Auditory Brainstem Response in Patients with Tinnitus Associated with Vitamin B_{12} Deficiency

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Abtract

Objective: The auditory brainstem response (ABR) has been reported as normal in patients with vitamin B12 deficiency, but there have also been reported cases of interference in amplitude responses. However, studies investigating the effects of vitamin B_{12} on auditory response are limited in patients with tinnitus. The aim of this study was to investigate the ABR findings in patients with tinnitus together with vitamin B_{12} deficiency.

Material and methods: Twenty-eight patients with tinnitus-related vitamin B_{12} deficiency were included in the study. Their serum vitamin B_{12} levels were lower than 200 pg/ml. Patients were between 19 and 58 years with a mean age of 36.82 ± 11.19 (ratio: male/female, 6/22). ABR was performed in all patients. Latencies (I, II, III, IV, V), interpeak latencies (I-III, III-V, I-V) and amplitudes were evaluated. Neurologic and ear physical examinations were evaluated and brain magnetic resonance imaging (MRI) was also performed in all patients.

Results: Neurologic,ear-auditory physical examinations and brain MRI findings were normal in all patients. Wave latencies and interpeak latencies were normal in all patients. Six patients (21.42 %) had low amplitude in their ABR. In one of them, the left-sided response showed a mild amplitude decrease in all waves compared to the right-side. Bilateral mild low amplitude was observed in 4 (66.6 %) patients in ABR findings.

Conclusion: These results support that ABR findings can be influenced in vitamin B_{12} deficiency patients having tinnitus. More detailed studies are needed in tinnitus associated with vitamin B_{12} deficient patients.

Key words: Auditory brainstem response, Tinnitus, Vitamin B_{12} deficiency, Neurophysiology, Low amplitude

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INTRODUCTION

In humans, vitamin B_{12} deficiency can affect the hematological and gastrointestinal systems, and may also adversely affect neurological systems. Neurological damage is the result of pathological changes, which may eventually lead to demyelination, axonal degeneration and neuronal death[1,2]. Abnormalities of brainstem auditory evoked potentials may develop secondarily to demyelinization and axonopathy caused by vitamin B_{12}

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deficiency and delayed diagnosis of vitamin B_{12} deficiency may result in an advanced neurological picture [3].

True tinnitus is a phantom auditory perception arising from a source or trigger in the cochlea, brainstem, or at higher centers and has no detectable acoustic generator[4]. However, the exact neuro-pathophysiological mechanism of tinnitus has not yet been fully elucidated. Some studies have reported that tinnitus is associated with vitamin B_{12} deficiency, with a possible relationship between vitamin B_{12} deficiency and dysfunction of the auditory pathway [5-7]. However, other investigations have failed to find any strong evidence to support such an association[8-10].

The auditory brainstem response (ABR) is a electrical field potentials generated by stimulation of the auditory pathways[11]. Some reports were determined that ABR were normal in vitamin B_{12} deficiency[12]. However, Shemesh et al observed that there is a relationship between vitamin B_{12} deficiency and dysfunction of the auditory pathway and these authors recommended routine vitamin B_{12} serum levels be determined when evaluating patients for chronic tinnitus[5]. The auditory brainstem response (ABR) in tinnitus subjects has been extensively investigated over the last decade with the hopes of finding possible abnormalities related to the pathology[13]. Despite this effort, the use of the ABR for tinnitus diagnosis or as an outcome measure is under debate[13].

In this study, we aimed to investigate whether ABR can be a guide for the etiology of patients with tinnitus who cannot show any brain and auditory pathology. Therefore, we studied ABR in patients with vitamin B_{12} deficiency having tinnutus. According to our knowledge, this study is the first study performed in patients with tinnitus associated with B_{12} deficiency.

MATERIAL AND METHODS

This study designed as open uncontrolled and cross-sectional. Twenty-eight patients were included. All patients gave informed consent prior to inclusion in the study. Patients were between 19 and 58 years. All patients had vitamin B_{12} deficiency and tinnitus.

