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Original Research Article

A Comparative Study of Sensory Nerve Conduction Indices in Hypothyroid Patients and Healthy Volunteers

Komal Sharma[1], Jyotsna Shukla[2], Abhishek Saini[3], Praveen Choudhary[4]

[1]M.Sc. (Medicine) student, Department of Physiology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India
[2]Sr. Professor, Department of Physiology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India
[3]Assistant Professor, Department of Physiology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India
[4]Senior Medical Officer, Department of Endocrinology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India

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Corresponding author: Dr. Abhishek Saini
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Abstract

Introduction: Thyroid hormone is important for neuronal cell integrity and cytoskeletal stability operating via regulation of various stress response intracellular signalling and target molecules. Alteration in thyroid hormone signalling in nerve and other tissues underlie observed manifestations like neuropathy and aberrant nerve conduction. The neurological complications are well established in hypothyroidism, however the exact pathophysiological events culminating in development of these complications are still obscure.

Aim and Objective: In view of the same, the present study was aimed towards exploring the possible missing links by assessing and comparing the extent of peripheral sensory neuropathy and its relation to disease duration among hypothyroids and matched controls.

Materials and methods: Nerve conduction parameters were recorded from 32 hypothyroid patients and 32 age and sex matched healthy control subjects. Sensory nerve study (SNS) of bilateral median nerve and bilateral sural nerve were recorded and compared.

Results: Significant changes were observed in the form of reduction in sensory nerve conduction velocity (SNCV) ($p<0.05$) in both examined nerves in hypothyroid patients in comparison to healthy control subjects. We also found significantly reduced amplitude ($p<0.05$) and prolonged sensory latencies ($p<0.05$) among hypothyroid patients as compared to healthy control subjects. Also, significantly reduced sensory amplitude of median nerve and sural nerve were observed in hypothyroid patients who suffered from the disease for a period of 5 years or more.

Conclusion: The present study proffered that the sensory polyneuropathy associated with hypothyroidism was largely of mixed type (demyelinating as well as axonal type). Also, the present study recommends performance of nerve conduction studies in cases of hypothyroidism early in the course of the disease for timely detection and management of peripheral nerve dysfunctions.

Keywords: Sensory latency, SNCV, hypothyroidism, polyneuropathy.

Introduction

Thyroid hormones are indispensable for normal development and maturation of the central nervous system (CNS) and peripheral nervous system (PNS). There is a period in brain development during which euthyroid status is crucial for natural development.[1] Experimental studies have described a delay in the development of the dendritic tree, defects in myelination, reduction in the number of glial cells and axo-dendritic synapses in newborn hypothyroid rats.[2-5] Effect of thyroid hormone is mediated via thyroid receptors (TRs) which are expressed throughout life in sensory neurons of dorsal root ganglia and many other type of spinal and CNS neurons as well in glial cells.[6]

Thyroid dysfunctions are the most common endocrine disorders across the world wherein hypothyroidism, that being a clinical condition with low levels of thyroid hormones and raised TSH affects nearly 5% of the general population across the world.[7] It has been proposed that about 42 million people in India suffer from disorder related to thyroid gland.[8] Hypothyroid patients develop symptoms of either myopathy or neuropathy over the time course of disease manifesting in symptoms like numbness, tingling, neuropathic pain, paresthesia and sensory loss. [9]

The elemental cause of neuronal derangements in hypothyroid patients is metabolic and the suggested mechanisms for these derangements include reduction of fatty acid and carbohydrate metabolism leading to diminished production of ATP.[10] In hypothyroid patients, it has been shown that deposits of mucopolysaccharide in peripheral nerves, metabolic disorders of Schwann cells might also contribute towards peripheral nerve compression and dysfunction.[11]

