Peripheral and Central Nervous System Involvement in Recently Diagnosed Cases of Hypothyroidism: An Electrophysiological Study

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Abstract

Background: Hypothyroidism, one of the most common endocrine disorders, may induce neurological abnormalities at an early stage of the disease. Aim: The study was designed to assess the electrophysiological alterations of some selected variables of nerve conduction, brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs) in hypothyroid patients. Subjects and Methods: Sixty patients of newly diagnosed hypothyroidism and an equal number of age-matched controls were selected for the study. Nerve conduction studies that included parameters as latencies, conduction velocities, and amplitude of motor nerves, i.e., median, ulnar, common peroneal, tibial nerve, and sensory nerves, i.e., median and sural nerves was performed in both hypothyroid patients and controls. Further, BAEPs and VEPs of all the patients were done. The data were compiled and statistically analyzed using Student’s unpaired t-test to observe any electrophysiological alterations in hypothyroid patients as compared to healthy controls. Results: On comparative evaluation, statistically significant increase in latency of median, ulnar, tibial, and sural nerves; decrease in conduction velocities of all the tested nerves and decrease in amplitude of median, tibial, and sural nerves was observed in hypothyroid patients. Statistically significant increase in latencies, interpeak latencies, and decrease in amplitudes of BAEP waves and statistically significant increase in P100 latency of VEP was seen in hypothyroid patients. Conclusion: The results of our study suggest that peripheral and central neuropathy develops in patients of hypothyroidism at an early stage of disease and the electrophysiological investigations of such patients can help in timely detection and treatment of neurological disorders that occur due to thyroid hormone deficiency.

Keywords: Brainstem auditory evoked potentials, hypothyroidism, nerve conduction, visual evoked potentials

Introduction

The thyroid gland secretes triiodothyronine (T3) and thyroxine (T4) hormones which play an important role in tissue development and metabolism. Both these hormones exert a number of effects on the neuromuscular system and brain. As a result, hypothyroidism may cause various neurological signs and symptoms. Some of the usual signs of hypothyroidism are muscle weakness, fatigue, muscular and mental sluggishness, weight gain, constipation and intolerance to cold.[¹] The prevalence of neuromuscular dysfunctions in thyroid disorders was found to be 20%–80%.[²]
Usually, hypothyroidism has both central and peripheral nerve involvement. Patients develop the usual manifestations of peripheral neuropathy as loss of reflexes, proximal muscle weakness, numbness, paresthesia, decreased sensations, and slowed muscle contraction and relaxation with prolonged.

In many studies conducted in the past, polyneuropathy was observed to be associated with hypothyroidism. The peripheral polyneuropathy may be due to the defect in nerve cell body, axons or myelin sheath and it results in decreased nerve conduction velocities and amplitudes in peripheral nerves. The most commonly involved nerves are the sural and median nerves, as the distal and sensory nerves are affected earlier. Carpal tunnel syndrome is the main cause of peripheral nerve damage in hypothyroidism due to median nerve entrapment.

Manifestations of cranial nerve involvement in thyroid dysfunction include sensory neural hearing loss and ophthalmopathy. About 37% of the patients of the patients with hypothyroidism were found to be suffering from hearing loss. Brainstem auditory evoked potential (BAEP) is a method used to assess the functional integrity of the thalamocortical projections relaying to the primary auditory cortex and association cortex. Some studies have reported prolongation of both central and peripheral conduction time even in subclinical hypothyroid conditions.

Hypothyroidism has been reported to be associated with prolonged latency and decreased the amplitude of visual evoked potentials (VEPs). VEPs are potential differences recorded from the scalp by electrodes in response to visual stimuli. It is a noninvasive and simple electrophysiological test to assess the effects of hypothyroidism on the central nervous system (CNS). It becomes important to know the abnormalities in VEP if electrodiagnostic techniques are to be used in the early detection of nerve involvement in hypothyroidism.

The present study was conducted to assess the electrophysiological alterations in peripheral and CNS in newly diagnosed hypothyroid patients.

**Subjects and Methods**

A cross-sectional prospective study was performed at Guru Gobind Singh Medical College, Faridkot from June 2015 to January 2016 in the Department of Physiology in collaboration with Department of Medicine. The protocol of the study was approved by the Institutional Ethics Committee.

**Study design**

A total of 120 participants of either sex between the age group 20 and 50 years were included in the study. The selection of participants was done by simple random sampling. The sample size was calculated to be 56 for each group using standard equation with a 95% confidence level and 80% power of the study.

The participants were divided into two groups:

- **Group A**: Consisted of 60 normal, healthy, age-matched individuals who were not diagnosed for any thyroid dysfunction; were considered as controls.
- **Group B**: Consisted of 60 newly diagnosed hypothyroid patients, who were not taking any treatment; were considered as cases.

