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Visual and brainstem auditory evoked potentials in infants with severe vitamin B_{12} deficiency

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Background/aim: Vitamin B_{12} plays an important role in the development of mental, motor, cognitive, and social functions via its role in DNA synthesis and nerve myelination. Its deficiency in infants might cause neuromotor retardation as well as megaloblastic anemia. The objective of this study was to investigate the effects of infantile vitamin B_{12} deficiency on evoked brain potentials and determine whether improvement could be obtained with vitamin B_{12} replacement at appropriate dosages.

Materials and methods: Thirty patients with vitamin B_{12} deficiency and 30 age-matched healthy controls were included in the study. Hematological parameters, visual evoked potentials, and brainstem auditory evoked potentials tests were performed prior to treatment, 1 week after treatment, and 3 months after treatment.

Results: Visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) were found to be prolonged in 16 (53.3%) and 15 (50%) patients, respectively. Statistically significant improvements in VEP and BAEP examinations were determined 3 months after treatment. Three months after treatment, VEP and BAEP examinations returned to normal in 81.3% and 53.3% of subjects with prolonged VEPs and BAEPs, respectively.

Conclusion: These results demonstrate that vitamin B_{12} deficiency in infants causes significant impairment in the auditory and visual functioning tests of the brain, such as VEP and BAEP.

Key words: Vitamin B_{12} deficiency, infant, visual evoked potentials, auditory evoked potentials

1. Introduction

Vitamin B_{12} is commonly found in foods of animal origin and is not synthesized in the human body. Vitamin B_{12}, along with folic acid, participates in DNA synthesis and plays a role in nerve myelination, cell division, and proliferation. In babies exclusively fed with breast milk, the most common cause of vitamin B_{12} deficiency is insufficient intake from vegetarian or vegan mothers who do not consume foods of animal origin (1). The severity of clinical symptoms is directly related to the severity of vitamin B_{12} deficiency in the mother (2). The most common findings of vitamin B_{12} deficiency are hematological and neurological signs. Several studies have reported that these neurological signs might be caused by demyelination, dysmyelination, and axonopathy (3). Abnormalities of visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) develop secondarily to demyelination and axonopathy caused by vitamin B_{12} deficiency. The persistence of VEP and BAEP abnormality in the deficiency of vitamin B_{12} might be associated with delayed diagnosis of vitamin B_{12} deficiency and advanced neurological picture (3–6). The other findings are as follows: growth-developmental retardation, gastrointestinal motility disorders (diarrhea), hyperpigmentation, stomatitis, glossitis, irritability, weakness, lethargy, hypotonia, ataxia, hyporeflexia, tremor, convulsion, movement disorders, abnormal mental states, retardation in acquired motor skills, and coma (2,4,7–9).

We could not find any controlled study in the literature about the effects of vitamin B_{12} deficiency on the evoked brain potentials in infants. Thus, in this study we aimed to determine the effects of vitamin B_{12} deficiency on VEP and BAEP in infants, and to investigate the results of treatment.

2. Materials and methods

2.1. Patient selection

A total of 30 infants aged 6–24 months with retardation of mental, motor, cognitive, and social functions and diagnosed with moderate or severe vitamin B_{12} deficiency

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were included in the study. Because vitamin B_{12} deficiency causes retardation of mental, motor, cognitive, and social development, the serum vitamin B_{12} levels of these patients were checked. A total of 30 healthy age-matched infants were enrolled in the study as the control group. Written informed consent was obtained from the families of each subject. Detailed nutrition and developmental history was obtained for each child, and the level of physical development was determined with a physical examination. Weight, height, and head circumferences were measured in each infant, and physical development by age was determined using the percentile curves developed by Neyzi et al. (10). This study was performed in a region where the population is large, birth rate is high, and nutritional vitamin B_{12} deficiency is common due to sociocultural and nutritional habits (11). All patients in the study group were normal by percentile curves for age.

Procedures were carried out according to the ethical standards for human experimentation established by the Declaration of Helsinki of 1975, revised in 1983. The study was approved by the ethics committee of Harran University. Consent forms were signed by the parents before the study began.

