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A STUDY OF SENSORY NERVE CONDUCTION AND REACTION TIME IN NEWLY DIAGNOSED UNTREATED HYPOTHYROID SUBJECTS

Physiology

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ABSTRACT

Long term and untreated Hypothyroidism is known to be associated with peripheral neuropathy. The peripheral nerve involvement may begin at the early phase of the disease and may or may not manifest by the time of diagnosis. Objective was to assess functional status of the peripheral sensory nerves with nerve conduction study and sensory-motor coordination with audiovisual reaction times in newly diagnosed and untreated hypothyroidism. The study included a total of 120 female subjects with age ranging from 20 to 45 years. The bilateral sensory nerve conduction parameters viz. onset latency, amplitude of sensory nerve action potential and sensory nerve conduction velocity in median and sural nerves and Audio-visual reaction times were recorded in them using standard protocols and settings. The observations revealed significantly altered sensory nerve conduction parameters in terms of prolonged latencies, reduced SNAP amplitudes and slowed SNCV along with significantly delayed reaction times in hypothyroid females. The study indicated impairment of peripheral as well as central nervous system functions at the early phase of hypothyroidism and suggested utility of electro-physiological studies as a useful non-invasive tool for the detection of clinically silent neural involvement at the early stage of the disease.

KEYWORDS

Hypothyroidism Nerve conduction study Reaction Time

Introduction:
The thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) play key roles in regulation of body development and govern the rate at which metabolism occurs in individual cells. Various epidemiological studies in India show a prevalence rate of subclinical hypothyroidism (SCH) varying between 9% and 11.4%.[1] The progression to overt hypothyroidism (OHT) is approximately 2% to 5% per year. Hypothyroidism affects 3.8 – 4.6% of general population, with four times common in women.[2]

The prevalence of neuromuscular disorders in thyroid dysfunction is about 20-80%.[3] Peripheral nerve functions are affected and severity increases over a period of time. It may be due to the defect in axons, nerve cell body or myelin sheath. Most of the neuropathy remains latent in the early phase of disorder. This latent subclinical neuropathy has been greatly facilitated by various electrophysiological evaluation.[4] Nerve conduction study (NCS) is simple and non invasive tool to detect any alterations on nerve functions. NCS establishes diagnosis early and accurately than other electrodiagnostic techniques because of its sensitivity to detect conduction slowing; which is one of the early indicators of neuropathy.[5] Thus, functional as well as structural changes can be evaluated by these nerve conduction studies in sensory nerves.

Also along with involvement of peripheral nerve hypothyroidism has deleterious effects on central nervous system. The conspicuous slowing of movements and neuronal conduction velocity, changes in the threshold of hearing and visual processing of hypothyroid subjects have been shown to correlate with peripheral sensory and motor nerve dysfunctions and abnormal neuromuscular transmission. [6] Reaction time is the parameter which depends on the integrity of neuromuscular system. It is an interval between the application of stimulus and the initiation of appropriate voluntary response under the condition that the subject has been instructed to respond as rapidly as possible.

Thus it indicates the time taken by an individual to react to the external stimulus.[7]

Many studies in the past documented involvement of motor nerves especially the median nerve entrapment in carpal tunnel for hypothyroid subjects. Very few report the sensory neuronal involvement along with processing of auditory and visual pathway.

Aim and objective: To study the sensory nerve conduction velocities bilaterally in Median and Sural Nerve and to study the Visual and Auditory reaction time in newly diagnosed hypothyroid females and compare them with that of euthyroid females

Methods:
The study was cross sectional case control study. Present study was carried out in the Department of Physiology, Indira Gandhi Government medical College, Nagpur, Maharashtra and was duly approved by the ethics committee of the institution.

Study groups:
Total 120 female participants with age ranging from 20 to 45 years were categorized into two groups of 60 each. The sample size was calculated to be 56 for each group using standard equation (8) with a 95% confidence level and 80% power of the study.

Hypothyroid Group: included 60 newly diagnosed hypothyroid females attending out patient department for first time and were not started with hormone replacement therapy.

Control Group: included 60 euthyroid adult females from general population.