Nerve conduction study (NCS) is extensively utilised to examine the stability of the peripheral nerve fibers being effective in delineating the extent and severity of neural dysfunction and in differentiating between axonal versus demyelinating forms of neuropathy. Nerve conduction studies are therefore utilised as an extension of standard clinical assessment of a patient for suspected peripheral neuropathy. Demyelinating neuropathies with prolonged latencies and slowed conduction velocities, as well as axonal neuropathies with reduced amplitudes and myopathic changes, with or without spontaneous activity were shown in electrophysiological investigations.[12]

Nerve conduction studies are of central importance for proper evaluation of peripheral nervous system (PNS) disorders. They help in the prognosis and longitudinal monitoring of the disease process and diagnosing the extent of neural lesion. It has been previously proposed that it is advantageous to design a nerve conductive study for delineating the typology and extent of such neuronal derangements.[13] The present study was aimed to explore the extent of peripheral sensory neuropathy in hypothyroids and to decipher the proposed relationship of nerve conduction abnormalities with disease duration.

Materials and Methods:

The present study was conducted on 64 subjects, comprising 32 hypothyroids and 32 age & sex matched healthy controls in the department of Physiology in collaboration with the department of Endocrinology, S.M.S. medical college and attached hospitals, Jaipur. It was a cross sectional comparative type of observational study. The study commenced after obtaining ethical approval from the institutional ethics committee and research review board. Written informed consent was obtained from all participants after explaining the purpose and outcome of the study prior to commencement of the test procedure. Detailed history was obtained and general physical examination was performed. The disease duration was

between 2 to 18 years and all hypothyroid patients were on thyroxine replacement therapy (irrespective of evidence of attainment of euthyroid status). Blood sample of the recruited subjects were collected in the immunoassay lab of S.M.S. hospital, Jaipur for measuring thyroid profile (serum T_3, serum T_4 and serum TSH) by chemiluminescence method using ADVIA CENTAUR XP machine. The age group of hypothyroid patients were between 30-40 years and were selected on the basis of clinical examination and their serum thyroid profile. Subjects with traumatic injuries or any acute illness, smokers and alcoholics, subject with chronic diseases affecting the nerve functions (like chronic liver disease, chronic renal disease & vasculitis), subjects suffering from myopathy, neuromuscular diseases and neurovascular complications, subjects who were not cooperative and not capable of understanding the procedure were excluded from the study.

Sensory nerve study:

Latency, amplitude, sensory nerve conduction velocity (SNCV) of bilateral median nerve and sural nerve were assessed by RMS EMG EP – 2 channels recorders & medicare system and analysed using SALUS software developed by Salus medical diagnostics, Hyderabad, India. Sensory nerve responses were recorded by metal type surface electrodes. Reference and active electrodes were surface disc type electrodes about 0.5-1.0 cm in diameter. The ground electrode was a metal plate that provided a large surface area of contact with the patient. Stimulating electrodes were two metal electrodes placed 1.5-3.0 cm apart. The sweep speeds for technical procedure allowed for a display of sensory potential waveform per horizontal division. The sweep speed setting was 2mS/D (millisecond per horizontal division) for sensory nerve study. Sensitivity/Gain settings were adjusted accordingly for accommodating low or high amplitude sensory responses. 5 to 10 microvolt per vertical division was the sensory sensitivity setting on the video display apparatus. Stimulation voltage was 20µV for SNS (Sensory Nerve Study). Frequency filter used in SNS was 20 Hz – 3 KHz. Electrical stimulus of 50 mA to 100 mA was used to define activity of nerve. Test procedure was properly explained to subjects for obtaining maximum cooperation. Subjects were asked to lie supine comfortably in a fully relaxed state and were made to acclimatise with the ambient conditions for 15 minutes before starting the test. Stimuli were applied along the nerve and the latency of the responses were measured. The difference in the latencies of response was obtained by measuring the time taken for the action potentials to travel along the nerve between the two stimulus point. The distance between the points of stimulation site was measured using a measuring tape. Nerve conduction velocity was then measured in m/s by the formula: Distance (d) [in mm] / Difference in latent period (t) [in ms]

Statistical Analysis:

Quantitative variables were expressed as Mean ± SD. Analysis was done using SPSS version 21. Significance of difference in mean in both main groups and both sub-groups were inferred by unpaired student t-test. Statistical significance was assigned at $p<0.05$.