2.2. Exclusion criteria

The exclusion criteria were as follows: patients with congenital abnormality, history of asphyxia during or after delivery, history of convulsion, degenerative and demyelinating diseases, or any chronic diseases were excluded from the study. Patients with malnutrition were also excluded due to the possible deficiency of other vitamins and minerals that would affect the VEP and BAEP examinations. Patients with iron deficiency anemia or folic acid deficiency alone or together with vitamin B_{12} deficiency were also excluded from the study.

2.3. Blood samples

Complete blood count was examined using an automatic blood count device (Celldyn 3500), and levels of vitamin B_{12}, folic acid, and ferritin were determined by electrochemiluminescence (Elecsys 2010) in 2 h. Blood samples obtained for the determination of serum iron and total iron binding capacity were centrifuged and stored at –80 °C to be examined by biochemical autoanalyzer (Abbot Aeroset, UK) using a photometric method within 1 month. A serum vitamin B_{12} level lower than 200 pg/dL was considered as a deficiency, and a level lower than 100 pg/dL was considered as a severe deficiency.

2.4. VEP examinations

VEP tests were administered to all subjects using a Dantec Keypoint standard EMG device (Dantec, Denmark). During VEP response assessment, subjects were placed 90 cm from the TV monitor (Philips, the Netherlands) in order to see a visual stimulus. These tests were performed using checker-board pattern reversal. Stimuli were introduced as a checker-board pattern of white and black squares changing every 20 ms on the monitor. In VEP tests, an electrode was placed on the scalp in the midline over the occipital region, 5 cm above the inion (Oz). A reference electrode was placed over the frontal region and the ground electrode was placed on the forearm. Frequency limits were 0.5–100 Hz and analysis time was 500 ms. A repeated trial to verify reproducibility of the test was performed. Section was chosen as 5 μV (12).

2.5. BAEP examinations

The BAEP test studies the brainstem-evoked potentials that are produced in response to an auditory click stimulus and are measured from the scalp during the first 8–10 ms. Measurements are made using superficial electrodes placed at the center of the vertex (Cz) and mastoid process (or earlobe). A minimum of 1000 stimuli are produced and the potentials (the signal is magnified 500,000–1,000,000 times) are recorded repetitively to demonstrate reproducibility. Seven potentials are determined in the first 10 ms and are represented by Roman numerals. Waves I to V are observed in all healthy adults, whereas waves VI and VII are seen in only 43%–84% of adults. Waves IV and V are the most marked components of BAEPs. The upper limit was accepted as 167 ms in the P100 latency wave of VEP, 2.73 ms in I–III interpeak latency waves of BAEP, 5.30 ms in I–V latency waves, and 2.35 ms in III–V interpeak latency waves in the age range of 1 month to 2 years. Prolongation of one of the interpeak latency periods determined in these tests was considered abnormal (13).

Intramuscular cyanocobalamin, a vitamin B_{12} derivative, was administered to the subjects with vitamin B_{12} deficiency at a dosage of 10 μg/day in the first 3 days, 100 μg on day 4, and 500 μg on day 5 of the treatment. Maintenance treatment was administered as 5 doses of 1 mg/day of vitamin B_{12} every other day. Hematological and biochemical tests as well as VEP and BAEP tests were repeated on day 8 (week 1 of treatment) and month 3 of treatment.

2.6. Statistical analysis

Intergroup rate comparisons were performed with Pearson chi-square test. Pre- and posttreatment median (interquartile range) values were compared using Friedman and Wilcoxon tests. The rates of abnormality in pre- and posttreatment VEPs and BAEPs were compared with Pearson chi- square and McNemar tests. All calculations were performed on a computer using SPSS 11.5.

