

A STUDY OF NEUROLOGICAL MANIFESTATIONS FROM CENTRAL TO PERIPHERAL NERVOUS SYSTEM IN THYROID DISORDERS

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Abstract

Background: Thyroid hormone is critical for the development and differentiation of neurons, oligodendrocytes as well as Schwann cells and hence for proper functioning of the entire neuraxis. **Materials and Methods:** Patient attending neurology op, endocrine op and patient admitted in neurology ward were recruited for the study. This study was done in Madras Medical College hospital and Rajiv Gandhi Govt General Hospital over a period of 15 months between May 2021 to July 2022. Routine investigations including thyroid function tests done in all patients and thyroid antibody profiles, neuroimaging and electrophysiological investigations were done in selected patients. **Result:** Hypothyroidism is associated with neurological manifestations like Hashimoto's encephalopathy, cerebellar symptoms, myopathy, myeloneuropathy, entrapment and peripheral neuropathy and increase in prevalence of headache compared to general population. Hyperthyroidism is associated with sleep disorders, movement disorders, headache, myopathy, periodic paralysis and peripheral neuropathy. **Conclusion:** Even if the thyroid function tests are normal it is important to consider immunological tests of thyroid as in Hashimoto's encephalopathy or myelopathy. It is important to treat with supplementation of thyroid hormones at the earliest to prevent dire consequences.

INTRODUCTION

There are two thyroid hormone receptor genes TR α and TR β . Thyroid hormone exhibits its action by combining with these receptors. In general, energy metabolism is regulated by TR α and feedback regulation are functions of TR β .^[1,2] T3 receptor mRNAs are located predominantly on neurons. T3 receptors in neurons likely mediate the effects of the hormone in neuronal cell migration and differentiation. It is well known oligodendrocytes are the principle glia of central nervous systems and schwann cells are the principle glia of peripheral nervous systems. Thyroid hormone is required for oligodendrocyte differentiation and myelination.^[3] Schwann cells have been reported to express T3 receptors which shows the necessity of thyroid hormones for its normal functioning.^[4] Hence it is well understood both central nervous system and peripheral nervous are depended on thyroid hormones for normal functioning.^[5-16]

Aim of the Study

- To assess the neurological manifestations of patients with thyroid disorders.
- To study the prevalence of various neurological manifestation in hyper/hypothyroidism.
- To emphasize the need for thyroid screening in patient with selective neurological symptoms

MATERIALS AND METHODS

With the aim of studying the neurological manifestations in patients with thyroid disorders this study was done in Madras Medical College hospital over period of 15 months between May 2021 to July 2022.

Methodology

Patient attending endocrine op with thyroid dysfunction who has neurological complaints, neurology op and patient admitted in neurology wards were recruited.

Blood investigations

Complete blood count, Renal function test, Liver function test, lipid profile, Elisa test for HIV, VDRL.

Thyroid function test - Thyroid-stimulating hormone(TSH), Free T4,Free T3,Thyroid peroxidase Antibody, Thyroglobulin Antibody, Vitamin B12.

Imaging of brain with CT/MRI

For those patients who have seizures, cognitive decline and other central nervous system manifestation

Electroencephalogram

For patients with seizures. **Polysomnography:**

Sleep related disorders

Nerve Conduction Studies

For those patients with entrapment syndrome, peripheral neuropathy and other peripheral nervous system manifestation

Electromyography

For Those with Suspected Myopathy

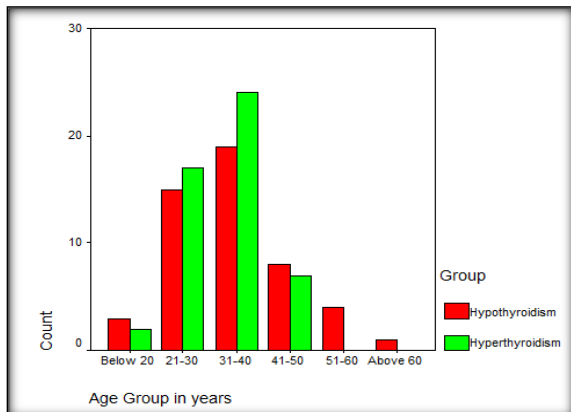
Exclusioncriteria

Chronic illness like diabetes mellitus, chronic renal failure, liver disease, malignancy, HIV infection are excluded from the study

Specific other diseases which could also accounted for the neurological manifestations are excluded like

