



Electrophysiological changes on brainstem auditory evoked potentials in hypothyroid patients

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ABSTRACT

Brainstem Auditory Evoked Potential (BAEP) refers to an evoked potential generated by a brief click which is usually used to assess the integrity of both peripheral and central auditory pathway. The waveform peaks are labeled I-VII, occur within a 10-millisecond time period after a click stimulus presented at 70-90 dB. Deafness of sensory neural hearing loss is the most common otolaryngological manifestations associated with thyroid dysfunction. Brainstem auditory evoked potential (BAEP) is one of the methods used for assessing the effect of hypothyroidism on the auditory pathway in the brainstem. Studies done earlier reported that there is prolongation of both peripheral and central conduction time in hypothyroidism while few studies concluded that there was no statistically significant difference in BAEP and hypothyroid subjects suffering from hearing loss. To evaluate the auditory sensory process using BAEP (Brainstem Auditory Evoked Potential) in hypothyroidism and the effect of treatment of the same, Fifteen acquired hypothyroid patients, fifteen hypothyroid patients with treatment and fifteen controls with the age between 20-50 yrs were taken for the study. Biochemical and hematological investigations like thyroid profile (fT_3 , fT_4 , TSH) and lipid profile (HDL, LDL, VLDL, TGL and Total Cholesterol) followed by otological examination and Pure Tone Audiometry (PTA) were done. Finally they were subjected to standard and sensitive BAEP recording by placing three surface electrodes in scalp with masking wide band. The results revealed a prolongation in absolute latency of wave III and wave V of BAEP and prolongation of Inter peak latency (IPL) I-V in acquired hypothyroid patients without treatment and significant improvement in absolute latency and IPL of BAEP waves in hypothyroid patients with treatment. There was also a significant decrease in amplitude of wave I and V in hypothyroid patients without treatment and significant increase in amplitude of BAEP wave I and V in patients with treatment. The results of the present study conclude that in hypothyroid state there might be a slow conduction at the periphery and with treatment there is a better recruitment of neuronal pool of the generators of the waves of BAEP in brainstem.

Key words: Hypothyroidism, Pure Tone Audiometry (PTA), Brainstem Auditory Evoked Potentials (BAEP), Sensorineural deafness.

INTRODUCTION

An evoked potential or "evoked response" is an electrical potential recorded from the nervous system of a human or animals following presentation of a stimulus which can be readily and non-invasively recorded using averaging techniques first employed by Dawson in 1947. The evoked responses can be quantified by measuring peak amplitudes and latencies, in the millisecond (ms) domain.^[1] The Brainstem Auditory Evoked Potential (BAEP) is an objective electrophysiological method for assessing the auditory pathways from the auditory nerve to the brainstem.^[2] The burden of thyroid disease in the general population is enormous and most common among all the endocrine diseases in India.^[3] Hypothyroidism is defined as a clinical state resulting from reduction ($fT_3 < 1.4$ pg/ml; $fT_4 < 0.8$ ng/dl;) in secretion of thyroid hormone.^[4] Thyroid hormone deficiency is associated with peripheral and central nervous system (CNS) dysfunctions.^[5] The electrophysiological changes seen in thyroid disease have been extensively documented. Deafness of sensory neural hearing loss is the most common otolaryngological manifestations associated with thyroid dysfunction. Various studies have shown that hypothyroidism, both congenital and acquired may be associated with hearing impairment.^[6] The actual incidence of hearing loss in hypothyroidism is uncertain, and it may affect 25% of the patients with acquired hypothyroidism and 35-50% of the patients with congenital hypothyroidism.^[7] Kempu was the first to document hearing impairment in severely hypothyroid females which was reversed upon administering thyroid extracts.^[8] Hilger was the first to document audiometrically the extent of hearing loss in acquired hypothyroidism.^[9] The hearing impairment may be conductive, sensorineural, or mixed and benefit from thyroid therapy. Auditory Brainstem Response (ABR) is one of the methods used for assessing the effect of hypothyroidism on the auditory pathway in the brainstem.^[10] In hypothyroidism, some studies reported that there was a prolongation of both peripheral and central conduction time in hypothyroidism^[7,10] while some studies showed that there were no statistically significant differences in ABR in hypothyroidism.^[11,12] The present study aims

to evaluate the auditory sensory process in the brainstem based on the latency, amplitude, inter peak latency & duration evaluation on hypothyroid patients and effect of treatment on the same.