3. Results

The 30 patients in the study group consisted of 17 males and 13 females with a mean age of 13.3 ± 4.9 months. The control group consisted of 18 males and 12 females with a mean age of 13.6 ± 4.2 months. There was no

statistically significant difference between groups in terms of sex and age (P > 0.05). Twenty-five (83.3%) of patients with vitamin B_{12} deficiency were exclusively breast-fed, whereas 3 (10%) subjects were breast-fed and also received additional nutrients. One subject (3.3%) was fed with formula milk and another (3.3%) with cow milk. Of the 30 patients in the study group, 73.3% had vitamin B_{12} levels lower than 100 pg/dL, which was considered as severe B_{12} deficiency, whereas 26.7% had a vitamin B_{12} level below 200 pg/dL, which was considered as mild B_{12} deficiency. The families of 90% of the patients were of low socioeconomic status. Consumption of meat and dairy products was quite low in these families, although there was no vegetarian mother. Maternal serum vitamin B_{12} levels were below 200 pg/dL in 77% of the 30 patients and were also below 100 pg/dL, defined as severe deficiency, in 28% of patients. The most common symptoms were motor retardation, hypotonia, skin hyperpigmentation, no eye contact, social retardation, papilla atrophy of the tongue, and hematologic manifestations (pallor, petechiae, etc.). The sociodemographic and clinical characteristics of the patients are presented in Table 1. Hematological findings in all patients improved significantly after the first and third month of treatment. Neuromotor retardation and hypotonia were observed in 28 patients; 24 patients had a good response to vitamin B_{12} treatment, whereas 4 patients did not respond to the treatment.

The laboratory examinations of each group are shown in Table 2. Values of hemoglobin and vitamin B_{12} were statistically significantly lower in the patient group compared to the controls. Pretreatment mean ferritin and mean corpuscular volume (MCV) were statistically significantly higher in the patient group compared to the controls. VEPs and BAEPs were abnormal in 16 (53.3%) and 15 (50%) of the infants in the patient group, respectively, and normal in all of the control subjects. These differences were statistically significant (P < 0.001). When the median VEP values from the right and left eyes of the patients were compared with those of the controls, statistically significant prolongation was found in the patient group. Additionally, when we compared these groups in terms of BAEP I–III, III–V, and I–V interpeak latencies, there was also a statistically significant prolongation in the patient group (Table 2). Three months after treatment, statistically significant improvements were observed in both VEP and BAEP interpeak latencies (Table 3). The comparison of median VEP and BAEP values of infants with vitamin B_{12} deficiency before and after treatment are shown in Table 4. When we compared the median VEP and BAEP interpeak latencies between pretreatment and 7 days after treatment, no statistically significant improvement was found, except for BAEP III–V interpeak latency. Additionally, when we compared the median VEP and BAEP interpeak latencies between 7 days and 3 months after treatment, no statistically significant improvement was found, except for the left-eye VEP values (Table 3).

Table 1. Sociodemographic and clinical characteristics of the patients.

	Number of patients (n: 30) (%)
Boys	17 (43)
Girls	13 (43)
Patient's vitamin B_{12} (<100 pg/dL)	22 (73)
Patient's vitamin B_{12} (100–200 pg/dL)	8 (27)
Exclusively breast-fed	25 (83)
Living in rural areas	27 (90)
Motor retardation	28 (93)
Hypotonia	28 (93)
Paleness	27 (90)
Skin hyperpigmentation	23 (76)
No eye contact, social retardation	19 (63)
Papilla atrophy of tongue	19 (63)
Irritability	7 (23)

The rates of infants with vitamin B_{12} deficiency who showed improved VEP and BAEP abnormality with treatment are shown. Before the treatment, 16 and 15 patients had abnormal (prolonged) VEP and BAEP examinations, respectively. After 7 days of treatment, improvements or normalization of VEP and BAEP examinations were observed in 3 and 5 patients, respectively. These improvement rates were not statistically significant. Three months after treatment, from a total of 16 infants with abnormal VEP and 15 infants with abnormal BAEP examinations, improvements or normalization of VEP and BAEP examinations were found in 13 and 8 patients, respectively. These improvement rates were statistically significant compared to pretreatment (Table 4). Subjects with persistent VEP and BAEP abnormality at 3 months were those with severe vitamin B_{12} deficiency (<100 pg/dL) at baseline.

4. Discussion

To the best of our knowledge, this study is the largest published study on a prospective cohort of patients with impaired visual and auditory potentials (VEPs, BAEPs) who might develop secondary to early vitamin B_{12} deficiency. Weakness and failure to thrive were the most commonly observed manifestations of vitamin B_{12} deficiency in the present study. Neurological, gastrointestinal, and

Table 2. Comparison of mean VEP, BAEP, and hematological and anthropometric parameters in patient and control groups.

