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Prevalence and Characteristics of Neuropathy in Hyperthyroidism: A Cross-Sectional Study

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Abstract

***Background:** Hyperthyroidism can cause various neurological manifestations, including neuropathy. However, the prevalence and characteristics of neuropathy in hyperthyroidism are not well understood.*

***Methods:** This cross-sectional study included 65 adult patients with newly diagnosed or established hyperthyroidism. Patients underwent clinical neurological examination, nerve conduction studies (NCS), and laboratory investigations. Patients with other possible causes of neuropathy, i.e., diabetes mellitus, chronic alcoholism, nutritional deficiencies, chronic liver or kidney disease, malignancies, Human Immunodeficiency Virus (HIV) infection, family history of neuropathy and use of drugs known to cause neuropathy were excluded.*

***Results:** 40% of patients had neurological symptoms, while 10.7% had abnormal NCS findings (n = 7). Axonal neuropathy was diagnosed in 6 out of 7 cases, with 1 case of mixed axonal and demyelinating neuropathy. Older age and longer disease duration were significantly associated with abnormal NCS results. 30% of patients with normal NCS results complained of paresthesias, suggesting that NCS may miss subtle neurological changes.*

***Conclusion:** Neurological symptoms are predominant in hyperthyroidism. NCS may miss subtle neurological changes despite significant neurological symptoms. The study also showed that older age and longer disease duration are the two factors which are linked to abnormal NCS result among the study population.*

***Key words:** Hyperthyroidism, Nerve conduction studies, neurological symptoms.*

Introduction

The thyroid gland secretes two major hormones: Thyroxine (T4) and Triiodothyronine (T3), with T4 accounting for 93% of the secretion and T3 for 7%. T4 acts as a prohormone and a reservoir for the more active T3, which is formed as needed in the tissues. Thyroid hormones play a crucial role in normal growth and metabolism, acting on nearly all nucleated cells[1]. Thyroid hormones are essential for normal brain development as they influence neurogenesis, neuronal and glial cell differentiation and migration, synaptogenesis, and myelination[2].

Hyperthyroidism is defined as suppressed thyroid stimulating hormone (TSH) and high serum concentration of T3 and/or free T4. Thyrotoxicosis refers to a hypermetabolic state that results from excessive amounts of circulating thyroid hormones including extrathyroidal sources such as exogenous intake or release of preformed hormone. The clinical presentation of hyperthyroidism or thyrotoxicosis varies from asymptomatic (subclinical) to life-threatening (thyroid storm). Common symptoms include palpitations, unintentional weight loss, hyper defaecation and heat intolerance[3]. Thyroid storm is an endocrine emergency, and when undiagnosed, can lead to serious complications such as delirium, muscle weakness, atrial fibrillation, congestive heart failure (CHF), cardiovascular collapse, and death[4].

Neurological manifestations of hyperthyroidism include seizures, encephalopathy, neuropsychiatric manifestations, tremors, choreoathetosis, myopathy, hypokalaemia periodic paralysis, and neuropathy. These conditions may be related to the effects of thyroid hormone on mitochondria, cytoskeletal elements, and neurotransmitter systems. Treatment of hyperthyroidism usually leads to the resolution of these neurological symptoms[5]. The pathogenesis of neuropathy in hyperthyroidism is not fully understood, but several mechanisms have been proposed. One theory suggests that excessive thyroid hormones have a direct neurotoxic effect, disrupting nerve function due to abnormal metabolic activity. Another possibility is an immune-mediated process, where the immune response

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that targets the thyroid in conditions like Graves' disease also affects the nerves. Additionally, the hypermetabolic state of hyperthyroidism may deplete nerves of essential nutrients and energy, impairing their function. Vascular changes affecting blood flow to the nerves have also been suggested as a contributing factor. Overall, neuropathy in hyperthyroidism likely results from a combination of these factors[6]. In a prospective study of hyperthyroid patients 19% had sensory-motor axonal neuropathy in nerve conduction studies (NCS)[7].

Neurophysiological features of axonal degeneration typically include normal or near normal nerve conduction velocity with reduced compound muscle action potential (CMAP) amplitudes, or reduced sensory nerve action potential (SNAP) amplitudes, and the presence of fibrillation in denervated muscles. On the other hand, neurophysiological features of segmental demyelination include conduction block, slowed nerve conduction velocity (NCV) across the affected segment, prolonged distal latency, and temporal dispersion[8].