MATERIALS AND METHODS

The study was conducted in electrophysiology laboratory of Department of Physiology, Meenakshi Medical College and Hospitals, Kancheepuram, Tamilnadu. Patients were selected from the surgical and medical outpatient and inpatient departments. After enrolment in the study, a detailed history and informed consent were obtained after explaining recording procedures. The study protocol was approved by institutional human ethical committee of Meenakshi university. The recordings were done between 10 A.M and 1.00 PM. All the techniques of measurement, duration, and instruments were maintained uniformly throughout the study.

Group I : Healthy control group (n=15)

Group IIa: Acquired hypothyroid patients who were not on treatment with thyroxine (n=15)

Group IIb: Acquired hypothyroid patients on treatment with thyroxine who became euthyroid and in regular follow up (n=15)

Acquired untreated and treated hypothyroidism patients in the age between 20-40 years and Subjects with normal hearing were included in the study. Age more than 60 years, prior ear surgery, noise-induced hearing loss and conductive hearing loss patients, use of ototoxic medication, prior history of hereditary hearing loss, history of drug abuse (nicotine, alcohol, opium etc) and subjects suffering from any systemic diseases were excluded from the study.

Detailed clinical examination of the study participants including general, systemic examination including cardiovascular system, respiratory system and neurological examinations were done. Temperature was measured by using digital thermometers.

Biochemical Analysis

All patients and control underwent laboratory evaluations like thyroid profile fT_3 (Free T_3 , normal range: 1.4 – 4.2 pg/ml); fT_4 (Free T_4 - normal range: 0.8– 2.0 ng/dl) & TSH (Thyroid Stimulating Hormone - normal range: 0.4 – 7.0 μ IU/ml) were measured by using a microplate immunoenzymometric assay (Accu – Bind ELISA Microwell method). Serum HDL (High Density Lipoprotein - normal range: 30-70 mg/dL; LDL (Low density lipoprotein - normal range: 30 – 150 mg/dL; TGL (Triglycerides - normal range: <150 mg/dL) and

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TC (Total Cholesterol - normal range :130 - 220 mg/dL) were measured by using Phosphotungstate method.

Audiological Examination

Before BAEP (Brainstem Auditory Evoked Potentials) study all subjects underwent otological examination followed by Rinne's & Weber's test and audiometric analysis to assess hearing loss.

AC IA 40 instrument was used for Pure Tone Audiometry Examination. Click sounds with notified frequencies of 250, 500, 1000, 2000 and 4000 Hz through ear phones and measured for both ears separately. Results were interpreted based on type and degree. Type of deafness were classified into: Conductive (airway thresholds above 25 dB and the normal bone conduction threshold, with an air-bone gap); mixed (air and bone conduction thresholds above 25 dB, with air-bone gap) and sensorineural (air and bone conduction thresholds above 25 dB, without air-bone gap). The patients with conductive or mixed hearing loss were taken off the study. Grading of hearing loss were classified into: Mild (thresholds between 26 and 40 dB); Moderate (thresholds between 41 and 70 dB); Severe (thresholds between 71 and 90 dB) and Profound (thresholds above 91 dB).