	Patient group mean ± SD	Control group mean ± SD	P
Hb (g/dL)	8.82 ± 2.60	11.22 ± 0.99	<0.001
MCV (fL)	87.87 ± 11,29	75.27 ± 2.51	<0.001
Ferritin (ng/dL)	56.46 ± 20.8	38 ± 9.4	<0.003
Vitamin B_{12} (pg/dL)	82.00 ± 47.80	486.66 ± 177.07	<0.001
BAEP I–III interpeak latency (ms)	2.4 ± 0.6	2.1 ± 0.2	<0.001
BAEP I–V interpeak latency (ms)	4.8 ± 1.5	4.2 ± 0.2	<0.001
BAEP III–V interpeak latency (ms)	2.5 ± 0.9	2.2 ± 0.2	<0.001
Right VEP (ms)	170 ± 65	126 ± 12.2	<0.001
Left VEP (ms)	165 ± 50	125 ± 11.2	<0.001

BAEP: Brainstem auditory-evoked potential, VEP: visual evoked potential.

Table 3. Median VEP and BAEP values of children with vitamin B_{12} deficiency before and after treatment.

	Pretreatment median (interquartile range) (ms)	7 days after treatment median (interquartile range) (ms)	3 months after treatment median (interquartile range) (ms)	P		
				Pretreatment vs. 7 days after treatment	7 days after treatment vs. 3 months after treatment	Pretreatment vs. 3 months after treatment
BAEP I–III interpeak latency	2.4 ± 0.6	2.3 ± 0.7	2.2 ± 0.3	>0.05	>0.05	<0.001
BAEP I–V interpeak latency	4.8 ± 1.5	4.6 ± 0.6	4.6 ± 0.4	>0.05	>0.05	<0.01
BAEP III–V interpeak latency	2.5 ± 0.9	2.4 ± 0.4	2.4 ± 0.3	<0.05	>0.05	<0.01
Right VEP	170 ± 65	145 ± 37	134 ± 26	>0.05	>0.05	<0.01
Left VEP	165 ± 50	142 ± 34	135 ± 22	>0.05	<0.05	<0.01

BAEP: Brainstem auditory evoked potential, VEP: visual evoked potential.

Table 4. VEP and BAEP abnormality with vitamin B_{12} deficiency before and after treatment.

	Pretreatment	7 days after treatment		3 months after treatment	
	Prolonged n (%)	Prolonged n (%)	Improved n (%)	Prolonged n (%)	Improved n (%)
VEP[¥]	16 (100)[a]	13 (81.3)	3 (18.7)[c**]	3 (18.7)	13 (81.3) [b**]
BAEP[€]	15 (100)[a]	10 (66.7%)	5 (33.3)[c]	7 (46.7)	8 (53.3) [b*]

[¥]: On admission, of a total of 30 patients, 16 had prolonged and 14 had normal VEP examinations.
[€]: On admission, of a total of 30 patients, 15 had prolonged and 15 had normal BAEP examinations.
BAEP: Brainstem auditory evoked potential, VEP: visual evoked potential.
a: No significant differences were determined in terms of VEP and BAEP abnormalities between the pretreatment and day 7 values.
b: Comparison of pretreatment and month 3 values, * $P < 0.01$, ** $P < 0.001$.
c: Comparison of 7 days and 3 months after treatment, ** $P < 0.001$.

hematological symptoms were observed in 18%, 27%, and 51% of the patients, respectively (14). These neurological signs may be caused by demyelination, dysmyelination, and axonopathy (3). Abnormalities of VEP and BAEP developed secondarily to demyelination and axonopathy caused by vitamin B_{12} deficiency. The persistence of VEP and BAEP abnormality in the deficiency of vitamin B_{12} might be associated with delayed diagnosis of vitamin B_{12} deficiency and advanced neurological view (4,6). In a study carried out by Biancheri et al. (6), out of 14 cases with congenital cobalamin metabolism disorder, the BAEP results of 9 and the VEP results of 8 cases were determined to be abnormal. It was observed that of the 6 patients with abnormal BAEP test results, 3 recovered completely 6 months after treatment and another 3 recovered completely 10 months after treatment. It was thought that the neurophysiological anomalies in these cases had arisen due to demyelination. In this study, 15 of 30 patients were determined as having abnormal BAEP test results. After treatment with vitamin B_{12}, 5 and 3 of these patients recovered in 1 week and 3 months, respectively.

