



Neurological Manifestations of Thyroid and Parathyroid Disorders

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INTRODUCTION

Endocrine diseases have protean manifestations and present with a wide variety of symptoms pertaining to different bodily systems. This results, at times, in diagnostic delays and dilemmas; hence it is important for the clinician to be familiar with the neurological manifestations of endocrinopathies. Amongst various endocrinal disorders, the thyroid diseases are common and to an extent, the parathyroid diseases are also encountered in clinical practice. This article highlights the symptomatology, clinical aspects, investigations and therapy of these diseases.

HYPOTHYROIDISM

Thyroid hormone has an important role in the early growth and development of the child and depending upon the time of onset of the deficiency, children may present with cretinism or juvenile myxedema or the onset may be in adulthood after the initial development has taken place. Thyroid deficiency can affect any part of the central and peripheral nervous system. More than one area may be affected but the brunt tends to be borne by some organ systems and this organ selectivity differs from individual to individual. It is also important to recognize that the neurological manifestations may be the presenting features and the other systems may be normal, to a large extent, at the time of presentation. Such cases test the clinical skills of the physician.

Headache is encountered in a proportion of patients with hypothyroidism. Generally, there are no specific features of the headache syndrome and the origin is unclear. The symptom recedes with replacement of thyroid hormone. At times, headache may be a manifestation of developing increase of intracranial pressure. This is seen in younger patients and the optic fundus shows presence of papilledema and CSF pressures are elevated. Such intracranial hypertension seen in hypothyroidism tends to be benign and reverts with achievement of euthyroid status at a variable time sequence. It is treated with anti-edema pharmacotherapy, keeping a watch on visual acuity and field of vision.

Giddiness and tinnitus are also common in hypothyroidism. It is often a presenting feature of the condition and other features may emerge with time. In such patients, there is no abnormality of ocular motility and vestibular function. In patients with unexplained giddiness or tinnitus, hypothyroid state should be kept in mind.

Encephalopathy related to immunological abnormalities of the thyroid gland has received much attention in the recent times. It is called as Hashimoto's encephalopathy. Encephalopathy associated with autoimmune thyroiditis was first described in 1966 by Brain and colleagues.¹ Current evidence suggests that the encephalopathy results from an autoimmune process, though the exact mechanism has not been elucidated. Some findings suggest that the process is similar to acute disseminated encephalomyelitis.² Patients present in middle ages of life and majority are women. Two types of clinical presentation can be observed. The first type is characterized by acute episodes with transient focal neurological deficits and epileptic seizures. The second form has insidious onset progressing to dementia, psychosis, and coma over several weeks. No focal neurological deficits are seen in the latter type. Thus it can be seen that the clinical features in themselves are not specific and a high degree of clinical suspicion is required to arrive at the diagnosis.

No specific diagnostic test exists for Hashimoto's encephalopathy. A positive antithyroid antibody titer is necessary but not sufficient in making the diagnosis of Hashimoto's encephalopathy. Other autoantibodies, such as anti-parietal cell antibody or anti-intrinsic factor antibody may also be present, increasing the suspicion of an immunological process. The cerebrospinal fluid tends to show high proteins, but is otherwise normal. Some patients may have mild pleocytosis. EEG shows nonspecific, intermittent slow wave activity. Epileptic activity has been documented in several cases. Neuroradiological studies frequently reveal nonspecific findings, such as bilateral subcortical high signal lesions on T2-weighted images, or mild cerebral atrophy with temporal predominance.

Patients with Hashimoto's encephalopathy respond very satisfactorily to steroid therapy. The response is rapid and is seen in initial few days of therapy. Remission rates are high, but some patients may require maintenance therapy and some others may not remain under satisfactory control.³

Psychiatric symptoms are among the most common, early, and prominent symptoms of hypothyroidism. In particular, depressive symptoms or even major depression may be the presenting feature of hypothyroidism.⁴ Psychiatric symptoms of hypothyroidism [the myxedema madness], including depressive symptoms, commonly resolve with treatment of the underlying thyroid disorder with thyroid hormone replacement therapy, but, on occasion, antidepressants may be required. As thyroid disease commonly presents with mood, anxiety, and cognitive symptoms,

it is a good policy to screen patients with depressive symptoms with routine or ultrasensitive thyroid hormone estimation.

