Immunoassay). This method offers high sensitivity and is less costly, easier to implement and safer than microbiological, chromatographic or spectrophotometric assays (12). A level of 200 pg/mL was identified as the cut-off B_{12} level.

2.4. Statistical Methods

Data analysis was performed using the SPSS for Windows 15 package software (Chicago, IL; SPSS, ©2006). Descriptive statistics were presented as the mean ± standard deviation for variables with a normal distribution and as the median (minimum - maximum) for variables without a normal distribution. Nominal variables were presented as the number of patients and percentages.

When there were two groups, the significance of the difference between mean values was evaluated using student's t test and the significance of the difference between median values was evaluated using the Mann-Whitney U test. Categorical variables were compared with dependent variables using Logistic Regression analysis. A P value < 0.05 was accepted as statistically significant.

3. Results

There were 190 (62.7%) male and 113 (37.3%) female patients. The age range was 2 month to 18 months (median = 7 months). The mean B_{12} level was 127.34 ± 31.153 (45 - 199) pg/mL in the mothers and 150.72 ± 32.43 (45 - 196) pg/mL in the children when the B_{12} level was under 200 in both the patient and the mother (Group 1). The mean B_{12} level was 283.81 ± 81.52 (200 - 600) pg/mL in the mothers and 158.07 ± 29.38 (46 - 199) pg/mL in the children when the B_{12} level was normal in the mother but low in the child (Group 2). The mean birth weight was 2778 ± 625 (1000 - 4280) gr in the group 1, and 2986 ± 545 (1300 - 4200) gr in the group 2 (P = 0.001) (Table 1).

No significant relationship with vitamin B_{12} level was found in terms of weight, height and head circumference at the time of diagnosis. The presenting symptoms of the patients were anemia in 62.3% (n = 189) patients, seizure in 9.9% (n = 30), hypotonia in 7.9% (n = 24), growth retardation in 4.3% (n = 13), tremor in 0.7% (n = 2), irritability in 2% (n = 6). The presenting signs were macrocephaly in 2.3% (n = 7), dermatitis in 2.3% (n = 7), frequent lower respiratory tract infection in 1.3% (n = 4), loss of appetite in 0.3% (n = 1), and pica in 0.3% (n = 1) patients. Neutropenia in 5.9% (n = 18) and thrombocytopenia in 0.3% (n = 1) patients were observed (Table 2). Anemia, neutropenia and thrombocytopenia improved following vitamin B_{12} treatment. A total of 55 children presented with neurological symptom in Group 1, but these symptoms were manifested in only 14 children in Group 2 (P = 0.000). The neurologic signs and symptoms were macrocephaly (n = 6), irritability (n = 6) and tremor (n = 2) in Group 2 whereas neurologic signs and symptoms were mostly seizure (n = 30), hypotonia (n = 24) and macrocephaly (n = 1) which were more complex in Group 1. The clinic distribution of the 30 patients with seizure was generalized tonic clonic seizure in 18, generalized tonic seizure

Table 1. Mean B_{12} Levels and Birth Weights in Group 1 and Group 2[a]

	Patient B_{12} Level pg/mL, Mean ± SD (Range)	Mother B_{12} Level pg/mL, Mean ± SD (Range)	Birth Weight (gr), Mean ± SD (Range)
Patient < 200 pg/mL	150.72 ± 32.43	127.34 ± 31.153	2778 ± 625
Mother < 200 pg/mL	(45 - 196)	(45 - 199)	(1000 - 4280)
Patient < 200 pg/mL	158.07 ± 29.38	283.81 ± 81.52	2986 ± 545
Mother ≥ 200 pg/mL	(46 - 199)	(200 - 600)	(1300 - 4200)

[a] P value = 0.001; Group 1, The B_{12} level was under 200 in both the patient and the mother; Group 2, The B_{12} level was normal in the mother but low in the child.

in 6 and simple partial seizure in 6 patients. EEG abnormalities were found in 12 patients; generalized epileptic activity was observed in 9 of them and focal epileptic activity in 3. A total of 69 patients with neurologic symptoms in both Group 1 and 2 underwent a MR evaluation, and 55 of these patients were in Group 1. Retardation in myelination (n = 18), demyelination (n = 4), thinning of the corpus callosum (n = 16) or ventricular dilatation (n = 7) findings were present on MR in Group 1 patients. No pathological findings were found in the remaining 10 patients (Table 3). Patients presented with macrocephaly (n = 6), irritability (n = 6) and tremor (n = 2) in Group 2. MR findings included ventricular dilatation (n = 3), retardation in myelination (n = 2) and normal (n = 9) results (Table 4). The logistic regression test revealed a close to significant or significant relationship in terms of low birth weight (P = 0.069) (OR; 1.0, 95% CI (0.99 - 1.0)), breastfeeding (P = 0.058) (OR; 2.27, 95% CI (0.972 - 5.333)) and frequent neurological signs and symptoms (P = 0.000) (OR; 4.1, (95% CI 2.11 - 7.96)) in Group 1 (Table 5).