In a study carried out by Misra et al. (15), a VEP test was carried out in 13 patients with neurological findings due to vitamin B_{12} deficiency. The VEP latencies of 7 patients were determined to be long, and these changes were attributed to the focal demyelination of white matter in the optical nerve and spinal cord due to vitamin B_{12} deficiency. In this study, 16 of 30 patients were determined as having abnormal VEPs. After treatment with vitamin B_{12}, 3 patients were observed to have recovered within 1 week and 10 patients after 3 months.

Studies have demonstrated that the rate of VEP abnormality ranges between 25% and 100% in patients with vitamin B_{12} deficiency (3,4). Although BAEP abnormality has been reported in 0%–100% of subjects in previous studies performed on small patient populations, it has been emphasized that VEP abnormality is more common compared to BAEP abnormality (3,16,17). The minimal alterations in BAEP have suggested that BAEP is affected minimally in the deficiency of vitamin B_{12} (3).

The main limitation of our study is the limited number of infants. However, in the present study, the number of subjects was greater compared to other studies in the literature, and VEP and BAEP were abnormal in 53.3% and 50% of subjects, respectively. The evident improvement in VEP compared to BAEP at 3 months has been considered as an indirect indicator that vitamin B_{12} deficiency affects VEP more significantly. VEP and BAEP values improved in 81.3% and 53.3% of patients at 3 months compared to pretreatment values, which suggested that the abnormalities in both VEP and BAEP developed secondarily to demyelination and axonopathy caused by vitamin B_{12} deficiency. Similar to other studies in the literature, these results suggest that vitamin B_{12} deficiency affects VEP more significantly than BAEP (3,4,6). However, the improvement of BAEP is slower than the improvement of VEP.

Previous studies have demonstrated that there is a positive correlation between the degree of vitamin B_{12} deficiency and abnormality of evoked brain potentials (4,6,18,19). Similarly, in this study, VEP and BAEP tests proved abnormal in 3 and 7 subjects who had serum vitamin B_{12} levels of <100 pg/mL, respectively. Two patients were presented by Renault et al. (19), and it was observed that one patient who showed apathy and lack of interest in the environment recovered at the end of the first week following treatment, whereas the neurological findings of the other patient healed after 2 months. The difference in the recovery of these neurological findings has been attributed to late diagnosis and late treatment (19). The persistence of VEP and BAEP abnormality in our patients at 3 months might be associated with delayed diagnosis of vitamin B_{12} deficiency and advanced neurological picture. We found maternal vitamin B_{12} deficiency in 77% of 30 patients with vitamin B_{12} deficiency, and the deficiency was severe (serum B_{12} levels <100 pg/dL) in 28% of mothers. The facts that vitamin B_{12} deficiency emerged most commonly between the ages of 6 and 18 months, that maternal serum vitamin B_{12} levels were reduced in most cases, and that maternal nutrition was poor in vitamin B_{12}-containing foods suggest that infantile deficiency of vitamin B_{12} was secondary to maternal deficiency. Therefore, our results support those of previous studies (11, 20–24).

Infants who were born to mothers with vitamin B_{12} deficiency have inadequate myelination during gestation and particularly in the last trimester, when myelination is normally at its most rapid. The neurological picture becomes even more severe in the absence of postpartum vitamin B_{12} replacement in the first 6 months of infancy, which is the rapid myelination period. As a result, brain atrophy and permanent neurological deficits develop (8,25). The neurological symptoms that arise due to the late diagnosis and treatment of vitamin B_{12} deficiency either do not recover completely or are healed over a long period of time (26).

In conclusion, this study has demonstrated that symptoms of mental, motor, cognitive, and social retardation with impaired visual and auditory potentials (VEP, BAEP) might develop secondary to early vitamin B_{12} deficiency in exclusively breast-fed infants whose mothers consume inadequate animal products. Early diagnosis and treatment of vitamin B_{12} deficiency might prevent severe mental and motor retardations, which might be difficult to treat or irreversible.

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