We decided to carry out a study to find the prevalence of neurological signs and symptoms in newly diagnosed patients of hyperthyroidism and to evaluate the electrophysiological evidence of neuropathy in these patients.

Material and Methods

This cross-sectional observational study was conducted at a tertiary care teaching hospital for a period of two years from July 2021 to June 2023. Adult patients of newly detected or established hyperthyroidism (supressed TSH and high free T4) attending internal medicine, endocrinology, or neurology out-patient departments were included in the study. Patients with other possible causes of neuropathy, i.e., diabetes mellitus, chronic alcoholism, nutritional deficiencies, chronic liver or kidney disease, malignancies, Human Immunodeficiency Virus (HIV) infection, family history of neuropathy and use of drugs known to cause neuropathy were excluded.

All patients fulfilling inclusion criteria were asked about any neurological symptoms and underwent a clinical neurological examination. NCS was carried-out for all participants according to standardised protocols. Laboratory investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), red blood cell (RBC) indices, liver function test (LFT), kidney function test (KFT), serum vitamin B12, serum folate, TSH, free T4 and free T3.

Axonal neuropathy was diagnosed if compound muscle action potentials (CMAP) were reduced in motor nerves, or reduced sensory nerve action potentials (SNAP), with normal or slightly reduced nerve conduction velocities. Demyelinating neuropathy was diagnosed if distal motor latencies were increased along with slowing of nerve conduction velocities, and absent or delayed F-waves[9].

Sample size was calculated by assuming an estimated prevalence of neuropathy in hyperthyroidism (p) to be 50%, and applying finite correction factor (N) as 75 (based on the average number of patients with hyperthyroidism likely to report during the study period). For 95% confidence level and a confidence limit of 5%, the sample size calculated was 63.

Data was analysed using open-source statistical software. Numerical variables were expressed as mean and categorical variables were reported as proportions. The two-sample t-test (Student's t) was used for analysing quantitative variables with normal distribution and Chi ($\chi 2$) square test was used for categorical variables. For all tests of significance, p-values less than 0.05 were considered to be statistically significant.

Results

Fig. 1 shows the flow of participants in the study. A total of 65 newly diagnosed or previously established cases of hyperthyroidism were included in the study. 29.23% were females (n = 19) and 70.74% were males (n = 46). The mean age of the study population was 42.3 ± 15 years. The most common diagnosis was Graves' disease (n = 44). 16 participants had toxic multi-nodular goitre and 5 patients had thyroiditis.

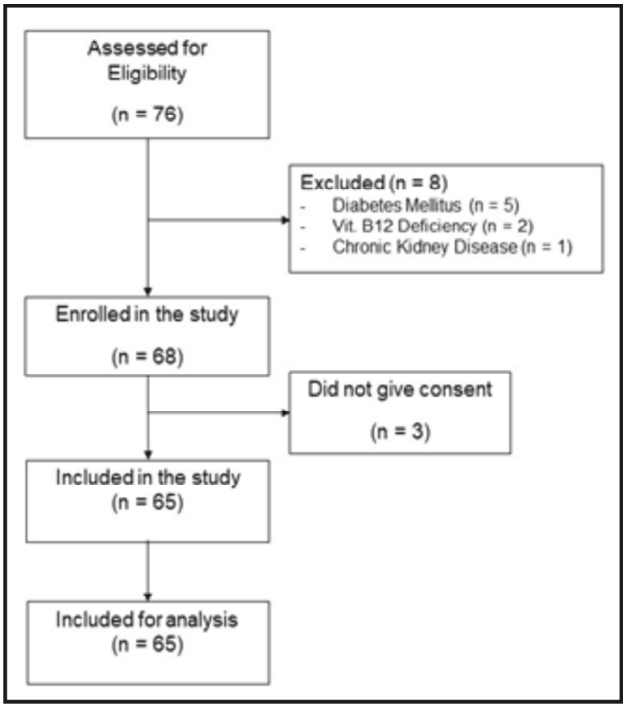

Fig. 1: *Flow of Participants in study.*

Commonest symptom which led the participants to seek medical attention were tremors and palpitations followed by weight loss. Fig. 2 depicts the presenting complaints with which the study participants reported to our hospital. The commonest symptoms were weight loss and tremors. 62 participants were treated with a combination of antithyroid medication (Carbimazole) and/or a non-selective beta blocker (Propranolol), while 3 participants did not require any treatment.