Their serum vitamin B_{12} levels were lower than 200 pg/ml (reference range, 211-480 pg/ml). Their tinnitus duration and level of vitamin B_{12} were recorded. But they didn't know how long they had vitamin B_{12} deficiency. In most patients with tinnitus, nonspecific symptoms such as paresthesia and numbness were accompanied. However, there were no urinary symptoms, paralysis, gait disturbances, tremors, jaundice, limb swelling, changes in skin colour, or delusion which may be a severe clinic of vitamin B_{12} deficiency. Patients had no known co-morbid disease.

Neurologic examination findings did not reveal any other abnormalities. To ensure reliability of results, all patients underwent an otoscopic examination before performing the ABR test. External auditory and auditory examinations of the patients were evaluated patients with a clean external ear channel and normal eardrum were included. Patients in whom have hearing loss, brain lesion presence, brain malformation, brain tumor, central pontine myelinosis, speech disorders, could not be obtained or with remarkable tinnitus histories rather than vitamin B_{12} deficiency and those who want to leave at the study were excluded.

ABR tests were performed by using superficial electrodes with Nihon Kohden Neuropack 2 (Nihon Kohden, Tokyo, Japan) device available in our neurology laboratory. ABR was performed as following: To elicit and record ABR, an aural stimulus is delivered to the patient via headphones. Surface electrodes placed at A1 (left mastoid), and A2 (right mastoid) positions record voltage differences generated by stimulation of auditory pathways, using Cz (vertex) as a common reference. As one ear was stimulated with clicks 90 desibel, the other was masked with 50 desibel. Eight to ten stimuli were given per second. It was recorded through 1000 Hz filtering. This process has been renewed at least 2 times for each party. Latencies (I, II, III, IV, V), interpeak latencies (I-III, III-V, I – V), amplitudes (I, II, III, IV, V) and waveforms of waves were evaluated. In all patients, brain magnetic resonance imaging (MRI) was performed in order to exclude brainstem pathologies that may adversely affect the test result and evaluated in detail.

STATISTICAL ANALYSIS

The statistical analysis was done using the SPSS 18 statistical package. Data were presented as mean values and standard deviation. All the parameters in the study were correlated with baseline data using Spearman's

rho correlation coefficient. Also, vitamin B_{12} levels were correlated with the different parameters of the stimulus-related potentials. The Student's t test was used to compare these parameters between the amplitudes/interpeak latency and wave latencies and reference data in the literature[14,15]. A p-value <0.05 was taken as statistical significant.

RESULTS

Neurologic physical examination, auditory and ear examinations were normal in all patients. Twenty-eight patients were included in the study and 14.28 % of the patients were male and 85.72 % were female (ratio of male/female: 4/24). Patients were between 19 and 58 years with a mean age of 36.82 ± 11.19 years. Their tinnitus were with a mean of 3.89 ± 2.72 months (1-11 months). Characteristics of the patients are given in table I.

When both ear test results were analyzed, the decrease of interpeak latency I-III in the right-side was statistically significant (p <.0.001). In addition, when vitamin B_{12} level was correlated with the our datas, it was seen that there was a positive moderate correlation with wave latency IV (p = 0.036, rho= 0.351) (Figure 1).

All of our patients learned that vitamin B_{12} deficiencies were the result of our tests. Therefore, detailed information about the duration of vitamin deficiency exposure could not be obtained. The following values were obtained in ABR investigation. Wave latencies (I, II, III, IV, V) and interpeak latencies (I-III, III-V, I-V) were normal in all patients (Table II). Twenty one percent of patients had

Table I. Characteristics of the study participants.