The patients presenting with the clinical and neurological manifestations of thyroid disease to the general medicine outpatient department were evaluated first by their detailed general physical, systemic, and neurological examination. Body mass index (BMI) in kg/m² of all the participants was calculated, and their biochemical profile for free T3 (FT3), free T4 (FT4), and thyroid-stimulating hormone (TSH) levels was evaluated by chemiluminescence method using automated analyzer ( Beckman Coulter Access 2). Detection limits were 0.9 pg/ml for FT3, 0.25 ng/dl for FT4, and 0.003 µU/ml for TSH. Normal ranges of serum concentration of FT3, FT4, and TSH were taken to be 2.5–3.9 pg/ml, 0.61–1.12 ng/dl, and 0.35–5.50 µU/ml, respectively. After biochemical investigations, electrophysiological studies were done.

Informed consent of all the participants was taken.

**Exclusion criteria**

Pregnant females, all the patients with past or family history of neuropathy or neuromuscular diseases, history of alcoholism, kidney and liver disease, diabetes mellitus, use of drugs known to cause neuropathy, myopathy or ototoxicity, history of any ear or eye disorder, malignancy, other serious illnesses as cardiac failure or HIV infection were excluded from the study.

**Methodology of electrophysiological studies**

These studies were performed using the Digital Data Acquisition and Analysis system (Neurostim) at room temperature of 28–30°C. Electrodagnostic procedure was carried out as per standardized protocols to record the motor and sensory nerve conduction studies, BAEPs and VEPs. The patients were examined while lying comfortbly in the supine position. The skin was adequately prepared before application of the stimulating and recording electrodes so that a good contact can be made between the electrodes and skin.

**Nerve conduction studies**

The filters were set at 2 Hz–10 kHz for the motor studies and 5 Hz–2 kHz for the sensory studies. The sweep speed was set at 2–5 ms/division for the motor studies and 1–2 ms/division for the sensory studies. Stimulus duration of 50–1000 µs and current of 0–100 mA was required for effective nerve stimulation to get adequate responses. The nerve stimulator and three surface 1 cm disc electrodes were used as recording, reference, and ground electrodes for motor and sensory studies.
The motor nerve conduction studies were performed on median and ulnar nerves bilaterally in upper limbs and common peroneal and tibial nerves bilaterally in the lower limbs. The sensory nerve conduction studies were performed on median and sural nerves bilaterally in upper and lower limbs, respectively.

The motor nerve conduction studies included: determination of distal motor latencies, motor nerve conduction velocity and amplitude of the compound muscle action potentials.

The sensory nerve conduction studies included: determination of sensory latencies, sensory nerve conduction velocity and amplitude of sensory nerve action potentials.

Brainstem auditory evoked potential
For recording of BAEP, three disc electrodes were placed as follows:
- Active electrode: At the mastoid process ipsilateral to acoustic stimuli
- Reference electrode: At the vertex of the skull
- Ground electrode: At the forehead in the midline.

Both the ears of all the participants were tested. The contralateral ear was masked with white noise of 40 dB below the ipsilateral click stimuli to get the right response. Brief click acoustic stimuli (0.1 ms square wave pulse) alternating in polarity with 40 and 70 dB intensities were presented to the ear by an earphone. With a filter setting of 100 Hz (low cut) to 3000 Hz (high cut), 2000 sweeps were averaged. Sweep speed was set at 1 ms/division and sensitivity at 0.5 µv/division. Skin to electrode impedance was kept below 5 kOhm.

Peak auditory brainstem response latencies (I, III, and V), interpeak latencies (I–III, I–V and III–V), and amplitudes of waves (I–a, V–a) were measured.

Visual evoked potentials
For recording of VEP, three disc electrodes were placed as follows:
- Active electrode: 5 cm above the inion
- Reference electrode: 12 cm above the nasion. Linked ear reference was used as noncephalic reference
- Ground electrode: At the vertex of the skull.

With a filter setting of 1–3 Hz (low cut) to 100–300 Hz (high cut), 100 epochs were averaged. Sweep duration was 250–500 ms and speed was set at 50 ms/division. Skin to electrode impedance was kept below 5 kOhm. The signal amplification was 20,000–100,000. Both the eyes of all the participants were tested (one eye at a time). During the test, the participants were allowed to wear spectacles, if any. A checkerboard stimulus was produced on a computer monitor by a video pattern generator showing white and black checks that changed phase suddenly and repeatedly. The participants were instructed to fix their gaze at the center of checkerboard, a red square to avoid interference of potentials from eyeball movements. The fixation point for full field size was >8°. The luminance modulation was selected to give the reversal mode of stimulation at a rate of 1 Hz every 500 ms. The size of the pattern was 16” × 14”. The contrast of bright and dark checks was adjusted to be 50%–80%. The black and white monitor was placed 70–100 cm from the study subjects. The participants were given short periods of rest between each measurement so as to avoid fatigue and any associated increase in response variability. The latency of P100 wave of VEPs from both the eyes was noted from the waveform recordings.