The hypothyroid patients were asked whether these symptoms were their first or main complaints, when they firstly visited to the OPD. They were evaluated first by detailed general physical and neurological examination. Then the biochemical profile was evaluated to confirm the diagnosis of hypothyroidism. The diagnosis of hypothyroidism was made by using Microwell ELISA technique with ERBA Thyrokit from ERBA Diagnostics Manheim GMBH, Germany.

The normal values of the hormones according to the laboratory kits were considered as follows:

TSH = 0.44 - 3.45 µIU/ml, total T4 = 5.3 - 12.1 µg/dL and total T3 = 0.51 - 1.58 ng/ml.

Inclusion and Exclusion Criteria:
Inclusion of the females in the age group of 20-45 years was done. Subjects having history of Diabetes Mellitus, Alcoholism/ substance abuse, Neuromuscular disorder, Leprosy, drug induced neuropathy, HIV, Liver diseases, Kidney disease and defect in vision and hearing were excluded from the study.

Study Protocol:
The subjects were asked to report for the study in the Department of

Physiology in the morning hours. All the participants were given detailed information about the project and written informed consent was obtained from every subject of the study.

After taking a detailed history, a complete general physical examination was carried out in day light. The neurological examination consisted of motor and sensory system separately on all the patients. The sensory modalities (tactile sensibility ie. Fine /gross touch, 2-point discrimination testing, pin prick, and vibration sense) were tested and graded according to a standard protocol. Anthropometric parameters like height and weight were measured, and body mass index (BMI) was calculated. After anthropometric measurements, all the participants were subjected to complete electrophysiological evaluation of peripheral sensory nerves.

Parameters studied:

Electrophysiological parameters
- Onset Latencies(OL) in milliseconds(ms)
- Sensory nerve action potential amplitude (SNAPA) in microvolts (μV)
- Sensory Nerve conduction velocities (SNCV) in meter per second(m/s)

Auditory reaction time was recorded for:
- Low frequency sound in milliseconds(ms)
- High Frequency sound in milliseconds(ms)

Visual reaction time was recorded for:
- Red light in milliseconds(ms)
- Green light in milliseconds(ms)

Recording procedure[9]
A standard 2 channel physiograph having RMS EMG EPMK II one of latest software in the study of nerve conduction was used for measurement. Subjects were acclimatized to standard room temperature for 10 minutes. After that the procedure was performed under following settings, for sensory nerve conduction Gain/sensitivity: 1-5μV/mm, Sweep speed: 1-2 ms/mm, Filter: 5-10 Hz (low frequency), 2-3 KHz. (High frequency)

Median nerve: The ring electrodes were placed after applying jelly to reduce resistance in air between electrode and skin surface. The Active electrode (A) was placed in contact with the radial sides of the digit being tested, slightly distal to the base of the digit. The Reference electrode (R) was placed 4cm distal to the active electrode. The Ground electrode (G) was placed on the dorsum of the hand. SNCV were measured by anti-dromic stimulation. Then the nerve was stimulated by placing the cathode of the stimulator 14 cm proximal to the active electrode (stimulation point 1, S1) over the median nerve at the wrist and the anode was directed proximally. Distances were measured by a standard measure tape and record was obtained on the screen.

Nerve fibers tested: C6 (2nd digit) and C7 (3rd digit) nerve roots through the upper and middle trunks, anterior division, and lateral cord of the brachial plexus.

Sural nerve: This study was performed with subject in side-lying or lateral position. The sensory conduction parameters in sural nerve were recorded by placing electrodes and stimulators on the foot. The Active electrode (A) was placed behind lateral malleolus. Reference electrode (R) was placed 4 cm distal to the active electrode. Ground electrode (G) was placed between the stimulating and recording electrodes.

Then the nerve was stimulated by placing the cathode of the stimulator 14 cm proximal to the active electrode (stimulation point, S1) in the midline or slightly lateral to the midline of the posterior lower leg. The anode was directed proximally. The record of SNAP was obtained on the monitor and was saved.