Variables	Tinnitus together with vitamin B_{12} deficiency patients (n=28)
Gender (male/female)	4 /24
Age (years) (mean ± SD)	36.82 ± 11.19
BMI (kg/m^2) (mean ± SD)	25.64 ± 1.09
Tinnitus duration (months) (mean ± SD)	3.89 ± 2.72
Vitamin B_{12} level (pg/ml) (mean ± SD)	163.23 ± 33.85

BMI, body mass index, SD, standart deviation

Table II. Mean ± SD ABR values of study participants according to literature data (Auditory Brainstem Response)

	Left Ear Response Mean ± SD	Right Ear Response Mean ± SD	According to reference value Left / Right P value
Wave Latencies			
I	1.54 ± 0.27	1.56 ± 0.28	0.521 / 0,309
II	2.59 ± 0.26	2.52 ± 0.57	0.653 / 0.655
III	3.65 ± 0.20	3.62 ± 0.27	0. 381 / 0.198
IV	4.80 ± 0.41	4.76 ± 0.42	0.617 / 0.942
V	5.45 ± 0.53	5.39 ± 0.52	0.477 / 0.193
Interpeak latencies			
I-III*	2.04 ± 0.49	0.48 ± 0.18	0.177 / 0.071
III-V	1.80 ± 0.42	1.70 ± 0.54	0,636 / 0,202
I-V	3.91 ± 0.57	3.82 ± 0.54	0.335 / 0.075
Amplitudes V/I ratio	0.550 ± 0.221	0.488 ± 0.181	/ 0,729

*There was a statistical significant difference between left and right interpeak latencies I-III (p < 0.001), Others analysis p > 0.05.(One sample T test) (Reference literature 14,15)

Table III. ABR findings results in the B_{12} vitamin deficiency with tinnitus patients (Auditory Brainstem Response)

Amplitude		Latency		Interpeak latency	
Low*	Normal	Normal	Delayed	Normal	Delayed
6 (21.42 %)	22 (78.58 %)	28	-	28	-

(*Wave V / wave I amplitude ratio was lower than 0.5, it was accepted as low).

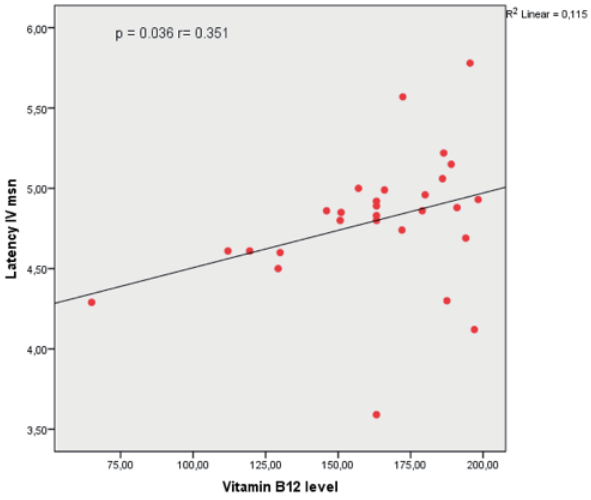

Figure 1: Scatter plots show significant positive correlations between vitamin B_{12} level and latency IV (p= 0.036)

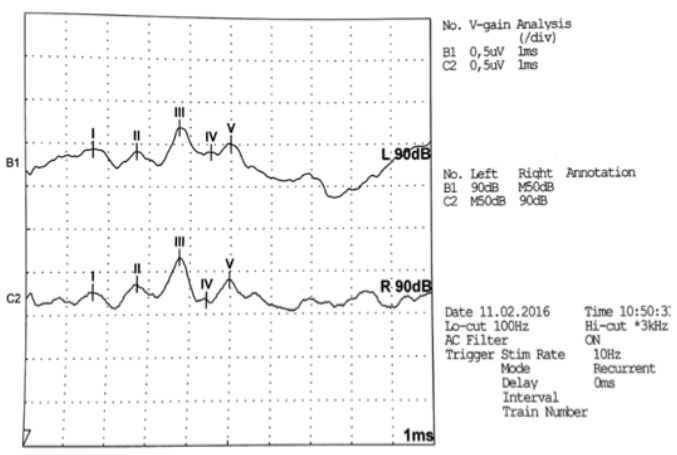

Figure 2: Normal response of ABR in our labaratory (AS left ear stimulation, AD right ear stimulation; Auditory Brainstem Response)

low amplitude (six patients, 21.42%) in their ABR results (Table III). A normal response in our study participants was shown in figure 2.

