

Visual Evoked Potentials in Overt Hypothyroid Patients before and after Achievement of Euthyroidism

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Abstract

Background: Visual evoked potential (VEP) measures the time taken for visual stimulus to travel from the eye to the occipital cortex. Hypothyroidism affects the central nervous system (CNS) through its role in gene expression, myelin production, axonal transportation, and neurotransmitters. Delay in the conduction of impulses results in abnormal VEP. **Objective:** Correlate the electrophysiological findings of VEP in newly diagnosed treatment-naïve hypothyroid patients before and after 3 months of treatment and to find the correlation with serum thyroid-stimulating hormone (TSH) levels. **Materials and Methods:** VEP was measured using Recorders and Medicare Systems Electromyograph Evoked Potential Mark II machine in 30 patients (serum TSH ≥ 10 mIU/L) between 18 and 50 years of age who were followed up after 3 months of treatment. **Results:** The mean age (\pm standard deviation) of the patients was 31.8 (± 8.3) years. There was prolongation of VEP latencies which tends to decrease following hormone replacement therapy. It was found to be most significant for P100 (ms) waveform ($P < 0.001$). The amplitude (P100-N75 mV) which was decreased in hypothyroid patients showed improvement following achievement of euthyroidism. Significant positive correlation was found between P100, N75 latency and pretreatment serum TSH levels. **Conclusion:** Hypothyroid patients may have changes in the latencies and the amplitude of VEP which are reversible to a great extent with thyroxine replacement therapy. VEP thus acts as a dependable marker for CNS affection in thyroid diseases to detect subtle early changes and to assess the response to treatment in correlation with the clinical improvement.

Keywords: Central nervous system, visual evoked potentials, thyroid-stimulating hormone

INTRODUCTION

Central nervous system (CNS) dysfunction is an important consequence of hypothyroidism.^[1] Visual evoked potentials (VEPs) is a simple, noninvasive electrophysiological test for evaluation of impulse conduction along the optic pathway. It measures the time taken for a visual stimulus to travel from the eye to the occipital cortex.^[2] Thyroid hormone affects the CNS through its role in gene expression, myelin production, axonal transportation, and neurotransmission.^[3] Abnormal VEP is the result of delayed conduction of impulses to the occipital cortex and is more prominent in untreated hypothyroid patients especially those in advanced stage of the disease.^[1]

MATERIALS AND METHODS

A single center prospective comparative study carried out in the Department of Physiology in collaboration with the

Department of Endocrinology, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana.

Patient population

Treatment-naïve newly diagnosed patients of overt hypothyroidism (serum thyroid-stimulating hormone [TSH] ≥ 10 mIU/L and decreased free T₄ and/or T₃) between the age group of 18 and 50 years ($n = 30$).

Objectives

To find the correlation between the serum TSH levels and the various VEP parameters both pre- and post-treatment.

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Study design

VEP was recorded in above patient population before and after (3 months) treatment. Serum TSH levels were repeated 3 months posttreatment with thyroxine supplement.

Baseline VEP of 30 age and sex-matched healthy volunteers (controls) was also recorded.

All participants gave their written informed consent to the study protocol which was approved by the Institutional Ethics Committee.

Exclusion criteria

Patients with chronic disorders, i.e., diabetes mellitus, cerebrovascular diseases, motor neuron diseases, parkinsonism, multiple sclerosis, neuromuscular disorders, smoking, alcoholism, chronic liver and kidney diseases, eye diseases, history of using miotic/mydriatic eye drops, altered sensorium, and psychiatric illness.

Recorders and Medicare Systems Electromyograph Evoked Potential Mark II machine settings for visual evoked potential recording

Full field size $>8^\circ$, size of pattern – 8×8 min, filter frequency 2–100 Hz, analysis time 100 ms, sensitivity $2 \mu\text{V}/\text{division}$, rate of stimulation 1.5 Hz and averaging 200, sweep speed – 50 ms/division, sweep duration – 300 ms, number of epochs – 100, mean luminance of the central field – $50 \text{ cd}/\text{m}^2$, background luminance – $30 \text{ cd}/\text{m}^2$, contrast – 70%.^[4]

Visual evoked potential recording

Patients were advised not to apply hair spray or oil on the scalp; glasses if any were to be worn during the test. The volume conducted evoked responses were picked up from scalp using disc type of AgCl electrodes placed as per 10–20 international system. An active electrode was placed on the scalp over the occipital cortex (Oz) with ground electrode on the forehead (Fz). Two reference electrodes were attached to right and left mastoid process designated as O1 and O2, respectively. All the electrodes were plugged to a junction box.