BAEP evaluations were done by using RMS EMG EP Mk2 recordings. The EP were recorded with Silver-Silver Chloride disk electrodes from standard scalp locations of the 10-20 International System. The electrodes were placed at Cz (Active electrode), FPz (Grounding electrode), A1 and A2 (Reference electrode) after cleaning the scalp or skin site with alcohol followed by Skinpure Skin preparation gel and EEG paste ElefixTM. The skin electrode contact impedance was kept at less than 5 KO. The subjects were instructed to close their eyes to avoid blink artifacts. 1000 click stimuli at the rate of 10 Hz with

duration of 0.1 ms were delivered at 60 dB above hearing threshold through shielded headphones with 40 dB white noise masking the contralateral ear. Signals were filtered with bandpass 100 Hz and 3 KHz and averaged to 1000 stimuli.

Peak latencies of all the waves, interpeak latencies of I-III, III-V and I-V and amplitudes of wave I and V was determined for each ear separately with the help of digital cursors. The amplitude was measured as the maximum height of the peak from the succeeding trough. Morphology, absolute latency and wave I, III and V amplitude, I-III, I-V and III-V inter peak interval latencies; I-V latency and amplitude relation for hypothyroid patients with treatment and hypothyroid patients without treatment were assessed and compared with control subjects.

RESULTS

The data obtained were analyzed using SPSS software version 17. The average of left and right ear were taken and analyzed. The statistical analysis for the comparison between controls and hypothyroid patients was done using unpaired 't' test. Paired 't' test was used for comparing the hypothyroid patients before and after treatment. All tests were two tailed. Results are expressed as Mean±SD. P < 0.05 was considered statistically significant. Nearly 83% of the participants were in the age group between 20 – 40 years. 86% hypothyroid patients were females. The common cause of hypothyroidism in the study group was Hashimoto's thyroidism.

Table 1 shows degree of impairment in pure tone audiometry of study groups. The audiogram threshold was significantly (*p<0.05) increased in Group II(a) when compared to that of other groups. It was found out that nearly 87% of the patients without treatment were having mild hearing loss and only 13% of them are normal but 96% of the patients were normal with treatment.

Table 2, (fig 1, 2 &3) shows the absolute peak latency, inter peak latency and amplitude of BERA. There was a significant (*p<0.05) reduction in wave III and wave V peak latency in Group IIa (hypothyroid without treatment) and significant increase in Group IIb of hypothyroid patients with treatment. However there was no statistical significance in other peak latencies. There was a significant (*p<0.05) increase in IPL I-V in Group II (a) and significant reduction in Group II(b), whereas regarding amplitude there was a significant (*p<0.05) reduction in amplitude I and V in Group II(a) and significant increase in Group II(b).

Table 1: Audiogram

Degree of impairment	Group I	Group IIa	Group IIb
Normal (<26 dB)	n = 15	n = 2	n = 14
Mild (27 – 40 dB)	n = 0	n = 13	n = 1
Moderate (41 – 70 dB)	n = 0	n = 0	n = 0
Severe (>91 dB)	n = 0	n = 0	n = 0

Table 2: BAEP – Right ear – Peak latency, IPL, Amplitude

	Peak latency (ms)					IPL(ms) I-III	I-V	III-V	Amplitude(ms)	
	I	II	III	IV	V				Ia	Va
Group I	1.7±0.09	2.7±0.15	3.6±0.28	4.9±0.39	5.6 ± 0.30	2.2±0.18	4.1 ± 0.18	2.1±0.25	0.21±0.09	0.32±0.17
GroupII(a)	1.8±0.05	2.7±0.25	5.2±0.63*	4.9±0.32	6.7±1.01*	2.2±0.17	6.7±1.95*	2.1±0.24	0.19±0.15*	0.28±0.23*
GroupII(b)	1.5±0.58	2.6±0.23	4.26±0.17*	5.0±0.41	5.65±0.56*	2.1±0.28	5.2±0.45*	2.0±0.21	0.36±0.12*	0.44±0.16*