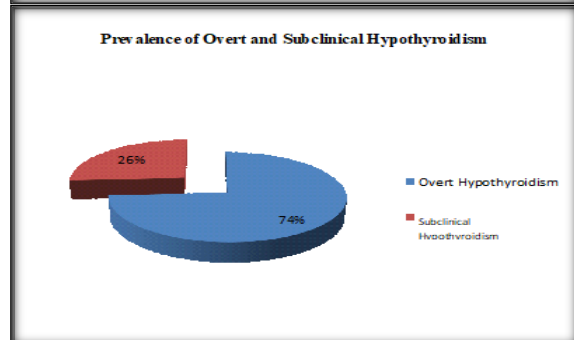
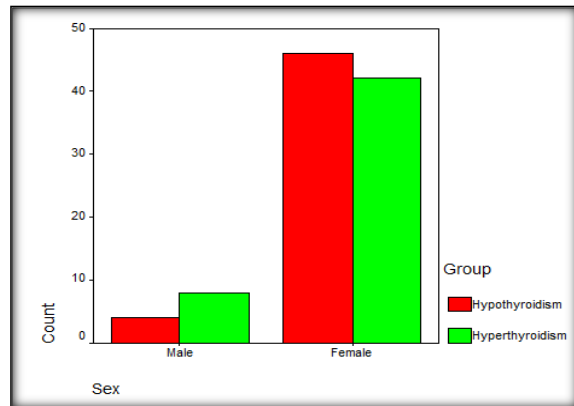
- CNS infection, structural lesion in suspected Hashimoto’s encephalopathy.
- CNS lesions by imaging in seizure disorder.
- Chronic alcoholism in peripheral neuropathy.
- Hereditary, inflammatory and other causes in myopathy.
-

RESULTS



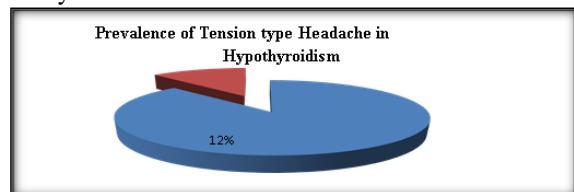
Thyroid disorders is more common in the 4th decade in study group.

Prevalence is very high in females as compared to males.



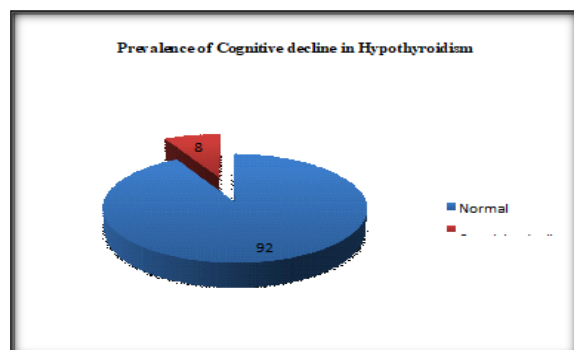
Those patients with elevated TSH and low levels of thyroxine are grouped under overt hypothyroidism and those with elevated TSH alone with normal levels of thyroxine are grouped under subclinical hypothyroidism.

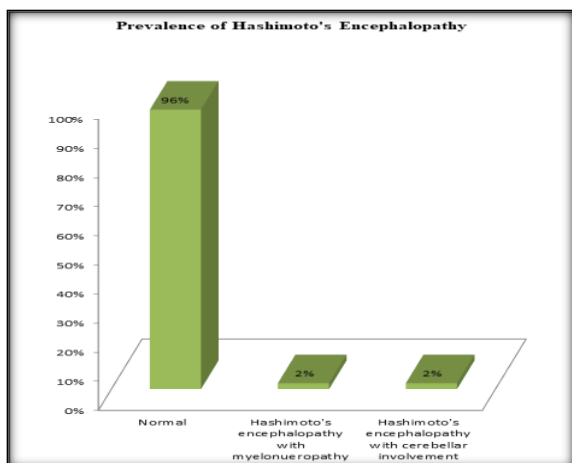
The Following Neurological Manifestations Were Seen In Patients With Hypothyroidism In Our Study.