VEP was recorded using a pattern-reversing black and white checkerboard. A pattern-reversal stimulus consists of black and white checks that can change phase (black to white and white to black) abruptly and repeatedly at specified number of reversals per second.

Procedure for pattern-reversal visual evoked potentials

The participant was asked to sit on a chair in a relaxed position about 100 cm from the monitor. Visual stimuli consisting of black and white checks generated by a TV system reversing at the rate of 1.5 Hz were presented to one eye with other one being covered. The participant was instructed to focus on a red rectangle displayed at the center of the screen. The same procedure was repeated with another eye. A total of 100 monocular stimulations were presented. The signals were picked up by the electrodes and filtered, amplified, averaged, and displayed on the screen of Recorders and Medicare

Systems Electromyograph Evoked Potential Mark II, and were recorded.^[2]

Recordings of pattern-reversal visual evoked potential

The normal recording of pattern-reversal VEP consists of 3 waves - N75, P100, and N145. The nomenclature consists of designating peak as negative (N) and positive (P) followed by the typical mean peak latency (e.g., N75 signifies peak of negative wave occurring after 75 ms of the stimulus). The amplitude of P100 from the preceding N75 peak was measured in mV (crest to trough).

Statistical analysis

The statistical analysis was done using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Data were analyzed/described using mean and standard deviation (SD). Student's paired *t*-test was used to compare the VEP parameters among the pre- and post-treatment patient population. Unpaired *t*-test was used for the comparison between healthy controls and pretreatment hypothyroid patients. Pearson's correlation coefficient (*r*) was calculated for correlation of TSH, T3, and T4 with VEP parameters (N75, P100, and N145). All the tests were two-tailed and $P < 0.05$ was considered as statistically significant.

OBSERVATION AND RESULTS

The mean age (\pm SD) of the patient population was $35.83 (\pm 6.7)$ years while that of the controls was $31.8 (\pm 8.32)$. There were 26 female and 4 male patients. The range of serum TSH levels in treatment-naïve hypothyroid patients was 10.4–500 mIU/L. The mean (\pm SD) serum TSH levels decreased from $93.51 (\pm 128.04)$ to $2.79 (\pm 1.72)$ mIU/L post 3 months of treatment with thyroxine supplement [Figure 1].

Comparison of visual evoked potential latency and amplitude of healthy controls versus pretreatment hypothyroid patients

- VEP latency N75, P100, N145 was found to be prolonged in the cases (overt hypothyroid patients) as compared to the controls both on the right as well as the left side. The difference was statistically significant ($P < 0.001$) for N75

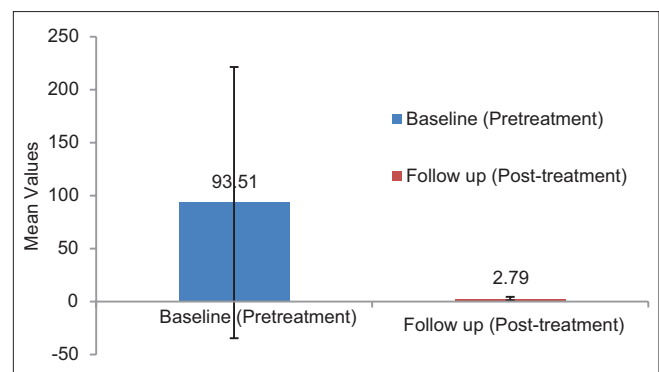


Figure 1: Pretreatment versus posttreatment thyroid-stimulating hormone levels in cases