Results:

Age group and anthropometric parameter like height of hypothyroid patients and healthy control subjects were comparable and the differences if present, were not statistically significant, however weight and BMI were significantly higher in hypothyroid patients as compared to healthy control subjects [Table1]. On the contrary, the difference in the thyroid profile of hypothyroid patients and healthy control subjects were statistically significant, along the lines of requirements

of the study's inclusion criteria [Table2].

The difference in mean ± SD of distal latency of sensory nerves between hypothyroid patients and healthy control subjects in median nerve and sural nerve were statistically significant, wherein hypothyroid patients had significantly increased distal latencies compared to healthy control subjects. Hypothyroid patients had decreased amplitude compared to healthy control subjects in median nerve and sural nerve. Statistically significant difference was noted in right median nerve and left sural nerve. The difference in mean ± SD of SNCV among hypothyroid patients and healthy control subjects in median nerve and sural nerve was statistically significant, wherein hypothyroid patients had significantly decreased conduction velocity compared to healthy control subjects [Table 3].

When distal latencies of median and sural nerve were compared between the two groups of hypothyroid patients with different disease duration, the differences came out to be non significant [Table 4]. Similarly, SNCV of median and sural nerve were not significantly different between the two groups of hypothyroid patients with different disease duration. Hypothyroid patients with >5 years disease duration had statistically significant reduction in amplitude compared to hypothyroid patients with ≤5 years disease duration in median nerve and sural nerve.

Table 1: Comparison of anthropometric parameters between hypothyroid patients and healthy control subjects

Parameters	Group (mean±SD)		p-Value	Significance
	Hypothyroid patients(n=32)	Healthy control Subjects (n=32)		
Age (year)	35.25 ± 2.97	35.22 ±2.80	0.998	NS
Height (m)	01.62 ± 0.08	01.63 ± 0.08	0.524	NS
Weight (kg)	66.28 ± 10.38	61.25 ± 6.52	0.024	S*
BMI (kg/m^2)	25.20 ± 2.64	23.00 ± 1.48	<0.001	HS**

NS = non-significant (p>0.05) *S = significant (p<0.05) **HS = highly significant (p<0.001)

Table 2: Comparison of thyroid profile between hypothyroid patients and healthy control subjects

Parameters	Group (mean±SD)		p-Value	Significance
	Hypothyroid patients (n=32)	Healthycontrol subjects(n=32)		
T3 (pg/ml)	2.49 ± 0.43	2.82 ± 0.34	0.001	S*
T4 (ng/dl)	0.87 ± 0.19	1.23 ± 0.14	<0.001	HS**
TSH (µIU/ml)	7.99 ± 1.44	1.79 ± 0.49	<0.001	HS**

*S = significant (p<0.05) **HS = highly significant (p<0.001)

Table 3: Comparison of sensory nerve parameters between hypothyroid patients and healthy control subjects

Parameters	Nerve	Groups mean (mean±SD)		p-Value	Significance
		Hypothyroid patients (n=32)	Healthy control subjects (n=32)		
Latency (ms)	Right median	02.71 ± 00.60	02.09 ± 0.24	<0.001	HS**
	Left median	02.50 ± 00.65	02.10 ± 0.19	0.001	S*
Amplitude (µV)	Right median	44.14 ± 08.21	50.13 ± 5.94	0.001	S*
	Left median	47.70 ± 08.57	49.84 ± 5.72	0.245	NS
SNCV (m/s)	Right median	50.97 ± 11.89	63.17 ± 6.82	<0.001	HS**
	Left median	54.37 ± 11.06	62.56 ± 6.62	<0.001	HS**
Latency (ms)	Right sural	02.54 ± 00.38	02.35 ± 0.29	0.022	S*
	Left sural	02.47 ± 00.31	02.26 ± 0.21	0.002	S*
Amplitude (µV)	Right sural	20.08 ± 06.40	21.98 ± 3.17	0.139	NS
	Left sural	17.15 ± 04.37	21.56 ± 2.75	<0.001	HS**
SNCV (m/s)	Right sural	55.53 ± 07.86	59.83 ± 7.65	0.030	S*
	Left sural	56.05 ± 06.88	61.83 ± 5.70	<0.001	H**