4. Discussion

Optimal vitamin B_{12} status during infancy is important for many aspects of child health, growth and development. Infants are dependent on the mother for vitamin B_{12} during pregnancy and while breastfeeding. B_{12} is transmitted from the mother to the infant especially through the transplacental route and stored in sufficient quantities to meet the needs of the child during the first 12 months. The symptoms of deficiency are therefore usually not seen in the initial 6 - 12 months of life in a healthy child; therefore, deficiency in the first 6 - 12 months only occurs in infants with maternal vitamin B_{12} deficiency (1, 13, 14). B_{12} deficiency not treated during pregnancy can lead to growth retardation, hypotonia, important neurological and functional losses in infants, and the symptoms can be permanent if only detected at a late stage (15).

Prevention of common vitamin deficiencies in the first two years of age is an important priority for developing countries. The relatively low concentrations of plasma vitamin B_{12} in younger infants identified by this study may be due to low maternal intake of vitamin B_{12} rich foods during pregnancy and lactation. Cultural beliefs and food taboos restrict intake of foods that are rich in vitamin B_{12} during pregnancy and breastfeeding, and low consumption of meat, fish and other animal source foods may also cause poor maternal nutritional status during pregnancy and breastfeeding. Furthermore, the relatively low coverage of vitamin B_{12} supplementation in younger children (6 to 12 months) may also contribute to the low concentrations of plasma vitamin B_{12} reported in this population (16).

Some studies suggest that vitamin B_{12} deficiency and marginal deficiency are highly prevalent worldwide and vitamin B_{12} deficiency is also of public health concern. Vitamin B_{12} deficiency may be more prevalent in vegetarians, vegans, and people living in low-income communities where they may have limited purchasing power to acquire animal food sources or may not have access to fortified foods or supplements (17, 18). Koc et al. found B_{12} deficiency in 41% of newborns in the Southeastern Anatolia Region of Turkey where B_{12} deficiency is common (5). They emphasized that detecting B_{12} deficiency and its early treatment in the regions where the socioeconomic level is low is important to prevent any developmental sequelae that could develop in the baby. Vitamin deficiency during pregnancy in the mother has similarly been reported to affect the infant starting in the intrauterine period in many studies (19, 20).

Although there is no complete consensus regarding the normal cut-off level of vitamin B_{12}, we accepted < 200 pg/mL as the cut-off in laboratory evaluations (21). We found vitamin B_{12} deficiency in 163 (53%) mothers of the 303 patients who were diagnosed with B_{12} deficiency under the age of two years. The most important characteristics in the group with low B_{12} level in both the mother and infant was the low birth weight of the infants (P = 0.001). Similar results are reported in different studies because the B_{12} deficiency of the mother during pregnancy may lead to many

Table 2. Clinical Symptoms, Signs and Results of investigation at Presentation in Group 1 and Group 2[a]

	Patient < 200 pg/mL, Mother < 200 pg/mL	Patient < 200 pg/mL, Mother ≥ 200 pg/mL	Total
Anemia	89 (54.6%)	100 (71.4%)	189 (62.4%)
Neurological symptoms	55 (33.7%)	14 (10.0%)	69 (22.8%)
Growth retardation	3 (1.8%)	13 (9.3%)	16 (5.3%)
Increased infections	3 (1.8%)	1 (0.7%)	4 (1.3%)
Dermatitis	3 (1.8%)	4 (2.9%)	7 (2.3%)
Neutropenia	10 (6.1%)	8 (5.7%)	18 (5.9%)
Total	163 (100%)	140 (100%)	303 (100%)

[a] P Value = 0.009.