Nerve fibers tested: First and second sacral nerve roots, through the anterior and posterior divisions of the lumbosacral plexus and the tibial and peroneal nerves.

Reaction time[10]
Auditory and Visual reaction times were measured by Response analyser Yantra shilpa system, Pune. The device had display range from 0 to 9.999 seconds with display resolution of 0.001 second. Accuracy of the instrument was ± 0.002 second and power consumption was upto 12 watts maximum. Power supply was 220 volts, 30 Hz A.C. and working voltage 12 volts D.C. The device was exclusively designed to measure time in milliseconds. Autodisplay on the analyser indicated the reaction time of the individual to the appropriate stimulus.

Auditory reaction time using low frequency and high frequency sounds was recorded. The subject was instructed to respond, as soon as she heard the sound, by pressing the response key with an index finger already on it. Visual reaction time using red and green light was recorded. The subject was instructed to respond, as soon as she saw the glow by pressing the response key with an index finger already on it.

Data Analysis: Descriptive statistics in the form of mean±standard deviation (SD) was calculated for all observations. Unpaired-t Test was used for comparison of two groups. p value less than 0.05 was considered as significant.

Results:
Both the study groups were comparable with no statistical significant difference observed in mean of age and height (Table 1). Majority of subjects were belonging to the age 40 years and above in control group (26.67%) and hypothyroid group (28.33 %) (Table 2).

TSH level in hypothyroid was found to be elevated as compared to that of control. This elevation was statistically significant. The levels of T4 and T3 in hypothyroid were found to be decreased as compared to that of control and the difference was statistically significant (Table 1). Weight and BMI were found to be increased in hypothyroid as compared to that of control. This increase in weight and BMI of hypothyroid was statistically significant (Table 1).

Onset latency is the time interval in milliseconds (ms) from the point of stimulation to the initial negative deflection from the baseline. The onset latency was found to be delayed in both the nerves under consideration in hypothyroid as compared to that of control. This delay was statistically significant (Table 3, 4).

SNAP amplitude is most commonly measured from baseline to the negative peak in microvolt (μV). The amplitude of sensory nerve action potential was found to be reduced in bilateral median nerves in hypothyroid as compared to that of control and it was statistically significant except for sural nerve on both sides (Table 3, 4).

Sensory nerve conduction velocity is the measure of the speed of conduction across the sensory nerve which is calculated by dividing the distance between cathode of stimulation point 1 (S1) and the active recording electrode by onset latency of SNAPA. The SNCV was obtained on the monitor by feeding this distance in millimeters (mm).

The sensory nerve conduction velocity was found to be attenuated in both the nerves of hypothyroid as compared to that of control. This slower conduction was statistically significant. (Table 3, 4)

The reaction time for high and low frequency sound in hypothyroids was significantly delayed as compared to controls (Table 5). Also hypothyroids showed delayed response in visual reaction time than controls. The delay in response for red light was significant except for green light (Table 6).

Table 1: Showing comparison and analysis of Thyroid profile and various anthropometric parameters in control and hypothyroid group. Values are Mean ± SD.

Variable	Control group (n=60)	Hypothyroid group (n=60)	P value
T_3 (ng/mL)	0.57 ± 0.189	0.45 ± 0.26	<0.001 S
T_4 (μg/mL)	5.30 ± 0.43	5.00 ± 0.58	<0.001 S
TSH (μIU/mL)	3.20 ± 0.30	3.86 ± 0.31	0.001 S

Age (yrs)	32.41 ± 8.04	32.53 ± 7.60	<0.01 NS
Height (cm)	157.57 ± 2.04	157.80 ± 2.12	0.55 NS
Weight (kg)	52.57 ± 1.95	53.49 ± 1.65	<0.01 S
BMI (kg/m^2)	21.17 ± 0.69	21.49 ± 0.80	<0.01 S

S: significant NS: not significant

Table 2: Showing Age (years) difference of Control and Hypothyroid groups.