* p<0.05 – statistically significant

Table 2: BAEP – left ear – Peak latency, IPL, Amplitude

	Peak latency (ms)					IPL(ms) I-III	I-V	III-V	Amplitude(ms)	
	I	II	III	IV	V				Ia	Va
Group I	1.7± 0.09	2.7±0.24	3.6±0.17	4.9±0.31	5.5±0.28	2.2±0.23	4.1±0.22	2.2±0.19	0.29±0.24	0.41±0.18
GroupII(a)	1.7±0.09	2.7±0.21	5.3±0.49*	4.9±0.36	6±0.68*	2.1±0.20	5.9±0.81*	2.2±0.25	0.18±0.17*	0.28±0.14*
GroupII(b)	1.8±0.30	2.7±0.29	4.52±0.25*	4.9±0.33	5.91±0.60*	2.2±0.20	5.2±0.74*	2.2±0.28	0.41±0.21*	0.56±0.19*

* p<0.05 – statistically significant

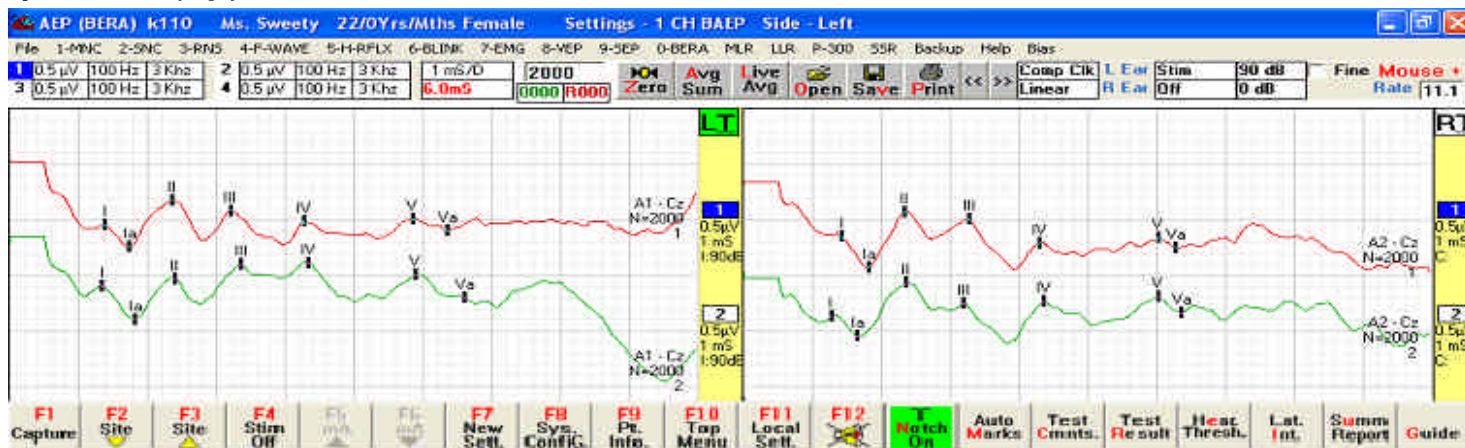


Figure 1: BAEP recording of control

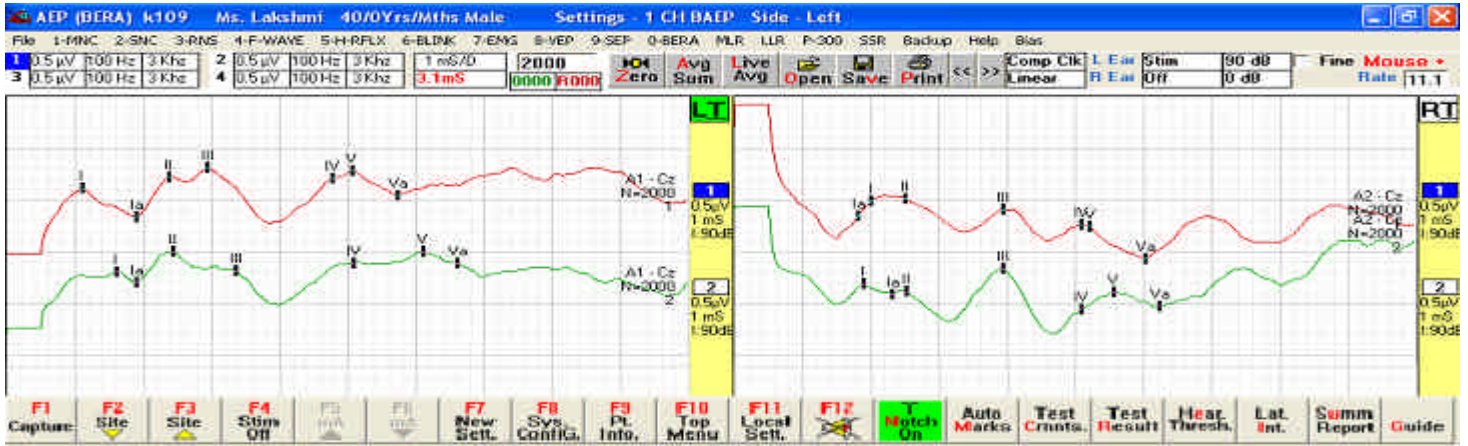


Figure 2: BAEP recording - Hypothyroid patient without treatment

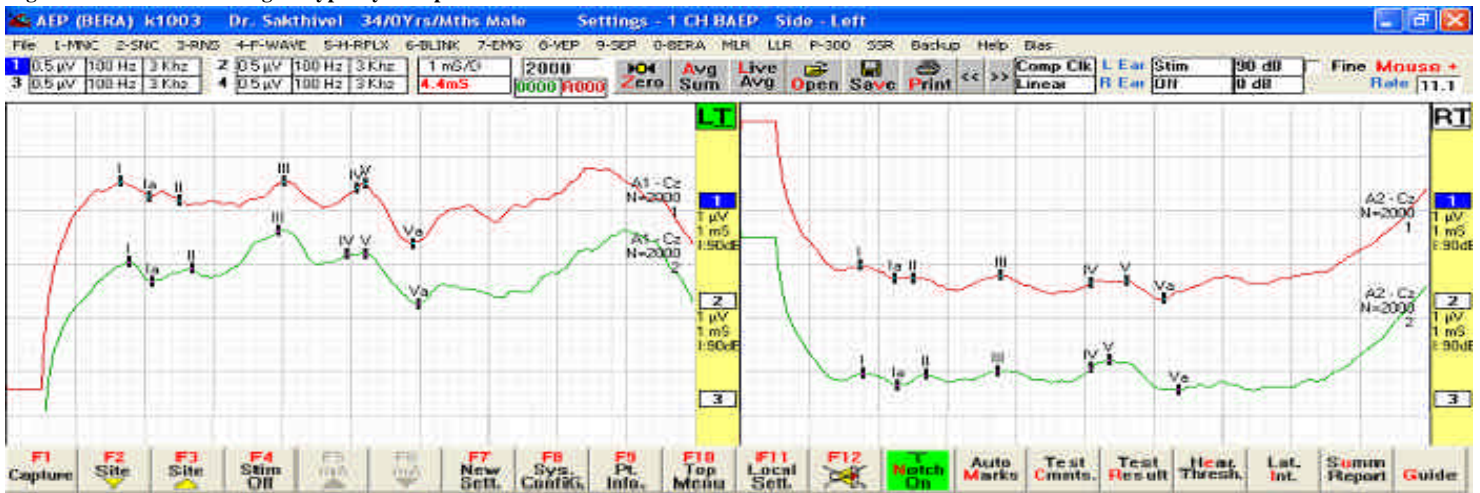


Figure 3: BAEP recording of Hypothyroid patient with treatment

DISCUSSION

The functional integrity of the auditory pathway depends on the intact anatomical pathway, functional relay stations, myelination and thickness of the tract and absence of any compression or pressure from outside.^[13] BAEP (Brainstem Auditory Evoked Potentials) have come into widespread use for the assessment of the clinical state of the middle portion of the brainstem. It allows evaluation of functional integrity of auditory pathway from hair cells to thalamic nuclei. Values of BAEP (particularly the absolute and inter-peak latencies) represents the peripheral (from acoustic nerve and pontomedullary portion) and central (pontomesencephalic) conduction time.^[13]