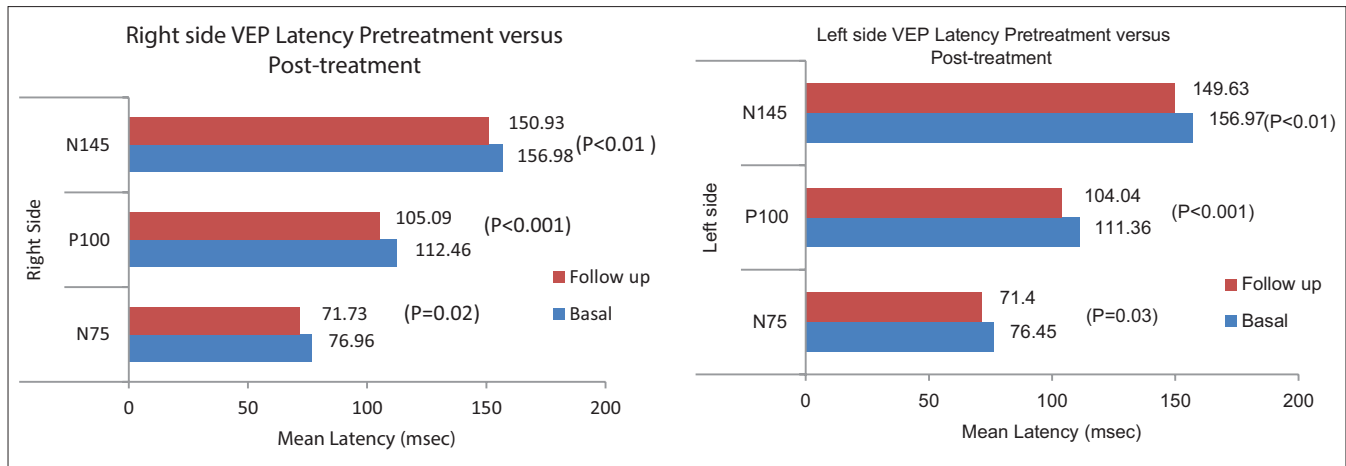


Figure 2: Comparison of visual evoked potential latency pretreatment versus post-treatment (before and after treatment)

and P100 waveforms both on the right as well as the left side

- VEP amplitude on both right and left side was lower in the cases as compared to controls. However, the difference was statistically significant only for the right side ($P = 0.05$).

Comparison of visual evoked potential latency and amplitude pretreatment versus post-treatment (before and after treatment)

- After 3 months of treatment with thyroxine supplements, the VEP latencies for N75, P100, and N145 decreased in both right and left side with the difference being statistically significant for P100 ($P < 0.001$) and N75 ($P < 0.05$) waveforms [Figure 2]
- Post-treatment, the VEP amplitude also showed an improvement although it was significant only on the left side ($P 0.01$) [Figure 3].

Correlation of visual evoked potential parameters with thyroid hormones

- Pearson’s correlation coefficient (r) showed moderate correlation between baseline TSH and baseline N75/P100 [Table 1]. N145 latency showed mild negative correlation with serum TSH levels which indicates that with increasing concentration of TSH, N145 latency decreased [Table 1]
- Post-treatment, Pearson’s correlation coefficient was mild [Table 2].

DISCUSSION

The present study confirms definite CNS involvement in hypothyroidism as supported by Khedr *et al.*^[5] We demonstrated prolongation of latency and decrease in the amplitude of VEP waveforms in hypothyroid patients which is consistent with the results of previous studies.^[1,6] These changes are reversible with thyroxine replacement therapy.^[7-9] The exact mechanism for this reversibility is not clearly known. However, central retinal dysfunction and

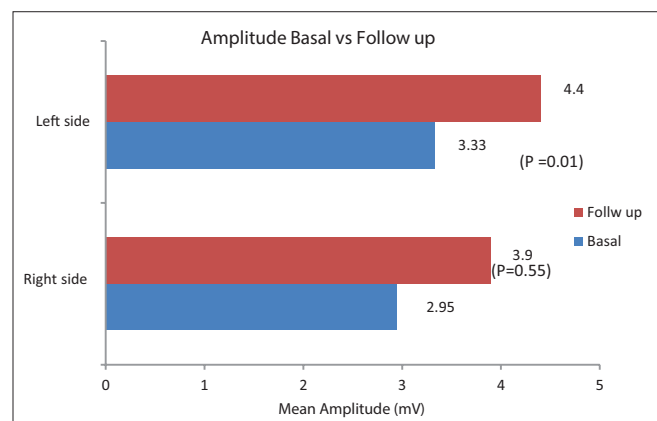


Figure 3: Comparison of baseline versus follow-up of patients' visual evoked potential amplitude (before and after treatment)