Statistical analysis
The data were expressed as mean (standard deviation), and the values in healthy and hypothyroid individuals were compared by statistical analysis using Student’s unpaired t-test. \( P < 0.05 \) was considered statistically significant.

Results
As shown in Table 1, there was no statistically significant variation in mean age of subjects of both groups. However, FT3 and FT4 values were statistically significantly decreased while BMI and TSH values were statistically significantly increased in hypothyroid patients as compared to controls.

The motor nerve conduction studies in Table 2 show that the latency of median, ulnar and tibial nerves was statistically significantly increased in hypothyroid patients as compared to controls. The conduction velocities of all the motor nerves and amplitudes of median and tibial nerves were statistically significantly decreased in hypothyroid patients in comparison to controls while there was no statistically significant variation in latency and amplitude of common peroneal nerve and amplitude of ulnar nerve in two groups. The sensory nerve conduction studies show a statistically significant increase in latencies and decrease in conduction velocities and amplitudes of median and sural nerves in hypothyroid patients as compared to controls [Table 3].

Statistical analysis of BAEP findings demonstrated statistically significant increase in latencies, interpeak latencies, and decrease in amplitudes of waves among the cases as compared to controls [Table 4]. Table 5 shows statistically significant variation in mean age of subjects of both groups. However, FT3 and FT4 values were statistically significantly decreased while BMI and TSH values were statistically significantly increased in hypothyroid patients as compared to controls.

### Table 1: Comparison of age, body mass index and thyroid profile of controls and hypothyroid patients

| Parameters          | Controls (n=60) | Hypothyroids (n=60) | t     | P     |
|---------------------|----------------|---------------------|-------|-------|
| Age (years)         | 38.5 (4.22)    | 39.11 (5.04)        | 1.01  | 0.31  |
| BMI (kg/m²)         | 21.06 (2.36)   | 21.81 (2.27)        | 2.50  | 0.01  |
| FT3 (pg/ml)         | 2.64 (0.42)    | 1.10 (0.17)         | 37.23 | <0.001|
| FT4 (ng/dl)         | 1.01 (0.21)    | 0.82 (0.11)         | 18.02 | <0.001|
| TSH (µU/ml)         | 3.25 (0.36)    | 5.91 (0.54)         | 44.89 | <0.001|

BMI: Body mass index, TSH: Thyroid stimulating hormone, SD: Standard deviation, FT3: Free triiodothyronine, FT4: Free thyroxine.
Table 2: Comparison of latencies, conduction velocities, and amplitudes of motor nerves of controls and hypothyroid patients

| Variable                  | Controls (n=60) | Hypothyroids (n=60) | t     | P      |
|---------------------------|----------------|---------------------|-------|--------|
| Latency (ms)              |                |                     |       |        |
| Median nerve              | 2.91 (0.63)    | 3.54 (1.05)         | 5.63  | <0.001 |
| Ulnar nerve               | 2.76 (0.52)    | 3.03 (1.13)         | 2.37  | 0.01   |
| Common peroneal nerve     | 3.96 (0.75)    | 4.11 (1.14)         | 1.20  | 0.22   |
| Tibial nerve Conduction   |                |                     |       |        |
| velocities (m/s)          | 3.79 (0.74)    | 4.00 (0.87)         | 2.01  | 0.04   |

SD: Standard deviation

Table 3: Comparison of latencies, conduction velocities, and amplitudes of sensory nerves of controls and hypothyroid patients

| Variable                  | Controls (n=60) | Hypothyroids (n=60) | t     | P      |
|---------------------------|----------------|---------------------|-------|--------|
| Latency (ms)              |                |                     |       |        |
| Median nerve              | 59.23 (4.67)   | 53.91 (4.45)        | 9.03  | <0.001 |
| Ulnar nerve               | 54.86 (5.21)   | 53.32 (5.90)        | 2.14  | 0.03   |
| Common peroneal nerve     | 48.12 (4.56)   | 46.56 (5.81)        | 2.31  | 0.02   |
| Tibial nerve Amplitude    |                |                     |       |        |
| (µV)                      | 41.21 (5.57)   | 39.21 (7.78)        | 2.28  | 0.02   |