In the present study, findings of PTA as shown in Table 1 show mild degree of bilateral conductive type of hearing impairment was present in 86% of the hypothyroid patients without treatment, but there was no moderate and severe hearing loss. In hypothyroid patients with treatment, the audiometric threshold was within normal limits but relatively higher than that of controls. Similar to this Vikas, et al., was found that nearly 48.83% & 40.62% of the hypothyroid patients had moderate and mild degree of hearing impairment respectively.^[14] He suggested that the conductive hearing impairment in these patients may be the result of reduced compliance due to hypertrophy and edema of the mucosal lining of the eustachian tube and middle ear and thickening of tympanic membrane. Meyerhoff, et al., based on experimental study reasoned out that the conductive type of hearing loss may be due to partial or complete obliteration of oval or round window because of changes in ossicles and round or oval window crystallized consistency of bone, fusion or distortion of incus and stapes.^[15] But the patients with thyroxine treatment showed only 0.06% of mild conductive hearing loss whereas 99.94% were normal, which is also correlated well with that of Anand VT et al.,^[16] & Vikas et al.,^[14] studies where they reported conductive hearing impairment in hypothyroidism which was shown improvement in air conduction after treatment.

In the present study, the findings of BAEP as shown in Table 2, there was a significant prolongation of wave III and V latency in hypothyroid patients without treatment and significant increase in wave III and V latency in hypothyroid patients with TH treatment. But there were no abnormalities in other waves. Similar to this, there was a slight increase in wave III as reported by Yumnam et al.^[13] and higher latencies of wave I, III and V as reported by Karols et al^[7] and they suggested that in hypothyroid state there may be some slow conduction at the periphery and with treatment, significant improvement was shown in wave I and III. De Vos et al.,^[17] study on neural maturation in low serum thyroxine concentration reveals a delayed nerve conduction velocity in low serum thyroxine concentration in infants. He attributed to two reasons for this, one is a delay in myelination and other is because of disturbance in the neurotransmitter mechanism. At a molecular level Bell, et al^[18] explained that thyroid hormone affects the central and peripheral nervous systems via its role in gene expression, myelin production, its effects on the neurotransmitter system and axonal transportation. Knipper, et al.,^[19] in his study discussed that the TH can accelerate gene expression not only in oligodendrocytes but also in schwann cells of the auditory tract, may lead to an improved understanding of the role of TH in the process of myelinogenesis. He also explained that the auditory system nerve conduction and impulse transmission from the cochlea to the brainstem can occur coincidentally with initial transduction of sound signals only in the presence of TH. Abbott RJ, et al^[20] reasoned, diminished myelin production and alteration in cerebral metabolism during acute hypothyroidism may be the possible explanations for the reduction of wave I, V Amplitudes, which can be reversed after treatment.

On the contrary to this Di Lorenzo, et al^[11] and Vanasse^[12], recorded abnormal BAEP in hypothyroid patients and found that they remain abnormal even after treatment. But Ozata, et al.,^[15] found no abnormalities in BAEP in

patients with subclinical hypothyroidism and concluded that BAEP are not affected in subclinical hypothyroidism. They explained that this could be due to variation in recording procedure, sample size and extent of dysfunction.