In one of them, the left-sided response showed a mild amplitude decrease compared to the right-side response (Figure 2). Bilateral mild low amplitude was observed in 4 (66.6 %) patients, unilateral low amplitude was shown 2 patients (33.3 %) in ABR findings as abnormal response (Figure 3). All of the patients had normal MR images.

DISCUSSION

Deficiency of vitamin B_{12} is widespread and is responsible for major morbidity across all age groups, and may have significant consequences for quality of life as it affects multiple systems in the body[16]. Animal experiments of B_{12} deficiency have revealed neuropathological effects[17]. Vitamin B_{12} deficiency may cause the demyelination of neurons in the cochlear nerve, resulting in hearing loss[17-19]. In addition, low levels of vitamin B_{12} is associated with the destruction of the microvasculature of the stria vascularis, which might result in decreased endocochlear potential and in hearing loss and tinnitus[6]. With all of these, the presence of tinnus in lack of vitamin B_{12} is still very controversial. Tinnitus is defined as the perception of sound in the absence of an external source and affects about 16 % of the adult population[20,21]. It is relatively difficult to pinpoint the relationship between the tinnitus and vitamin B_{12} deficiency. One of the etiopathologic reason in tinnutus that it is believed to be at play in vitamin B_{12} deficiency neuropathy is hypomethylation in the central nervous system. Inhibition of the B_{12}-dependent enzyme methionine synthase results in a fall in the ratio of S-adenosylmethionine (SAM) to Sadenosylhomocysteine; the resultant deficiency in SAM impairs methylation reactions in the myelin sheath. The methylation of homocysteine to methionine requires both methylcobalamin (an active form of vitamin B_{12}) and

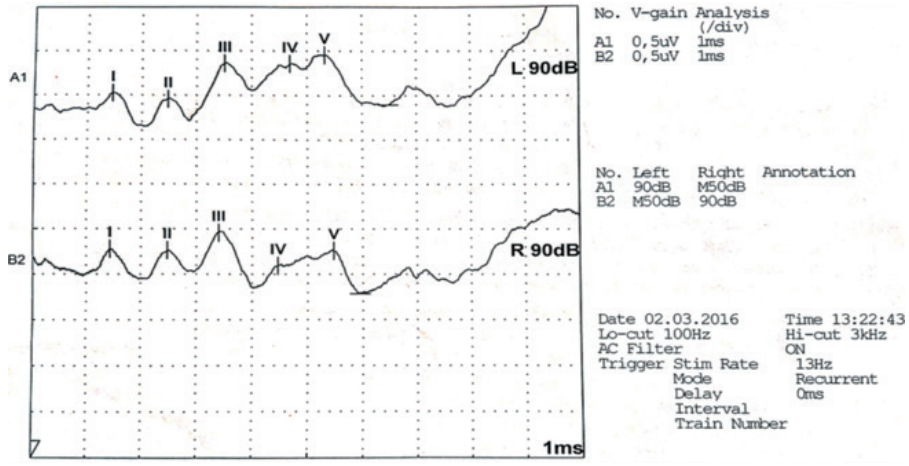

Figure 3: This ABR finding is from a 23-yr-old woman with vitamin B_{12} deficiency. Unilateral mild low amplitude (according to the patient's right) was seen. There were no reported symptoms rather than tinnutus and brain MRI was normal.