Table I lists the neurological symptoms and signs observed among the study participants. The predominant symptom seen among the study participants was paraesthesia (n = 22) and the most common neurological sign observed was graded sensory loss in the lower limbs (n = 9). 2 patients had hypokalaemia induced flaccid quadriparesis and 2 patients had sensory ataxia.

Table I: Neurological symptoms and signs among the study participants.

Neurological Symptoms/Signs	Number of participants
Paraesthesia in one or more limbs	22
Flaccid paralysis of all 4 limbs	2
Ataxia	2
Graded sensory loss in lower limbs	9
Attenuated deep tendon reflexes	4
Loss of proprioception	2

10.7% participants (n = 7) had abnormal NCS findings. Table II summarises the abnormal NCS findings observed. A diagnosis of axonal neuropathy was made in 6 out of 7 cases. 3 had sensory axonal neuropathy, 2 had sensory motor axonal neuropathy and 1 participant had pure motor axonal neuropathy. 1 participant was found to have mixed axonal and demyelinating sensory neuropathy in the ulnar nerve distribution.

Table II: Abnormal NCS findings among the study participants.

NCS Findings		Number of participants
Axonal Neuropathy	Sensory axonal neuropathy involving bilateral lower limbs	3
	Pure motor axonal neuropathy bilateral common peroneal nerve	1
	Sensory motor axonal neuropathy in all 4 limbs	2
Axonal + Demyelinating Neuropathy	Axonal + demyelinating sensory neuropathy bilateral ulnar nerves	1

The mean age of participants with abnormal NCS was 61.6 ± 16.1 years as compared to those with normal NCS being 39.7 ± 12.9 years (p value <0.0001). 6 out of 7 participants with abnormal NCS had duration of illness more than 4 years, compared to 15 out of 58 participants with normal NCS (p value 0.00067). There was no statistically significant