*S =significant (p<0.05) **HS = highly significant (p<0.001)

Table 4: Comparison of nerve parameters between hypothyroid patients with ≤5 years disease duration and hypothyroid patients with >5 years disease duration

Parameters	Nerve	Groups mean (mean±SD)		p-Value	Significance
		Hypothyroid patients (≤5 years)	Hypothyroid patients (>5 years)		
Latency (ms)	Right median	02.91 ± 0.65	02.61 ± 00.56	0.201	NS
	Left median	02.54 ± 0.78	02.47 ± 00.59	0.807	NS
Amplitude (µV)	Right median	51.85 ± 5.65	40.63 ± 06.68	<0.001	HS**
	Left median	55.10 ± 7.39	44.34 ± 06.86	<0.001	HS**
SNCV (m/s)	Right median	46.92 ± 8.64	52.81 ± 12.85	0.198	NS
	Left median	54.24 ± 9.87	54.43 ± 11.78	0.966	NS
Latency (ms)	Right sural	02.48 ± 3.67	02.57 ± 00.38	0.539	NS
	Left sural	02.37 ± 0.22	02.52 ± 00.34	0.217	NS
Amplitude (µV)	Right sural	26.88 ± 6.52	16.99 ± 03.18	<0.001	HS**
	Left sural	19.31 ± 3.70	16.16 ± 04.36	0.057	NS
SNCV (m/s)	Right sural	58.94 ± 5.14	53.98 ± 08.47	0.098	NS
	Left sural	58.98 ± 5.06	54.72 ± 07.27	0.105	NS

NS = nonsignificant (p>0.05) **HS = highly significant (p<0.001)

Discussion:

The present study was designed to assess and evaluate the nerve conduction indices in hypothyroid patients and healthy control subjects and also to assess the probable effect of disease duration on parameters of nerve conduction tests. Clinical features of hypothyroid subjects were numbness, weakness, weight gain, fatiguability, stiffness & swelling in joints, cramps, thinning of hair, puffy face, muscle aches and tenderness.

The BMI of hypothyroid patients was found to be significantly higher than that of healthy control subjects in the present study (p<0.05) [Table 1]. Fox CS et al, 2008 stated a positive correlation between TSH and the progressive increase in weight and

BMI.[14] Reinehr T et al, 2010 also found a similar correlation between TSH and BMI. It was proposed that such a correlation could be mediated by leptin produced by adipose tissue.[15] Oge A et al, 2005 described that Leptin physiologically regulates energy homeostasis by informing the central nervous system about adipose tissue reserves. Leptin is also an important neuroendocrine regulator of the hypothalamic-pituitary-thyroid axis acting via regulation of TRH gene expression in the paraventricular nucleus and TSH in turn stimulates leptin secretion by human adipose tissue.[16] According to Zimmermann- Belsing T et al, 2003 Leptin also affects thyroid deiodinase activities hence affecting T4 to T3 conversion.[17]

In our study, sensory nerve conduction study (SNS) revealed increased latency, decreased amplitude and decreased conduction velocity (SNCV) of median sensory nerve and sural nerve in hypothyroid subjects as compared to healthy subjects. Increased bilateral distal latency, decreased amplitude of right median nerve and decreased bilateral conduction velocities of median sensory nerve were found to be statistically significant when difference of mean was compared between the two groups. Increased bilateral distal latency, decreased amplitude of left sural nerve and decreased bilateral conduction velocities of sural nerve were found to be statistically significant when difference of mean was compared between the two groups [Table3]. The findings of the present study support the results obtained by by Garg R et al, 2015 who found significantly increased latency, decreased amplitude and decreased SNCV of sural nerve in hypothyroid patients compared to euthyroid controls.[18] Our study results are coherent with the findings of Sharma S et al, 2020 who found significantly increased latency, decreased amplitude and decreased SNCV of median nerve in hypothyroid patients compared to healthy control subjects.[19]