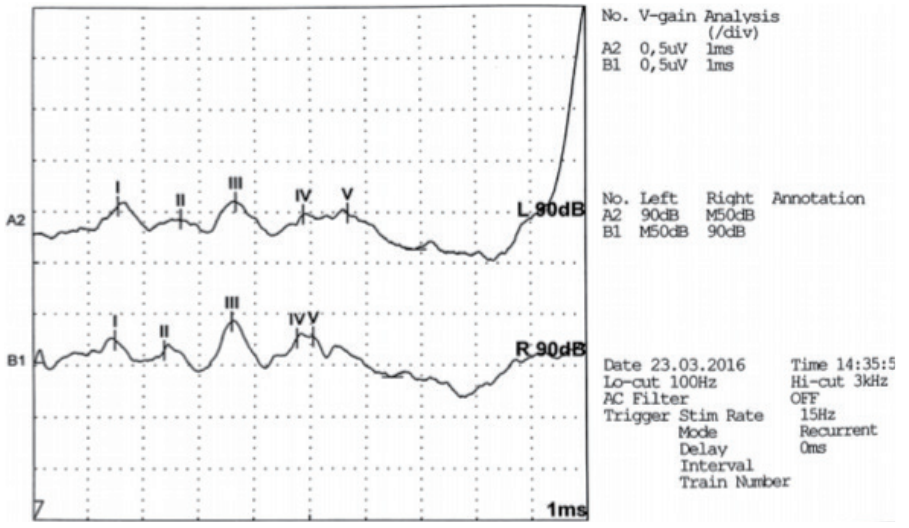

Figure 4: These waveform is from a 36-yr-old woman with vitamin B_{12} deficiency. Bilateral mild low amplitude was seen. There were no reported symptoms rather than tinnitus.

the active form of folic acid (5-methyltetrahydrofolate). Deficiency of vitamin B_{12} leads to accumulation of homocysteine which is a neurotoxin and vascular toxin. Cochlear function is dependent on adequate vascular supply and the normal functioning of nerve tissue. B_{12} deficiency is associated with axonal degeneration, demyelination, and subsequent apoptotic neuronal death [4,18,23]. Activity in associative auditory cortical areas, such as the medial temporal gyrus, was more closely correlated with the functional attributes of tinnitus than primary auditory cortex[24]. In an other study, Mirz et al. identified an increase of neuronal activity mainly in the right hemisphere with a focus on middle temporal regions[25] accordingly our results revealed that lower interpeak latency I-III in the right ear. A correlation between higher brain metabolism in the medial temporal gyrus and tinnitus severity has already been documented in a Positron Emission Tomography study (PET)[26]. The

prevailing opinion, based on electrophysiological studies in animals and brain imaging studies is that tinnitus is generated by aberrant firing patterns or high levels of spontaneous neural activity in the central auditory pathway and not the cochlea[27,29]. ABR is recorded from the ear and vertex in response to a brief auditory stimulation. Wave I is generated from the proximal acoustic nerve (segment near cochlea), wave II from the distal acoustic nerve (segment near brainstem) or cochlear nuclei, wave III from the superior olive and projections to the lateral lemniscus; medial nucleus of trapezoid body might generate a part of wave III, wave IV from the most likely the lateral lemniscus, but data is not definitive, wave V from the high pontine or lower midbrai n structures: probably the lateral lemniscus, inferior colliculus, or a combination thereof, wave VI from the most likely the medial geniculate nucleus or projections from the inferior colliculus and wave VII from the most likely the auditory radiations to primary auditory cortex[12]. In our study, it was seen that the brain region most affected by vitamin deficiency was the lateral lemniscus region according to our ABR results.

It was reported that ABR was normal in B_{12} deficiency, previously[13]. This is the first study that ABR findings in tinnitus associated B_{12} deficiency patients. Our results support that ABR findings may influenced in B_{12} deficiency patients having tinnutus. Our study demonstrates that tinnitus associated B_{12} deficiency patients may not have normal ABR findings. We thought that more prominent findings can be obtained in cases with long duration of B_{12} deficiency and tinnitus.

CONCLUSION

This study demonstrates that ABR measurements may be related in patients with tinnitus-related vitamin B12 deficiency. We think that detailed cohort studies including large patient series will contribute more to the literature. Because the possibility of improvement of tinnitus complaints with replacement therapy is clinically important.

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Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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