Table 4. Neurologic Signs at Presentation in the Group 2 Patients

Patient No.	Neurologic Signs	MR Results
1	Macrocephaly	Normal
2	Macrocephaly	Ventricular dilatation
3	Macrocephaly	Normal
4	Macrocephaly	Normal
5	Macrocephaly	Ventricular dilatation
6	Macrocephaly	Ventricular dilatation
7	Irritability	Normal
8	Irritability	Retardation in myelination
9	Irritability	Normal
10	Irritability	Normal
11	Irritability	Normal
12	Irritability	Retardation in myelination
13	Tremor	Normal
14	Tremor	Normal

metabolic and neurological problems starting with the intrauterine period and especially low birth weight in the newborn (22, 23).

The vitamin B_{12} levels in breast milk and the mother are parallel in the lactation period and sufficient B_{12} cannot be obtained from breast milk (the most important B_{12} source of the infant) when the mother has B_{12} deficiency (24). We found that 274 children had received breast milk regularly during the first 3 - 6 months; breastfeeding was not regular and formula was started early in the other 27 patients. We found a high rate (91%) of breastfeeding in the group with low vitamin B_{12} levels in both the mother and the child in our study (P = 0.058). The deficiency in the mother affects the baby during the intrauterine period at the first stage and complicated clinical pictures can be encountered if the deficiency is not treated during the breast feeding period.

The cells that are mostly affected by vitamin B_{12} deficiency are the central nervous system cells with rapid mitotic activity. The clinical findings include lethargy, apathy, hypotonia, tremor, and convulsions. In individuals with B_{12} deficiency, methylmalonyl-CoA accumulates and is used in the synthesis of fatty acids instead of acetyl-CoA. This results in unstable myelin that degrades more easily and negatively affects the brain development and cognitive performance of growing children (25).

The exact mechanism underlying neurological deficits in Vitamin B_{12} deficiency is not clearly understood. However, vitamin B_{12} deficiency is thought to cause imbalance between the growth factors influencing the central nervous system and neurotoxic cytokines, and increased lactate, glutamate and excitatory amino acids (26-28). There-

Table 5. Logistic Regression Results with OR and P Value

	OR	95% CI		P Value
		Lower	Upper	
Birth weight	1.00	0.999	1.000	0.069
Breastfeeding	2.27	0.972	5.333	0.058
Neurologic signs	4.10	2.113	7.961	0.000

fore, epilepsy is triggered and EEG abnormalities are manifestations of vitamin B_{12} deficiency in pediatric patients. Several studies currently exist describing an association between vitamin B_{12} deficiency and EEG abnormalities and epilepsy (29-34). We encountered central nervous system signs and symptoms especially in rapidly growing infants in the early period between 2 and 18 months. A remarkable finding was the simultaneous low levels of vitamin B_{12} in the mother in 55 of the 69 children who presented with neurological symptoms ($P < 0.05$). The presenting signs and symptoms of these 55 patients were seizure, hypotonia, and macrocephaly. The type, severity and duration of involuntary movements related to vitamin B_{12} deficiency varies considerably. In this study seizures types were generalized tonic clonic, generalized tonic and simple partial. EEG evaluations of the 30 infants revealed generalized epileptic activity in 9 and focal activity in 3. Atrophy of corpus callosum, retardation in myelination, demyelination areas and ventricular dilatation findings were seen on the MR images. Cortical atrophy, hypoplasia of the corpus callosum, delayed myelination, and ventricular dilatation are the most common neuroradiological findings in the literature (3, 30, 31, 34). Patients only presented with macrocephaly, irritability and tremor and we did not observe any seizure in the group where B_{12} levels of mothers were normal. MR findings were mostly normal apart from ventricular dilatation and demyelination. Neurologic findings were more severe and complex in the group where B_{12} levels were low both in the mother and infant rather than the group where B_{12} levels normal in mother. The fact that neurological symptoms can be detected before the emergence of megaloblastic anemia symptoms is critical for clinicians. The rate of presentation with neurologic findings but without anemia was high in studies conducted on adults. Anemia may not be a presenting symptom or its rate can be lower than other symptoms (2, 9, 35). However, the most common symptom in this study was anemia (62.4%) followed by neurological findings (22.8%). Although there is no clear consensus regarding the treatment of vitamin B_{12} deficiency, we administered vitamin B_{12} parenterally to our patients as recommended. The dose was 100 μg per day for 7 days, 100 μg per week for 4 weeks, and then 100 μg per month for 3 months (1, 36). The mothers were also prescribed vitamin B_{12} parenterally. The head circumference of 3 of the 7 patients that had presented with macrocephaly was within the normal percentile range during follow-up. Those who showed the fastest response to vitamin B_{12} treatment were the hypotonia and tremor patients. The seizures did not recur, and the antiepileptic drugs were discontinued during the follow-up with vitamin B_{12} treatment in patients who had experienced a generalized tonic clonic seizure. No other complications were observed during a median follow-up duration of 1 year (6 months to 2.5 years).