The synthesis of protein and the production of myelin sheath and enzymes are known to be influenced by thyroid hormone. The speed of impulse transmission along the nerve length is determined by presence of the myelin sheath.[20] The demyelinating peripheral neuropathy occurs in hypothyroidism due to disturbed myelin synthesis. Hormonal and metabolic factors associated with thyroid functioning are responsible for the electrophysiological changes in the form of aberrant peripheral nerve conduction in hypothyroidism

It has been previously reported that severity of the neuromuscular signs and symptoms depends on duration and severity of hormonal deficiency.[21] Investigators reported electrophysiological and histological findings in hypothyroid neuropathy and concluded that the predominant pathology was in the Schwann cells, leading to segmental demyelination of peripheral nerve fibers.[22] The median nerve is usually vulnerable to compression within the carpal tunnel by the flexor retinaculum in hypothyroidism. There have been a number of descriptions about the pathological changes in the peripheral nerves wherefore some researchers emphasized the role of mucoid degeneration and the accumulation of mucoid material, evidently a mucopolysaccharide-protein complex, in and around the nerve.[23]

Thyroid hormone is responsible for the stimulation of mitochondrial respiratory activity to produce energy in the form of ATP, under normal physiological condition. Thyroid hormone seems to increase ATPase activity and consequently the activity of ATP dependent Na+/K+ pump. Therefore, in hypothyroidism ATP deficiency and reduced ATPase activity with decreased Na+/K+ pump activity cause subsequent alteration of pump dependent axonal transport and thereby

may lead to peripheral neuropathy.[24-26] Decreased glycogen degradation may also leads to energy deficit in hypothyroidism.[27] Though the neuropathy due to compression and the peripheral neuropathy due to axonal degeneration are not fully distinguished, there may be a combination of these two factors, which results in the development of peripheral sensory neuropathy in hypothyroidism.[28]

A true neuropathic pain is an activity originating from sensory axons, while activation of nociceptors present in muscles, perineurium or nerve blood vessel during a disease of peripheral nerves, produces nociceptive pain.[29]

In our study decreased distal latency, decreased amplitude and increased conduction velocity of median sensory nerve was found in hypothyroid patients with >5 years disease duration as compared to hypothyroid patients with ≤5 years disease duration. The decreased amplitude of right median nerve and left median nerve were found to be statistically significant in hypothyroid patients with >5 years disease duration as compared to hypothyroid patients with ≤5 years disease duration. This unexpected finding may indicate that myelination may have reinitiated as the patient might have resumed euthyroid state due to therapeutic administration of thyroid hormone. In our study increased distal latency, decreased amplitude and decreased conduction velocity of sural sensory nerve was found in hypothyroid patients with >5years disease duration as compared to hypothyroid patients with ≤5 years disease duration. Statistically significant decrease in amplitude of right sural nerve was found in hypothyroid patients with >5 years disease duration as compared to hypothyroid patients with ≤5 years disease duration.

Peripheral neuropathy may be a manifestation of hypothyroidism which usually develops over a long period of time. These findings may indicate that demyelination and axonal dysfunction may have progressed with duration of disease. This might be due to late diagnosis of disease, irregularity in treatment or insufficient treatment.

Conclusion:

The present study proposes that the polyneuropathy associated with hypothyroidism is largely of mixed type (axonal as well as demyelinating type) liable to progress as the disease advances in its duration. Due to a likely lack of awareness of the consequences and complications which might set in as a result of peripheral neuropathy, the present study proposes the importance of non invasive methods like nerve conduction studies for screening and evaluation of a possible development of polyneuropathy in patients of hypothyroidism. It is imperative to detect the neuropathic changes early, so as to counter the altered neurophysiology effectively and efficiently leading to a better prognostic outcome.

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