hormonal imbalance causing metabolic and/or structural alterations ultimately leading to segmental demyelination have been put forth as plausible explanations.^[10-12] Hyponatremia, a feature of hypothyroidism, may also result in disorder of nerve excitability. The latency depends on an intact, myelinated nerve as myelin, and saltatory conduction is essential for fast action potential propagation in normal participants. In contrast, the amplitude of the waveform depends primarily on the number of axons functioning within the nerve. Slowing of conduction velocity or prolongation of latency usually implies defects in myelination and loss of amplitude due to axonal dysfunction. In hypothyroidism, the mitochondrial oxidative activity, synthesis, degradation of proteins, and sensitivity of tissues to catecholamine are affected, and hence, demyelination occurs due to oxidative damage to myelin membrane and oligodendroglial cells. P100 is a prominent peak that shows relatively little variation between the participants, minimal within interocular difference, and minimal variation with repeated measurements over time.^[12]

Our study showed statistically significant improvement in amplitude and latency of VEP after treatment with

Table 1: Pretreatment Pearson’s correlations of thyroid hormone levels with baseline visual evoked potential latency and amplitude both in the right and left eye

	Right side				Left side			
	N75	P100	N145	Amplitude	N75	P100	N145	Amplitude
TSH	0.329*	0.324*	-0.198	-0.103	0.464*	0.365*	-0.119	-0.227
T3	-0.170	0.063	0.085	-0.126	-0.283	-0.176	0.072	-0.075
T4	-0.236	-0.115	-0.001	-0.047	-0.186	-0.162	-0.057	-0.130

<0.3: Mild correlation, 0.3-0.5: Moderate correlation, >0.5: Strong correlation. Positive correlation: +ve values, Negative correlation: -ve values. TSH: Thyroid-stimulating hormone

Table 2: Posttreatment Pearson’s correlation of thyroid-stimulating hormone with follow-up visual evoked potential latency and amplitude - right and left side

	Right side				Left side			
	N75	P100	N145	Amplitude	N75	P100	N145	Amplitude
TSH	0.046	0.103	0.108	0.097	0.165	0.218	0.038	0.007

TSH: Thyroid-stimulating hormone

thyroid supplements indicating that hypothyroidism affects myelination. We also demonstrated moderate correlation of baseline N75 and P100 latency with serum TSH levels in pretreatment hypothyroid patients. Study done by Huang *et al.* showed no correlation between the VEP parameters and pretreatment thyroid hormone profile, while the study by Tamburini *et al.* showed there was a significant correlation between P100 latency and total T3 and T4 levels.^[6,11] To the best of our knowledge, this is the first study in the Indian population documenting correlation of all VEP waveforms in hypothyroid patients pre- and post-treatment with serum TSH levels. Our findings signify that there is a definite neurological deficit in thyroid deficiency, which can involve the CNS at a much earlier stage and increases with an increased duration of the disease.^[5]

The sample size of our study was small; a larger sample size would have provided better statistical analysis. We did not perform subgroup analysis to correlate the severity of VEP abnormality with various categories of serum TSH levels due to the small sample size and did not include patients with subclinical hypothyroidism in our study. However, our study provides a framework on the basis of which larger studies can be carried out to look for association of severity of hypothyroidism with changes in VEP. The use of robust statistical analysis along with healthy controls for comparison is the strength of our study.

CONCLUSION

VEP acts as a dependable marker for CNS affection in hypothyroidism.^[13] This neurophysiologic parameter permits quantization of the effects of hypothyroidism on the CNS and the extent and rate of response to thyroid hormone replacement therapy.^[10] The hormonal and metabolic changes which are responsible for the electrophysiological changes may occur early in the disease course and can cause

symptoms before the diagnosis of the thyroid disease.^[11] After thyroxine replacement, VEP studies revealed significant improvement, in correlation with clinical amelioration. The electrophysiological study provides an objective method for monitoring the function of CNS in hypothyroidism before and after thyroxine treatment.^[10]

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Conflicts of interest

There are no conflicts of interest

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