In the IPL of BAEP, there was a significant prolongation of IPL I-V in hypothyroid patients without treatment and significant increase in hypothyroid patients with TH treatment. But no abnormalities were found in IPL I-III and III-V. Anand, et al.^[16], Vikas, et al.^[14], and Thorton, et al.^[10] were also showed that there was a significant prolongation in wave I-V in hypothyroid patients and significant improvement after TH treatment. The abnormalities on the basis of low metabolic rate and a low body temperature of these patients and confirmed no evidence of retrocochlear lesions. Stockard, et al.,^[21] first showed that the effect of hyperthermia on the ABR was to increase the I-V interval. They reported an increase of approximately 0.18 ms per °C drop in temperature. Two further studies by Kusakari, et al.,^[22] also confirmed the previous work and gave estimates of 0.42 and 0.28 ms increase per °C drop in temperature. Cuddon, et al.,^[23] have explained the biochemical reason behind changes in neural transmission. Increased amounts of glycogen and glucosaminoglycans in the cytoplasm, e.g. in Schwann cells and perineural cells in humans, has been described as well as signs of demyelination and axonal degeneration and causes neuropathy by compression as a result of myxoedematous deposits which occur in and around especially the nerves like vestibulocochlear and facial where they exit through os temporale. Bell, et al.,^[18] have shown that a decreased absorption of calcium in hypothyroidism and this could affect the synaptic transmission within auditory pathway.

Recently Thomas Weber, et al.,^[24] studied at the molecular level and had identified a protein called as cochlear motor protein, "prestin", which is a sulphate/ anion transport protein and he proposed this as OHC (Outer Hair Cell) motor molecule. Likewise Niels Brandt, et al.^[25] in his experimental study using patch clamp recording immunocytochemistry in hypothyroid rats have identified similar protein also in IHC (Inner Hair Cell). "Otoferlin" is one of the IHC protein thought to play an essential role in voltage gated K⁺ conductance and rapidly activating Ca²⁺ channels resulting in missing expression of BK (voltage gated K⁺) current. They proved that thyroxine is a first transcriptional regulator of these motor proteins as a direct or indirect modulator of subcellular distribution which is important for sound transmission. But vanasse, et al.^[12] reported that audiometry and BAEP values increased with age and were not modified when repeated after treatment. He suggested that the hearing loss in these patients could be secondary more to aging than to hypothyroidism.

In the present study, amplitude of BAEP as shown in Table 2, there was significant reduction in amplitudes I-Ia and V-Va in hypothyroid patients without treatment and significant increase in amplitudes I-Ia and V-Va in hypothyroid patients with treatment. Fors, et al.,^[2] study on neurological manifestations of hypothyroidism, explained that the hypothyroidism causes an ATP deficiency and diminished ATPase-activity impairs sodium-potassium pump activity, with a change in pump-dependant axonal transport in neurons as a result leads to reduced axonal transport in nerve fibres. Yumnam, et al.,^[13] also reported that there was decrease in amplitude of wave I and significant decrease in amplitude of wave V and significant improvement after treatment. He explained that this could indicate that there is a better recruitment of neuronal pool of the generators of these waves of BERA in the brainstem which may further go in favor of subjective hearing improvement.

Normal levels of thyroid hormones are required for proper excitability of the peripheral auditory pathway, thalamocortical projections and auditory processing at the cortical level. The changes in BAEP could be multi etiological factors such as low body temperature, alteration in cerebral metabolism, myxoedematous infiltration, defective myelination and regulator proteins like "otoferlin" and "prestin" which is entirely depend upon the metabolic action of thyroxine.

The TH therapy can induce axonal regeneration. The mechanism of improvement in sensory functions may be multi factorial as it has been shown that thyroid hormone do influence synthesis and release of neurotransmitter and sensitivity of receptors particularly H1 and H2 receptors in the brain. Thus in hypothyroid state, sensory functions might be deranged and they revert back to normal after treatment. The present study thus provides elec-

trophysiological evidence to this effect. However the exact mechanism for such improvement remains to be further investigated.

CONCLUSION

The results of the present study conclude that in hypothyroid state there might be a slow conduction at the periphery and with treatment there is a better recruitment of neuronal pool of the generators of the waves of BAEP in brainstem. In conclusion, the acute hypothyroidism may lead to reversible alteration in auditory pathway in central nervous system as determined by BAEP recordings. So brainstem auditory evoked potential could be useful to evaluate the effect of hypothyroidism on auditory pathway in the central nervous system and to monitor response to treatment.

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