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Original Article

Physiology Section

Evaluation of the Female Patients with Subclinical Hypothyroidism by Brainstem Auditory Evoked Potentials: Case-Control Study

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ABSTRACT

Introduction: Hypothyroidism, a common endocrinological disorder is quite prevalent in its subclinical state in the adult population. Nervous system involvement is frequent in hypothyroidism with documentation of peripheral and central conduction delays as abnormal latency prolongations in Brainstem Auditory Evoked Potential (BAEP) records. Subclinical hypothyroidism however, has been less extensively studied for investigating the involvement of the auditory functions.

Aim: To assess the auditory functions and Central Nervous System (CNS) involvement in the patients with subclinical hypothyroidism by recording BAEP.

Materials and Methods: The study comprised of 50 females (25 females with subclinical hypothyroidism and 25 age-matched healthy females) in the age-group of 30-50 years. BAEP absolute and Interpeak Latencies (IPLs) (I, III and V, I-III, III-V and I-V) were compared between the two groups by unpaired t-test. The $p<0.05$ was considered as statistically significant.

Results: Mean BAEP absolute latencies (III and V) increased in the subjects with subclinical hypothyroidism as compared to controls ($p<0.001$) (both the ears) and wave I absolute latency also increased with $p<0.001$ (both the ears) by unpaired t-test. Among IPLs (interpeak latencies), III-V and I-V IPLs exhibited increase ($p<0.01$), while I-III IPL did not vary with statistical significance (both the ears) in the two groups.

Conclusion: Patients with subclinical hypothyroidism were found to demonstrate central as well as peripheral auditory pathway affections. BAEPs can prove valuable and sensitive tests to detect involvement of the CNS and auditory dysfunctions earlier in hypothyroidism.

Keywords: Absolute latency, Auditory pathways, Interpeak latency, Thyroid stimulating hormone

INTRODUCTION

Thyroid disorders are the most common endocrine disorders in India [1]. Hypothyroidism affects 1 in 10 people in our country while the prevalence in the United Kingdom and United States is less than 5% [2,3]. The highest prevalence of hypothyroidism has been reported in the age group of 46-54 years (13.1%) with female preponderance, as reported by the various researches [2,3].

Hypothyroidism is an insidious clinical condition with significant morbidity. Subclinical hypothyroidism is a state of hypothyroidism defined as serum Thyroid Stimulating Hormone (TSH) concentration above the statistically defined upper limit of the reference range and serum free T4 (FT4) concentration within its reference range [4].

BAEP, the electrophysiological tests which assess the functional integrity of auditory pathways can be useful measures to evaluate the effect of hypothyroidism on the auditory pathways. BAEPs are responses of the auditory nerve, brainstem, and higher subcortical structures to acoustic stimulation [5]. Early subclinical neurological dysfunctions may be evaluated by using BAEP as a useful tool. Peripheral and central conduction delays have been documented as abnormal latency prolongation in hypothyroidism while there are also some studies which state no statistically significant alterations in BAEP [6-10]. Most of the above studies however, have been performed in the patients with overt hypothyroidism. The documentation for the assessment of auditory functions in subclinical hypothyroidism is meagre and conflicting [11-13].

Subclinical hypothyroidism is not only a prevalent condition but also its progression to overt disease is not infrequent [14-16]. Detection of subclinical involvement of auditory functions and brainstem affection at this earlier stage in these subjects can prove valuable. Hence, the present study was planned to assess the auditory functions in the patients with subclinical hypothyroidism, an earlier stage of hypothyroidism, by recording BAEP.

MATERIALS AND METHODS

It was a case-control study which comprised of 25 females diagnosed with subclinical hypothyroidism and 25 age-matched healthy females. Sample size was estimated on the basis of the mean difference in wave V absolute latency among subclinical hypothyroid cases and controls in a previous similar study [12]. Taking the mean difference of 0.51 ms in wave V latency (as the difference was significant) among subclinical hypothyroid cases and controls with SD of 0.62 ms among cases and 0.26 ms among controls [12], a sample size of twenty-four in each group was calculated at 95% confidence interval and power of 95%. Hence twenty-five subjects in each group were finally included in the study.