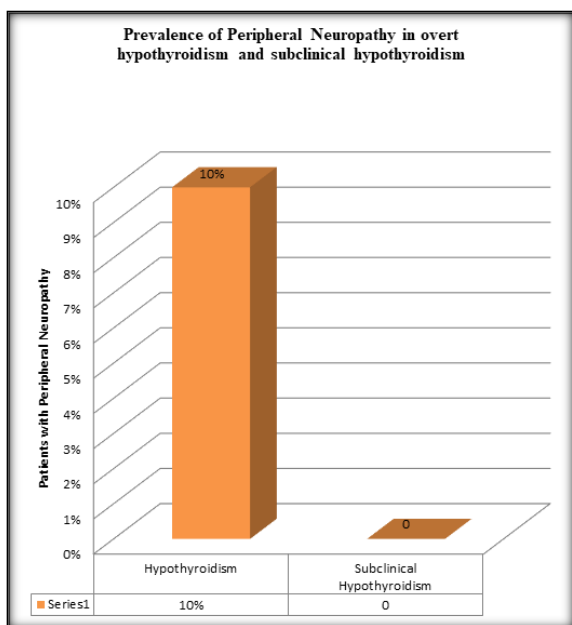
In hypothyroidism 12% of patients has headache which is of episodic Tension type headache.

8% adult hypothyroid patients have cognitive decline. Of these 4% had Hashimoto’s associated encephalopathy mediated cognitive decline which is a part of autoimmune encephalitis. 4%.had decrease in cognitive function which is directly due to under action of thyroid hormones.





Hashimoto's encephalopathy is diagnosed after exclusion of other causes which could account for the same symptoms and signs and high titers of TPO antibodies. Here we like to highlight the immune mediated mechanism operating causing encephalopathy in both cases but the same mechanism causing myelopathy in one patient and cerebellar involvement in other patient.^[17,18]



10% of the population in the study group have peripheral neuropathy.

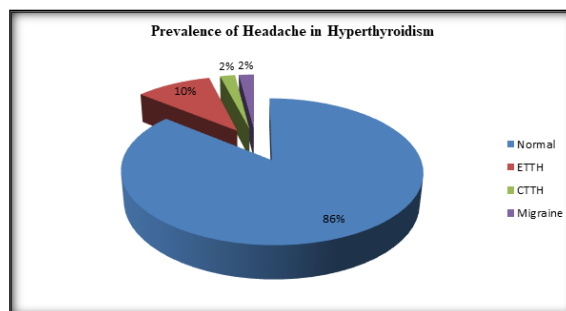
The prevalence of carpal Tunnel syndrome in hypothyroidism is 10%.

Only 2% of patients had myopathy and the weakness is mild as assessed by MRC grading ≥ 4 .

Graph To Be Included

After excluding illness like headache the association is mere a coincidence, the number of population with core neurological manifestations in our study is 36%.

The Following Neurological Manifestations Were Seen In Patients With Hyper Thyroidism In Our Study.



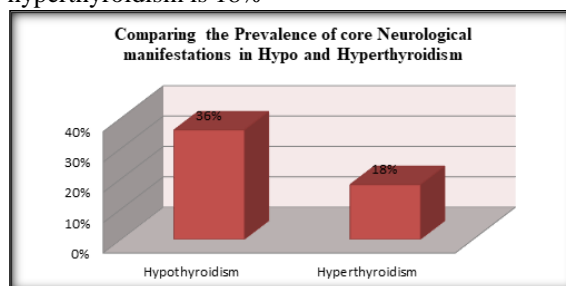
14% of patients with hyperthyroidism had headache. 8% of patients with sleep disorders in hyperthyroidism is predominantly insomnia.

Most patient in hyperthyroidism presents with tremulousness of hands. In our study 74% of patients had tremor.

4% of patients had proximal muscle weakness associated with hyperthyroidism. However CK value in these patients were normal.

Only one male patient is diagnosed to have thyrotoxic periodic paralysis in our study group.

The core neurological manifestations in hyperthyroidism is 18%



On comparing the neurological manifestation in hypo and hyperthyroidism the prevalence of neurological manifestation in hypothyroidism is more than in hyperthyroidism.

Peripheral neuropathy is more common in hypothyroidism and myopathy is more common in hyperthyroid patients.

DISCUSSION

Neurological manifestations of hypothyroidism

PREVALENCE OF OVERT AND SUBCLINICAL HYPOTHYROIDISM

In our study group of 50 patients of hypothyroidism most patients 74% had overt hypothyroidism and 26% had sub clinical hypothyroidism. Those patients with elevated TSH and low levels of thyroxine are grouped under overt hypothyroidism and those with elevated TSH alone with normal levels of thyroxine are grouped under subclinical hypothyroidism.

Association of headache with hypothyroidism

On analyzing headache associated with thyroid dysfunction only 10% percentage of had headache. The type of headache is episodic tension type headache (ETTH). Globally, the percentages of the

adult population with an active headache disorder are 46% for headache in general, 42% for tension-type headache, 11% for migraine and 3% for chronic daily headache. In a large, population-based study of epidemiology of Tension-type Headache, the 1-year period prevalence were 38.3% for ETTH and 2.2% for CTTH⁵.