Variable Range	Control group		Hypothyroid group	
Years	Number	Percentage (%)	Number	Percentage (%)
20-24	14	23.33	13	21.67
25-29	13	21.67	6	10.00
30-34	7	11.67	8	13.33
35-39	10	16.67	16	26.67
40+	16	26.67	17	28.33
Total	60		60	

Table 3: Showing comparison and analysis between control and hypothyroid group for various sensory conduction parameters of Median nerve. Values are Mean ± SD.

Variable	Nerve	Control group (n =60) Mean ± SD	Hypothyroid group (n = 60) Mean ± SD	P value
OL (msec)	Right nerve	2.86 ± 0.49	3.94 ± 0.60	0.001 S
	Left nerve	2.72 ± 0.79	3.93 ± 0.60	0.001 S
SNAP amplitude (μV)	Right nerve	24.63 ± 2.40	22.99 ± 4.51	0.01 S
	Left nerve	24.88 ± 3.08	23.11 ± 5.51	0.03 S
SNCV (m/sec)	Right nerve	54.54 ± 1.49	48.35 ± 5.56	0.001 S
	Left nerve	54.54 ± 2.57	48.02 ± 6.43	0.001 S

S: significant

OL: Onset latency, SNAP: Sensory nerve action potential,
SNCV: Sensory nerve conduction velocity.

Table 4: Showing comparison and analysis between control and hypothyroid group for various sensory conduction parameters of Sural nerve. Values are Mean±SD

Variable	Nerve	Control group (n =60) Mean ± SD	Hypothyroid group (n = 60) Mean ± SD	P value
OL (msec)	Right nerve	2.38 ± 0.70	2.94 ± 1.65	0.01 S
	Left nerve	2.50 ± 0.76	3.25 ± 1.59	<0.001 S
SNAP amplitude (μV)	Right nerve	15.85 ± 2.66	15.01 ± 2.67	1.73 NS
	Left nerve	15.49 ± 2.67	14.60 ± 2.69	0.07 NS
SNCV (m/sec)	Right nerve	53.35 ± 3.36	45.33 ± 7.67	0.001 S
	Left nerve	53.84 ± 2.77	45.94 ± 5.81	0.001 S

S: significant, NS: not significant

OL: Onset latency, SNAP: Sensory nerve action potential,
SNCV: Sensory nerve conduction velocity.

Table 5: Showing comparison and analysis between control and hypothyroid group for auditory reaction time (seconds). Values are Mean ± SD.

Variable	Control group (n =60) Mean ± SD	Hypothyroid group (n = 60) Mean ± SD	P value
Low frequency sound	0.160 ± 0.01	0.164 ± 0.01	<0.001 S
High frequency sound	0.157 ± 0.01	0.161 ± 0.01	<0.01 S

S: significant

Table 6: Showing comparison and analysis between control and hypothyroid groups for Visual reaction time (seconds). Values are Mean ± SD.

Variable	Control group (n = 60) Mean ± SD	Hypothyroid group (n = 60) Mean ± SD	P value
Red light	0.188 ± 0.01	0.195 ± 0.01	<0.01 S
Green light	0.190 ± 0.01	0.196 ± 0.02	0.06 NS

S: significant, NS: not significant

Discussion:

In the current study, we investigated the sensory nerve conduction and audiovisual reaction time in newly diagnosed untreated hypothyroid females. Our data illustrated significant main effects of low thyroid hormone levels on weight and BMI as well as altered sensory nerve conduction parameters and delayed reaction time as compared to that of controls.

The increased weight in hypothyroids might be due to accumulation of mucopolysaccharides, hyalorunic acid and chondroitin sulphate in the interstitial spaces which, because of their hydrophilic nature, retain water along with them resulting in weight gain.[11] Although the BMI was increased in hypothyroid, the increment was within normal range. It indicates the absence of true obesity in them. These findings related to weight and BMI[12,13]

The thyroid hormone affects the central and peripheral nervous system via its role in gene expression, myelin production, its effects on the neurotransmitter system and axonal transportation. [14] In hypothyroidism the metabolic alteration caused by hormonal imbalance affects the Schwann cell, inducing a segmental demyelination. Primary axonal degeneration has also been shown electrophysiologically in hypothyroidism. Initially only functional loss is seen in nerve, but later structural alteration may occurs as the disease progresses.[15,16]