BAEP was recorded in the Electrophysiology laboratory in the Department of Physiology, Maharishi Markandeshwar Institute of Medical sciences, Mullana, Ambala, Haryana. Patients were selected from the outpatient and inpatient departments of surgery and medicine and age and sex matched controls were the inhabitants of the area of study. Ethical committee approval from the institute was obtained to conduct the study. Informed consent from the subjects was taken and a detailed clinical history obtained. Subjects underwent detailed clinical examination including neuro-otological examination and were explained about the recording procedure. Among the anthropometric measures, head size of the subjects was measured from nasion to inion. Body Mass Index (BMI) was calculated as weight (kg)/height (m^2). The subjects were classified into two groups: Group I (controls) with 25 healthy females in the

age-group of 30-50 years (mean age: 36.92±6.2 years) and Group II (cases) with 25 females with subclinical hypothyroidism in the age-group of 30-50 years (mean age: 38.28±6.84 years)

Inclusion Criteria

Patients with acquired subclinical hypothyroidism with TSH level >6μIU/ml (lab serum reference ranges in adults: 0.28-6 μIU/ml) and FT_4 >0.8 ng/dl (lab serum reference ranges in adults: 0.8-2.8 ng/dl) (by Chemiluminescence immunoassay method) in the age group of 30-50 years with normal hearing were included in the study as cases; and subjects with TSH and FT_4 levels within the lab reference ranges (by Chemiluminescence immunoassay method) in the age group of 30-50 years with normal hearing were included as controls.

Exclusion Criteria

Subjects with metabolic or other endocrine disorders, use of ototoxic drugs, and history of drug abuse (nicotine, alcohol, opium etc.), hereditary and degenerative diseases, cigarette smoking, ear surgery, radiotherapy or chemotherapy were excluded from the study. Also, elderly patients, obese patients and other reasons known to cause raised TSH but not subclinical hypothyroidism like TSH secreting pituitary adenoma, impaired renal functions and adrenal insufficiencies, formed the exclusion criteria for the study group.

Biochemical Analysis

All patients and controls underwent thyroid profile tests by Chemiluminescence immunoassay method. The laboratory reference ranges were: TSH: 0.28-6 μIU/ml, Free T3: 2.3-4.2 pg/ml and Free T4: 0.8–2.8 ng/dl.

The time from the diagnosis to the time of BAEP recording ranged from less than one month to six months. Subclinical hypothyroidism was confirmed three to six months after the initial results in order to exclude the transient causes of a raised TSH [14].

Brainstem Auditory Evoked Potential Recording

The recording was done by using Allengers Scorpio-EMG, EP, NCS equipment. Standard disc surface electrodes were placed after preparing the scalp skin. Electrode placement was according to international 10/20 system. Active electrode was placed at Mi, reference electrode at Cz and ground electrode at Fpz [5]. Monaural auditory stimulus with rarefaction clicks of 0.1 ms pulse was provided. Click intensity of 80 dB nHL was delivered through headphones at a rate of 11.1/s with masking of contralateral ear with white noise of 30 dB below the BAEP stimulus. The system band pass filter setting was at 100-3000 Hz. A total of 2000 clicks were presented. To verify the reproducibility of the waveform, two responses were recorded and superimposed.

STATISTICAL ANALYSIS

The study parameters were absolute latencies of wave I, III, and V (most clinically useful waves) and IPLs I-III, III-V and I-V [17]. The data was expressed as mean±SD. Amplitudes were not considered for comparisons in our study because of their high variability [18]. Unpaired Student's t-test was used for the comparison between the two groups and correlation of TSH levels with BAEP latencies was obtained using Pearson correlation coefficient using Statistical package for social science (SPSS) version 20.0 statistical software. The p<0.05 was considered as significant.