Hence the prevalence of tension type headache it is no more greater than in general population when compared to previous studies. The prevalence of headache is comparable to general population and hence the association of headache cannot be attributed to hypothyroidism.

Prevalence of sleep disorders in hypothyroidism

8% of patients with hypothyroidism had sleep related problems. Most had increase in the duration of sleep. They feel sleepy and tired even though they had adequate sleep during night. One patient had sleep apnea causing lethargy and somnolence which may be attributed to hypothyroid associated sleep problems in addition to direct hormonal effect. One patient had insomnia.

Cognitive decline

8% of patients had minimal cognitive impairment on cognitive function assessment.^[16] Of these in 4% of patient it is associated with encephalopathy features. Only the other 4% of cases had cognitive decline only. They have difficulty in learning and memory. They had impairment in higher cortical function especially for executive function testing and recent memory impairment. These patients had long standing symptoms before starting treatment. Their symptoms showed moderate impaired after thyroxine replacement^{6,7}. Frank dementia not occurred in our study population.

Hashimoto's Encephalopathy

Two of the patient in our study had encephalopathy associated with elevation of anti TPO antibodies.^[8,9,10] These patients had cognitive decline. One patient had associated myeloneuropathy and the other had cerebellar involvement. Both patients showed improvement following treated with injection methylprednisolone 1gm IV od for 5 days followed oral steroids. Hence the immune mediated mechanism affecting encephalon and spinal cord in one patient and encephalon and cerebellum in other patient can be considered.^[8]

Cerebellar involvement in a patient with hypothyroidism

There are two separate mechanisms resulting in cerebellar dysfunction in patients with thyroid disorders. One due to decrease in level and thus function of thyroxine itself and the other is immune mediated mechanism occurs irrespective of thyroid hormone levels.^[11]

In our patient it is associated with Hashimoto's encephalopathy. Hence immune mediated mechanism is the likely possibility. This patient symptoms improved slowly in a period of 3 months after treatment with IV methyl prednisolone 1 gram od followed by oral prednisolone. she is also treated

with thyroxine supplementation because of associated hypothyroidism.

Neuropathy

Entrapment neuropathy

10% of patients had sensory symptoms confined to upper limb. These patients nerve conduction study suggestive of carpal tunnel syndrome. This is far less when compared to other studies. There was no patients with symptoms of Tarsal Tunnel syndrome.

Peripheral neuropathy

10% of patient in our study had peripheral neuropathy. Of these 6% of patients had distal motor sensory neuropathy. Nerve conduction study of these patient showed axonal changes of both sensory and motor nerves predominantly in lower limbs. In other 4% of patients had sensory symptoms confined to lower limbs only. Nerve conduction studies of these patients were normal. This probably attributes to small fiber neuropathy. Only the patient having overt hypothyroidism is affected. Those patient having subclinical hypothyroidism were not affected. The prevalence of peripheral neuropathy is far less when compare to other studies, which showed 42% had sensorimotor axonal neuropathy.^[12,13,14,15]

Myopathy

Only 2% percent of patients in our study has complaints of proximal muscle weakness^{16,17}. MRC power grading shows only 4 to 4+ power in proximal muscles and distal muscle power were normal. There was no hypertrophy, wasting or fasciculations noted and deep tendon reflexes were normal. Sensory symptom examination were normal. Nerve conduction studies was normal. The CPK levels showed borderline elevation of 178U/L. EMG test suggestive of myopathy.^[18] This is far less when compared to other studies, which showed 79% hypothyroid patients had neuromuscular symptoms, 39% had clinical weakness in at least one muscle group.^[19]

Neurological manifestations of hyperthyroidism

Association of headache with hyperthyroidism

On analyzing headache associated with hyperthyroidism only 14% percentage of had headache. The type of headache is episodic tension type headache and migraine. This also shows like hyperthyroidism the prevalence of tension type headache it is no more greater than in general population when compared to previous studies. The incidence of headache is comparable to general population and hence the association of headache cannot be attributed to hyperthyroidism.

Prevalence of sleep disorders in hyperthyroidism

Patient with sleep disorders in hyperthyroidism is 8%. Almost all patients had insomnia in the form of unable to initiate sleep, unable to sustain sleep and getting up very early in the morning.

Incidence of tremor in patient with hyperthyroidism

In our study 74% of patients had tremor initially which disappears with treatment as thyroxine level normalizes.