Our findings showed that there was significant slowing of peripheral conduction velocity in Median and Sural sensory nerves in hypothyroidism which can be explained by a reduction in myelination, and the gene for myelin basic protein is, in fact, regarded as one of the few genes known to be directly regulated by thyroid hormone.[17]

Concerning the action of thyroid hormone on neuronal excitability there seems to be a common finding that the density of voltage-gated Na+currents is up-regulated by thyroid hormone rendering the cells more excitable.[18]

Our study also showed significant prolonged onset latencies and decreased sensory nerve amplitudes in median and sural sensory nerves. However, a decrease in sodium current density could as well explain the increases in latencies of sensory nerve action potential found in both the sensory nerves and reversely the decreased amplitudes of sensory action potentials in bilateral median and sural nerves in hypothyroidism. Because of the temperature sensitivity of the activation of sodium and calcium currents the fall in core temperature during hypothyroidism could further exacerbate the symptoms.[19,20]

Our study on reaction time showed that hypothyroid females had prolonged latencies of auditory and visual reaction time and the delayed response by the hypothyroid individuals might be because of generalized decrease in metabolic rates affecting the sensory receptors, neural pathways and skeletal muscles due to low levels of thyroid hormones.[21]

Even mild hypothyroidism produces cognitive defects in selective visual attention and speed of visual information processing mainly in tasks with attentional requirements like reaction time testing. [22]The thalamocortical projections of the auditory pathways are also adversely affected in the hypothyroids.[23]

The overall central nervous system dysfunction leading to cognitive changes reported in hypothyroid patients might be responsible for slow mental processing of visual and auditory information and slower response in reaction time testing by the hypothyroids. Thus the delay in auditory and visual reaction times in untreated hypothyroids might be due to involvement of central nervous system, peripheral nervous system and skeletal muscles leading to impairment in perceptual and motor coordination. Thus, the sensory-motor neural dysfunction in hypothyroidism in the present study may be linked to the various functional and structural changes in peripheral nerves associated with deficiency of thyroid hormones.

The neuropathy due to compression and that due to axonal degeneration are not fully distinguished. There may be a combination of both these two which results in the development of peripheral neuropathy in hypothyroidism.[13]

Thyroid hormone has been shown to induce protein secretion from glial cells, including basic fibroblast growth factor (FGF-2) and epidermal growth factor. Furthermore, thyroid hormone has been shown to elevate nerve growth factor, neurotrophin-3 and brain derived neurotrophic factor (BDNF) in the brain.[24, 25] The degree and extent of disturbances in peripheral nerves are related to duration of low thyroid hormones levels and can be reversed by hormone replacement therapy.

Conclusion:

A good number of patients are suffering from hypothyroidism which varies in severity as well as duration of disease. Most of the patients are not aware about the consequences as well as the neurological complications of delayed diagnosis and treatment. Therefore, we propose more studies on sensorineural evaluation should be done for early assessment of degree and severity of nerve compromise and reversal with hormone replacement therapy.

Limitations: Our study has been done with female subjects who need to be generalized.