RESULTS

Mean ages in the groups (controls and subjects with subclinical hypothyroidism) were 36.92±6.2 years and 38.28±6.84 years respectively with no statistically significant difference (p>0.05). Similar non-significant statistical differences were also observed for the comparisons between anthropometric data (head sizes as well as BMI) in the two groups (p>0.05) [Table/Fig-1]. Mean TSH level in

	Number of subjects	Age (years) (Mean)	BMI (kg/m²) (Mean)	Head size (cm) (Mean)	Thyroid profile*	
					TSH Levels (μIU/ml) (Mean)	Free T4 levels (ng/dl) (Mean)
Group I (Controls)	25	36.92 ±6.2	23.5± 2.5	32.1±1.57	1.99±0.54	1.77±0.4
Group II- (Cases with subclinical hypo-thyroidism)	25	38.28 ±6.84	24.25± 4.69	32.76±1.44	24.76±28.08	1.43±0.41
p-value		0.47 (NS)	0.48 (NS)	0.13 (NS)	<0.001	<0.01

[Table/Fig-1]: Demographic and anthropometric data and the thyroid profile (mean±SD) compared in the two groups.
BMI- Body mass index, kg-kilogram, m-meter, cm- centimetres, TSH-Thyroid stimulating hormone, T4-Tetraiodothyronine, NS-Not significant.
*p<0.05 for the comparison between the two groups by unpaired t-test

controls was 1.99±0.54 μIU/ml while in cases it was 24.76±28.08 μIU/ml (p-value <0.001). Free T4 measurements revealed that the mean values in the two groups varied (controls: 1.77±0.4 ng/100 ml and cases: 1.43±0.41 ng/100 ml) with a statistical significance of p<0.01 [Table/Fig-1].

Mean BAEP absolute latency comparison revealed that wave III and wave V latencies increased in the Group II (subjects with subclinical hypothyroidism) as compared to Group I (controls) with p<0.0001 (both the ears), while the increase in wave I absolute latency in the group II revealed a statistical significance of p<0.001 (both the ears) (unpaired t-test) [Table/Fig-2].

Increase in mean interpeak latencies was also observed in the group II with p<0.01 for IPLs III-V and I-V while I-III IPL did not vary with

Study groups	Number of subjects	Absolute latency wave I (ms ± SD)		Absolute latency wave III (ms ± SD)		Absolute latency wave V (ms ± SD)	
		R*	L*	R**	L**	R**	L**
Group I (Controls)	25	1.62 ± 0.097	1.60 ± 0.09	3.57 ± 0.11	3.59 ± 0.09	5.55 ± 0.099	5.56 ± 0.14
Group II (Cases with subclinical hypothyroidism)	25	1.77 ± 0.17	1.75 ± 0.17	3.74 ± 0.12	3.73 ± 0.12	5.81 ± 0.14	5.87 ± 0.26

[Table/Fig-2]: Mean BAEP absolute latencies compared in the two groups. ms-milliseconds, SD-Standard Deviation, R-Right, L-Left.
* p<0.001 for the comparison between the two groups by unpaired t-test
**p<0.0001 for the comparison between the two groups by unpaired t-test

Study groups	Number of subjects	Interpeak latency I-III (ms ± SD)		Interpeak latency III-V (ms ± SD)		Interpeak latency I-V (ms ± SD)	
		R	L	R*	L*	R*	L*
Group I (Controls)	25	1.95 ± 0.13	1.99 ± 0.11	1.98 ± 0.1	1.97 ± 0.13	3.93 ± 0.11	3.95 ± 0.16
Group II (Cases with subclinical hypothyroidism)	25	1.98 ± 0.19	1.977 ± 0.21	2.08 ± 0.2	2.15 ± 0.27	4.03 ± 0.15	4.13 ± 0.3

[Table/Fig-3]: Mean BAEP interpeak latencies compared in the two groups. ms-milliseconds, SD-Standard deviation, R-Right, L-Left.
*p<0.01 for the comparison between the two groups by unpaired t-test.
I-III interpeak latency differences between the groups were not significant (both right and left ears) (p>0.05) (unpaired t-test).

statistical significance (both the ears) (unpaired t-test) [Table/Fig-3].

The correlation-coefficient (r) for mean TSH levels and absolute latencies of wave I was 0.1 and 0.09; for wave III, it was 0.19 and 0.24 and for wave V it was 0.18 and 0.34 (for right and left ears respectively). A p-value was not significant (p>0.05) for the correlations obtained. Similar findings (p>0.05) were obtained for the IPL studied (for III-V, r= 0.22 and 0.23 and for I-V, r =0.2 and 0.21, for right and left ears respectively.