Myopathy

Only 4% percent of patients in our study has complaints of proximal muscle weakness. MRC power grading shows only 4- to 4power in proximal muscles and distal muscle power were normal. Nerve conduction studies and CPK levels were normal. Needle EMG suggestive of myopathy. This is far less when compared to other studies which showed 67% of hyperthyroid patients had neuromuscular symptoms¹⁹.

Thyrotoxic periodic paralysis

The incidence of thyrotoxicosis in gender male;female ratio is 17:1 to 70:121.Hence it is ideal to screen patients with thyroid function test presenting with hypokalemic periodic paralysis and at the most in males because of the more common association.^[20,21,22.] Only one male patient is diagnosed to have thyrotoxic periodic paralysis

Peripheral neuropathy

2% of patient in our study had peripheral neuropathy. These patient presented with burning sensation over both foot and the sensory symptoms confined to lower limbs only. There is mild objective sensory loss to pain and temperature over the toes. Nerve conduction studies of these patients were normal. This probably attributes to small fiber neuropathy. There were no other co-morbid illness which could account for the same.However this is less in comparison to previous studies which showed 19% of hyperthyroid patients had sensorimotor axonal neuropathy.

Comparing the neurological manifestation in hypo and hyperthyroidism

Overall neurological manifestation in hypo and hyperthyroidism

The association is significantly high in hypothyroidism. This emphasis the need for assessing neurological manifestations in both groups but more importantly in hypothyroidism.

Comparing the association of peripheral neuropathy in hypo and hyperthyroidism.

10% of patient hypothyroid patients had peripheral neuropathy. Of these 6% ofpatients had distal motor sensory neuropathy and 4% had small fiber neuropathy.In contrast only 4% had neuropathy in hyperthyroid group and their symptoms and investigations suggestive of small fiber involvement. Hence it is well understood there is less chance of developing neuropathy in hyperthyroidism and in affected patients it is of lesser severity when compared to hypothyroidism.

Comparing the association of peripheral neuropathy in hypo and hyperthyroidism

10% of patient in our study had peripheral neuropathy. Of these 6% ofpatients had distal motor sensory neuropathy. Nerve conduction study of these patient showed axonal changes of both sensory and motor nerves predominantly in lower limbs. Remaining 4% had small fiber neuropathy.Only the patient having overt hypothyroidism is affected. Those patients having subclinical hypothyroidism were not affected.

In contrast to this only 2% of patients with hyperthyroidism had symptoms confined to lower limb which is burning in nature. The nerve conduction study was normal in this patients.

Comparing the association of myopathy in hypo and hyperthyroidism

4% patient in hyperthyroidism had myopathy in comparison only 2% had myopathy in hypothyroidism. There was significant wasting and more severe weakness in hyperthyroid patients. The CK is typically normal in hyperthyroidism whereas it is elevated in hypothyroidism. Hence it is well understood there is more chance of developing myopathy in hyperthyroidism and in affected patients it is more severe when compared to hypothyroidism.

Neurological system confined only to hypo and hyperthyroidism

Carpel tunnel syndrome is confined only to hypothyroidism. Tremor occurs only in hyperthyroidism. Hence when examining either hypo or hyperthyroidism it is ideal to look for specific neurological manifestations.

CONCLUSION

It is important to consider thyroid function test in patients presenting as neurological abnormalities only even without other symptoms and signs of thyroid dysfunction because of the following reasons.

Patient can also present as emergency like thyrotoxic periodic paralysis, myxedema coma or myasthenia gravis masking the thyroid symptoms.

Thyroid disorders can affect almost the entire neuro axis like cerebrum, cerebellum, subcortical structures,cranial nerves, spinal cord, myoneural junction and muscle.

Even if the thyroid function tests are normal it is important to consider immunological tests of thyroid as in Hashimoto's encephalopathy or myelopathy as in our case.

It is important to treat with supplementation of thyroid hormones at the earliest rather than waiting for thyroid function test results as in cases like myxedema coma.

In adult, hypothyroidism lead to mild to moderate cognitive impairment rather than frank dementia. To prevent hypothyroid associated cognitive decline it is mandatory to treat within 5 to 7 months⁵. Hence suspicion of hypothyroid is a must in patient presenting with minimal cognitive decline because being a treatable condition and delay in treatment would result in permanent cognitive impairment.

Patient presenting with hypokalemia induced paralysis should be screened for thyroid function tests when the cause is not known(if hypokalemia not due to diarrhoea, vomiting etc)and it is always mandatory in male patients because of the high incidence of thyrotoxic periodic paralysis.

Similarly it is important to screen patients with fine tremor with thyroid function test to identify hyperthyroidism because of the high incidence of associated tremor in hyperthyroidism.

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