References

1. Patil V. P, Shilpasree A. S, Patil V. S, Pracvinchandra K. R, Ingleshwar D. G, Vani A. C. Evaluation of renal function in subclinical hypothyroidism. J Lab Physicians. 2018; 10:50 – 5.
2. Balaraman A, Natarajan G, Rao V, Kabali B. A Study of Nerve Conduction Velocity in Newly Diagnosed Hypothyroid Females. World Journal of Medical Sciences. 9 (4): 198-201, 2013
3. Garg R, Bansal N, Singh N, Maria A. K., Arora K. S. Nerve Conduction Studies in Newly diagnosed cases of Hypothyroidism. Sch. Acad. J. Biosci. 2015; 3(5):479-488.
4. Eileen black stock, Geoffrey.Electrophysiological studies in alcoholism. Journal of neurology, neurosurgery, and psychiatry. 1972;35: 326-334.
5. Pal GK, Pal P. Nerve conduction study. In: Textbook of Practical Physiology. 2nd Ed. Universities Press: 2007; 227-234.
6. Dietzel I D, Mohanasundaram S, Niederkinkhaus V, Hoffmann G, Meyer J W, Reiners C, Blasl C, Bohr K. Thyroid Hormone Effects on Sensory Perception, Mental Speed, Neuronal Excitability and Ion Channel Regulation. http://dx.doi.org/10.5772/48310
7. Nikam L, Gadkari J. Effect of age, gender and BMI on visual and auditory reaction time in Indian population. Indian J Physiol pharmacol 2012; 56(1): 94-99.
8. Eng J. Sample size estimation: How many individuals should be studied? Radiology. 2003; 227: 309–13.
9. Ralph M. Buschbacher, Nathan D. Prahlow. In: Manual of Nerve Conduction Studies. 2nd Ed. New York, Demos Medical publishing: 2006
10. Misra N, Mahajan KK, Maini BK. Comparative study of visual and auditory reaction time of hands and feet in males and females. Ind Jr Physiology Pharmacology 1985; 29(4): 213-218.
11. http://e.hormone.tulane.edu/learning/thyroid.html 25/12/12
12. Kasper DL, Braunwald E, Fauci AS, Hauser SI, Longo DL, Jameson JL. Disorders of thyroid gland. In: Harrison's Principles of Internal Medicine. 16th Ed. The McGraw Hill Companies: 2005; 2104-2113.
13. Yeasmin S, Begum N, Begum S, Rahman SMH. Sensory neuropathy in hypothyroidism: Electrophysiological and clinical findings. J Bangladesh Soc Physiol 2007 Dec; 2: 1-6.
14. Nemni R, Bottacchi E, Fazio R, Mamoli A, Corbo M, Camerlingo M, et al. Polyneuropathy in hypothyroidism: clinical, electrophysiological and morphological findings in four cases. J Neurol Neurosurg Psychiat 1987; 50: 1454- 1460.
15. Ozata M, Ozkardes A, Corakci A, Gundogan MA. Subclinical hypothyroidism does not lead to alterations in peripheral nerves or in brainstem auditory evoked potentials (BAEPs). Thyroid 1995 June; 5(3): 201-205.
16. Schwartz MS, Mackworth-Young CG, McKeran RO. The tarsal tunnel syndrome in hypothyroidism. Journal of neurology and Psychiatry 1983; 46: 440-442.
17. Bernal J. Thyroid hormones and brain development. Vitam.Horm 2005; 71:95–122.
18. Hodgkin A. The optimum density of sodium channels in an unmyelinated nerve. Phil.Trans.R.Soc.Lond.B 1975; 270:297–300.
19. Short MJ, Wilson WP, Gills JP, JR. Thyroid hormone and brain function. IV. Effect of triiodothyronine on visual evoked potentials and electroretinogram in man. EEG clin.Neurophysiol 1968; 25:123–7.
20. Takahashi K, Fujitani Y. Somatosensory and visual evoked potentials in hyperthyroidism. EEG clin.Neurophysiol 1970; 29:551–6.
21. Shah SH, Nahar PS. Reaction time in hypothyroid and hyperthyroid patients before and after drug treatment. IOSR Journal of Pharmacy Mar-Apr.2012, Vol.2 (2): 218-221.
22. Dugbartey AT. Neurocognitive aspects of hypothyroidism. Arch intern Med 1998; 158(13): 1413-1418.
23. Anjana Y, Vaney N, Tandon OP, Madhu SV. Functional status of auditory pathways in hypothyroidism: Evoked potential study. Indian J Physiol Pharmacol 2006 Oct-Dec; 50(4): 341-349.
24. Trentin AG, Alvarez-Silva M, Moura Neto V. Thyroid hormone induces cerebellar astrocytes and C6 glioma cells to secrete mitogenic growth factors. Am.J Physiol Endocrinol.Metab 2001; 281(5):E1088.
25. Gomes FCA, Maia CG, Menezes JRL de, Moura Neto V. Cerebellar astrocytes treated by thyroid hormone modulate neuronal proliferation. Glia 1999; 25(3):247–55.