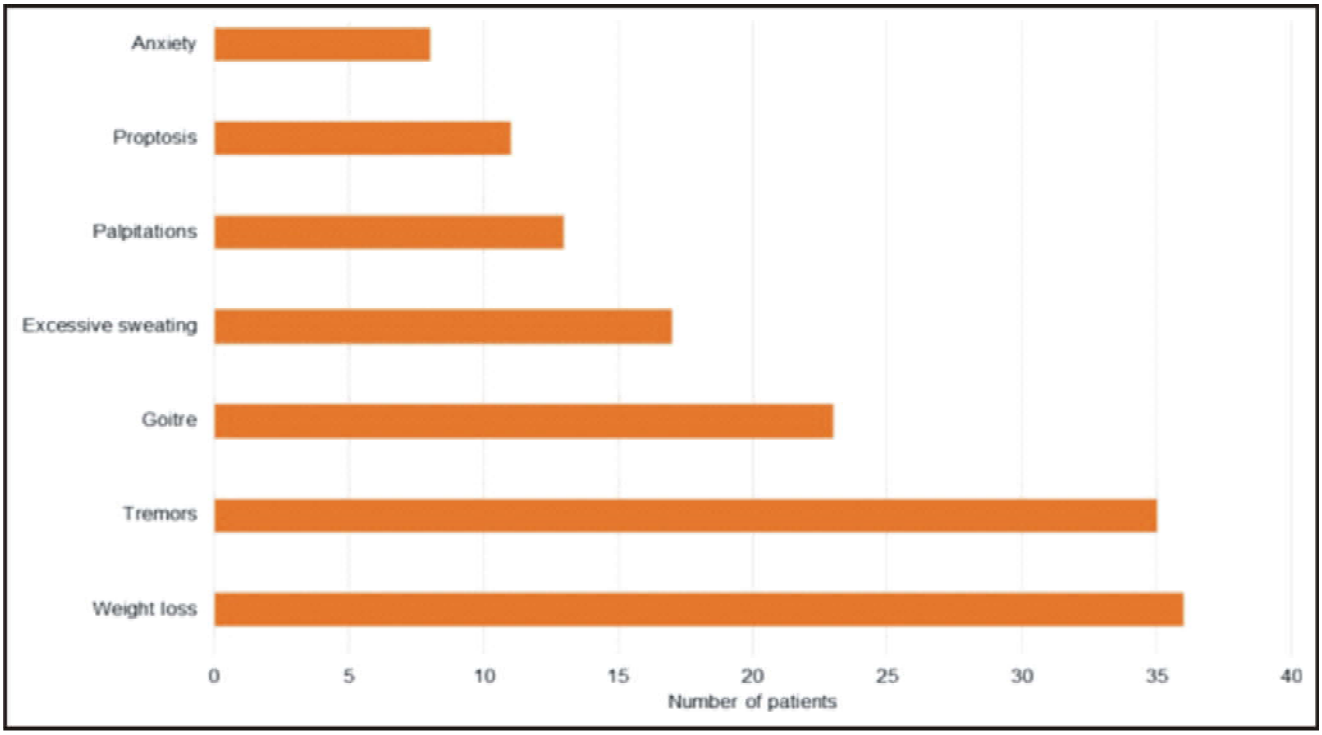

Fig. 2: *Presenting complaints among the study participants.*

difference in the thyroid function test between those with normal NCS and abnormal NCS findings.

Discussion

In our study, among 65 participants with newly diagnosed or previously established hyperthyroidism, 7 had abnormal NCS findings (10.7%). Duyff *et al* evaluated 21 patients with hyperthyroidism and found that symmetric distal sensory disturbances in the limbs combined with depressed ankle tendon jerks, clinically consistent with a polyneuropathy, was present in 4 patients (19%) and 2 patients had subclinical sensory carpal tunnel syndrome[10]. In a similar study by Berlit *et al* 8 out of 27 hyperthyroid patients (29.6%) were found to have sensory neuropathy of the Sural nerve in NCS[11].

Out of the 7 participants with abnormal NCS, 4 had sensory and 1 participant had pure motor axonal neuropathy. 2 participants were found to have thyrotoxic paralysis associated with hypokalaemia. Their NCS showed sensory motor axonal neuropathy in all 4 limbs. Kumar *et al* studied 400 patients with thyroid disorder and reported that 144 of them had neuropathy, of which 4 patients had hyperthyroidism and 56 had hypothyroidism[12]. Kelly *et al* reported that 7 out of 10 patients with thyrotoxic periodic paralysis showed reduced CMAP on NCS[13].

Proximal myopathy has predominantly been associated with hyperthyroidism especially Graves' disease[12]. However, our study demonstrates that electro-physiologically confirmed neuropathy can also be found in patients with hyperthyroidism. Review of literature showed few case reports from India, demonstrating the occurrence of polyneuropathy in hyperthyroid patients. Mohamed *et al* reported that in 45-year-old male patient with Basedow's paraplegia, NCS showed mixed motor and sensory polyneuropathy[14]. Malakar *et al* reported thyrotoxic neuropathy in a 47-year-old female with NCS showing mixed sensory motor neuropathy[15].

Age and duration of illness were the two factors which were found to be significantly associated with the presence of abnormal NCS results in the study population. The age of participants with abnormal NCS was significantly higher than those with normal NCS (p value <0.0001). Majority of patients with abnormal NCS has disease duration longer than 4 years as compared to those with normal NCS (p value 0.00067).

There are few limitations of the present study. We did not have a control group of normal individual to compare the results of NCS. Electromyography was not carried out as part of electro-diagnostic studies. This was a cross-sectional study and the participants were not followed-up over time to look for resolution or worsening of symptoms. Longitudinal case control studies are required to further establish the natural course of neuropathy in hyperthyroid patients.

Conclusion

To conclude, in our study of 65 hyperthyroidism patients, 40% had neurological symptoms. However, only 10.7% had abnormal NCS result. 6 out of 7 had axonal neuropathy and 1 had mixed axonal and demyelinating neuropathy. 30% patients had normal NCS results, despite complaining of paresthesias, suggesting that NCS may miss subtle neurological changes. The study also showed that older age and longer disease duration are the two factors which are linked to abnormal NCS result among the study population.

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