DISCUSSION

BAEPs allow for the evaluation of the functional integrity of the auditory pathways. Assessment of the clinical state of the middle portion of the brainstem can be attempted by way of these investigations. Overt hypothyroidism has been found to have many electrophysiological alterations in the form of peripheral and central conduction delays. On the other hand, subclinical hypothyroidism, an earlier state with possible progression to overt form of the disease has been studied less extensively for investigating the involvement of the auditory functions.

The present study investigated 25 female subjects with subclinical hypothyroidism by BAEP studies and compared the records with those of the age-matched female controls. Only female patients could be included in the study, who visited the surgery and medicine departments during our study period. A greater difference in the prevalence rates of hypothyroidism among males and females might have contributed to the same [2,3]. The results from the present study indicate a prolongation of all BAEP absolute latencies studied (I, III and V) and also III-V and I-V IPLs in both the ears [Table/Fig-2,3]. Correlation studies between TSH levels and BAEP latencies however did not reveal significant findings. A recent similar study in the past by Sharma K et al., reports similar correlation results, with prolongation of wave V absolute latencies when compared to the control group in both the ears [12]. In another similar study by Figueiredo LC et al., significant increase in the absolute latencies of waves III and V in the subclinical group compared to the control group was observed [13]. Ozata M et al., also studied subclinical hypothyroidism, however, they have not reported abnormal BAEPs in the study group [11]. Other researchers have reported the BAEP latency delays in both absolute as well as IPLs in the previous studies but in the cases with overt hypothyroidism [6-8]. The present study however, strongly suggests the involvement of the auditory pathways in subclinical hypothyroidism, in a state before clinical hypothyroidism. Findings of delayed wave I latencies in both the ears in the present study are also attributed to hypothyroidism and not to inner cochlear abnormalities as the patients in the present study had normal audiograms. Hence, peripheral as well as central portions of auditory pathways are suggested to be affected, owing to the prolongation of both absolute latency of wave I and IPLs (III-V and I-V) in the present study.

In search of the pathogenetic mechanisms for the auditory dysfunctions and CNS involvement in the form of conduction delays in acquired hypothyroidism, several postulated mechanisms have been presented in the previous studies [19-22]. Knipper M et al., in their study discussed that the thyroid hormones can accelerate gene expression not only in oligodendrocytes but also in Schwann cells of the auditory tract thus emphasizing their role in the process of myelinogenesis.

The initial transduction of sound signals followed by signal transmission in the auditory system from cochlea to the brainstem largely depends on the presence of thyroid hormones [19]. Lai CL et al., recorded an early prolongation of I-V and III-V IPLs in the BAEP study of thyrex rats and the involvement of CNS was attributed to their hypothyroid states [20]. Low body temperature has also been implicated in the prolongation of BAEP latencies but in overt hypothyroids [21].

Hypothyroidism is a state believed to cause a decrease in cell energy production, affecting the microcirculation and consequently the metabolism and oxygenation of the involved organ is affected. Thus, auditory pathway dysfunctions in hypothyroidism have been speculated to be originating in the cochlea, central auditory pathway and/or in the retrocochlear region [22]. Regarding the probability of progression of subclinical hypothyroidism to overt hypothyroid state, it has been suggested that it is higher in women who had serum TSH concentrations >2.0 μIU/ml [23]. In our study, all the subjects with subclinical hypothyroidism were females with serum TSH concentrations >2.0 μIU/ml (mean value: 24.76±28.08 μIU/ml), hence likelihood of development of the overt form was more and evidences of neurological involvement by BAEP obtained at this stage warrants careful monitoring and follow up in these subjects.

LIMITATION

A follow up of the study group which could not be included in the study would have extended our knowledge regarding changes in the electrophysiological records of the patients, if any, with respect to the progression or recovery of their hypothyroid status.

CONCLUSION

The present study suggests the involvement of central as well as peripheral auditory pathways in subclinical hypothyroidism. Early involvement of the CNS can be detected through neurophysiological investigations like BAEP. It can help monitoring the progress of neuropathy and to reduce the morbidity of hypothyroid patients. Further studies evaluating the correlation between the electrophysiological parameters and duration of the disease and also those with the TSH levels are required, to strengthen the importance of preventive measures for CNS involvement and for a better prognosis of the condition.

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