Detecting B_{12} deficiency and starting treatment early is important for preventing irreversible symptoms. B_{12} deficiency in mothers particularly is a risk factor in infants developing neurologic symptoms, thus mothers should be checked after delivery and during lactation as well as their infants. Nutritional deficiency patients can present with confusing signs and symptoms such as macrocephaly or microcephaly, hypotonia, tremor, irritability, and seizure that can make things difficult for the clinicians and require further investigations for the differential diagnosis. Physicians should be aware that attempts to solve the problem should start during pregnancy, and a social consciousness needs to be developed to prevent B_{12} deficiency. It is known that irreversible complications can develop if the diagnosis and treatment of B_{12} deficiency are delayed. Early screening of blood vitamin B_{12} levels will obviously improve the health of mother and child and make things easier for clinicians.

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Table 3. Neurologic Signs and Symptoms at Presentation in Group 1 Patients

No.	Symptoms	Type of Seizure	EEG Results	MR Results
1	Seizure	GTC	GEA	Retardation in myelination
2	Seizure	GTC	GEA	Demyelination
3	Seizure	GTC	GEA	Atrophy of corpus callosum
4	Seizure	GTC	Normal	Atrophy of corpus callosum
5	Seizure	GTC	Normal	Retardation in myelination
6	Seizure	GTC	Normal	Ventricular dilatation
7	Seizure	GTC	Normal	Atrophy of corpus callosum
8	Seizure	GTC	GEA	Demyelination
9	Seizure	GTC	GEA	Ventricular dilatation
10	Seizure	GTC	Normal	Retardation in myelination
11	Seizure	GTC	Normal	Ventricular dilatation
12	Seizure	GTC	Normal	Retardation in myelination
13	Seizure	GTC	Normal	Normal
14	Seizure	GTC	GEA	Atrophy of corpus callosum
15	Seizure	GTC	Normal	Atrophy of corpus callosum
16	Seizure	GTC	Normal	Atrophy of corpus callosum
17	Seizure	GTC	GEA	Ventricular dilatation
18	Seizure	GTC	Normal	Ventricular dilatation
19	Seizure	GT	FEA	Retardation in myelination
20	Seizure	GT	Normal	Retardation in myelination
21	Seizure	GT	Normal	Normal
22	Seizure	GT	GEA	Demyelination
23	Seizure	GT	Normal	Normal
24	Seizure	GT	GEA	Atrophy of corpus callosum
25	Seizure	simple partial	Normal	Atrophy of corpus callosum
26	Seizure	simple partial	FEA	Normal
27	Seizure	simple partial	Normal	Retardation in myelination
28	Seizure	simple partial	FEA	Normal
29	Seizure	simple partial	Normal	Retardation in myelination
30	Seizure	simple partial	Normal	Atrophy of corpus callosum
31	Hypotonia	-	-	Normal
32	Hypotonia	-	-	Retardation in myelination
33	Hypotonia	-	-	Atrophy
34	Hypotonia	-	-	Retardation in myelination
35	Hypotonia	-	-	Retardation in myelination
36	Hypotonia	-	-	Demyelination
37	Hypotonia	-	-	Normal
38	Hypotonia	-	-	Atrophy of corpus callosum
39	Hypotonia	-	-	Retardation in myelination

40	Hypotonia	-	-	Normal
41	Hypotonia	-	-	Atrophy of corpus callosum
42	Hypotonia	-	-	Atrophy of corpus callosum
43	Hypotonia	-	-	Retardation in myelination
44	Hypotonia	-	-	Retardation in myelination
45	Hypotonia	-	-	Atrophy of corpus callosum
46	Hypotonia	-	-	Normal
47	Hypotonia	-	-	Retardation in myelination
48	Hypotonia	-	-	Retardation in myelination
49	Hypotonia	-	-	Atrophy of corpus callosum
50	Hypotonia	-	-	Ventricular dilatation
51	Hypotonia	-	-	Normal
52	Hypotonia	-	-	Retardation in myelination
53	Hypotonia	-	-	Atrophy of corpus callosum
54	Hypotonia	-	-	Retardation in myelination
55	Macrocephaly	-	-	Ventricular dilatation

Abbreviations: FEA, focal epileptic activity; GEA, generalized epileptic activity; GT, generalized tonic; GTC, generalized tonic clonic.