SD: Standard deviation

Discussion

Thyroid hormones regulate many functions and processes of the nervous system.[1] The findings of the present study show involvement of peripheral sensory and motor nerves of both upper and lower limbs in hypothyroid patients as assessed by nerve conduction and also of central nerve pathways as diagnosed by evoked potential studies. One of the mechanisms of deterioration of nerve conduction parameters may be the weight gain as shown by significantly high BMI in hypothyroid patients. In hypothyroidism, accumulation of mucopolysaccharides, chondroitin sulfate, and hyaluronic acid occurs in the interstitial spaces which tends to retain water and hence result in weight gain.[3] Their deposition in the tissues surrounding the nerves may lead to compression over the peripheral nerves resulting in swelling and degeneration of the nerves.[4,12]

Another cause of peripheral neuropathy in hypothyroidism can be energy deficit due to decreased oxidation of nutrients as thyroid hormones are involved in stimulation of the mitochondrial respiratory activity to produce energy in the form of adenosine triphosphate (ATP) during aerobic metabolism.[1] Furthermore, decreased degradation of glycogen leads to accumulation of glycogen deposits around the nerves. Hypothyroidism induced metabolic alterations may initially damage the functions and later on bring about structural changes in the nerves.[4] Thyroid hormones also increase ATPase activity and hence Na-K pump activity in healthy individuals.[1] In hypothyroidism, deficiency of ATP and decreased activity of ATPase and Na-K pump leads to alteration of pump dependent axonal transport and hence peripheral neuropathy.[13] Decrease in thyroid hormones can also cause primary axonal degeneration in the form of axon shrinkage, disintegration of neurofilaments and neurotubules, and active axonal breakdown.[4]

Nerve compression and axonal degeneration may act together to produce peripheral neuropathy in hypothyroidism. However, in another electrophysiological study done on subclinical hypothyroid patients, no alterations in electrodagnostic parameters was observed which signifies that there are no peripheral nerve dysfunctions in subclinical hypothyroidism.[15] In other morphological and neurophysiological studies,[16,17] peripheral neuropathy was linked to segmental demyelination of axons which was primarily due to metabolic alterations affecting Schwann cells and in some cases due to axis cylinder disease. In another study on hypothyroid patients, it was suggested that mucinous infiltrates may accumulate in peripheral nerves that can interfere mechanially with the metabolic exchange of nutrients in the neurons resulting in entrapment neuropathy.[18]

In another study, decrease in intraepidermal nerve fiber...
density was found to be cause of neuropathy in subclinical hypothyroidism.\textsuperscript{[19]}

In this study, results of BAEP and VEP are suggestive of CNS involvement in early stage of hypothyroidism. As far as VEP studies are concerned, our results are consistent with other studies\textsuperscript{[3,12,20]} which also observed VEP delay in hypothyroidism that was reversible after treatment. In hypothyroidism, mentation becomes slow and cerebrospinal fluid protein is elevated which may affect mitochondrial oxidative activity and synthesis of proteins along with sensitivity of tissues to catecholamines. Oxidative damage to myelin sheath and oligodendroglial cells results in demyelination causing prolongation of P100 latency in VEP.\textsuperscript{[21]}

Prolongation of I, III, and V wave latencies as found in other studies\textsuperscript{[7,8,22]} and reduction of wave I, V amplitudes in BAEP signifies that thyroid hormone deficiency affects the transmission in CNS. The involvement of CNS may be due to role of thyroid hormones in gene expression in oligodendrocytes and Schwann cells which cause myelination, its effects on neurotransmitters and axonal transportation in nerve fibers.\textsuperscript{[23]} Prolongation of interpeak latencies in hypothyroid patients may be caused by decrease in body temperature due to low metabolic rate,\textsuperscript{[7]} peripheral neuropathy due to demyelination, axonal degeneration and nerve compression by myxoedematous deposits,\textsuperscript{[24]} decreased synaptic transmission in auditory pathway due to decreased calcium absorption.\textsuperscript{[25]}

### Conclusion

Most of the neuropathy remains latent in the early phase of disorder, but the electrophysiological changes can be detected during this phase. Hence, we suggest electrophysiological studies such as nerve conduction studies in motor and sensory nerves of both upper and lower limbs, BAEP and VEP in hypothyroid patients early in the course of disease to alleviate the neurological symptoms. A follow-up study will be conducted for the same patients after 1 year treatment to see the results of hormone replacement therapy.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

### Table 5: Comparison of visual evoked potentials of controls and hypothyroid patients

| Wave | Mean (SD) Controls (n=60) | Mean (SD) Hypothyroids (n=60) | t | P |
|------|--------------------------|-----------------------------|---|---|
| Latency of P100 (ms) | 98.72 (0.89) | 109.47 (1.71) | 61.08 | <0.001 |

SD: Standard deviation

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