Gradual cognitive decline, dementia and alterations of sensorium even leading to frank coma are encountered in extreme instances of hypothyroidism. Such patients may present during a stressful event in life and show prolonged recovery time. They tend to have overt hypothyroidism of severe nature.

The cerebellum may be also a target on rare occasions. This results in difficulty in balance, gait and inability to perform tasks requiring precision. The examination shows signs of affection of the cerebellar system. In an adult onset sporadic case of ataxia, hypothyroidism is an important reversible cause and should be actively sought for.

Thyroid myopathy Thirty to forty percent of hypothyroid patients manifest with neuromuscular symptoms.^{5, 6} Muscle manifestations can occur at any time in the presentation of hypothyroidism. Many patients report muscle stiffness and cramps and a quarter of patients show slow relaxation of tendon reflexes on examination. These symptoms can be the presenting symptoms of hypothyroidism.

On clinical examination, weakness is seen mainly in the proximal muscles, symmetrically and in a non-selective manner. It is usually mild and is more pronounced in the lower limbs. The combination of muscle pains and cramps with weakness is a strong pointer towards the diagnosis of hypothyroid myopathy. The presence of systemic symptoms of hypothyroidism cannot be relied upon for identifying patients with hypothyroid myopathy, as they may be absent. Delayed relaxation of deep tendon reflexes represents a primary feature of hypothyroidism. This occurs from impaired calcium sequestration by sarcoplasmic reticulum, which prolongs twitch duration.⁷

Myoedema is the phenomenon of mounding up of muscle tissue after light percussion.⁵ It occurs in approximately one third of patients with hypothyroidism, but is not specific for hypothyroidism.^{5,6} This phenomenon has no electrophysiological correlates.

Spontaneous rhabdomyolysis and myoglobinuria leading to transient acute renal failure has also been reported.^{8,9} Hypolipidaemic agents (statins) may exacerbate myopathy in hypothyroid patients.^{10,11}

The curious phenomenon of muscle hypertrophy is sometimes seen in children and adults with hypothyroidism, the Kocher-Debre-Semelaigne syndrome¹² or the Hoffmann syndrome. The usual clinical features are those of hypothyroidism and occasionally the patients may complain of muscle cramps or stiffness.¹³ The degree of short stature and severity of the hypothyroidism is variable and correlates directly with the severity of the muscle pseudohypertrophy.^{13,14} The pseudohypertrophy is generalized but striking in the limb musculature imparting an athletic or Herculean appearance. The muscle pseudohypertrophy is extensive, firm to feel and involves the calves, thighs, neck, tongue and facial muscles. Apart from the muscles of the extremities, limb girdles and trunk, small muscles of the hands and feet may also be involved.^{12,14} The pseudohypertrophic form of hypothyroid myopathy in adults is called Hoffmann's syndrome and may simulate muscular dystrophy.^{2,4}

A polymyositis-like syndrome has also been described. In patients with hypothyroid myopathy, the combination of muscle pains, proximal muscle weakness and high CK would raise the suspicion of inflammatory myopathy, particularly polymyositis. This is a very important differential diagnosis, because the therapy of the two conditions differs totally.

Peripheral neuropathy: Like the myopathies, peripheral nerve involvement is an important part of the neuromuscular affection of hypothyroidism. About 40% of hypothyroid patients have a sensori-motor neuropathy early in the course of thyroid disease. Carpal tunnel syndrome, often bilateral, is also commonly seen.⁷

Two types of peripheral nerve involvement have been described.¹⁵ The first, a sensorimotor polyneuropathy related to axonal damage or myelin changes, is more common. Sensorimotor polyneuropathy has distoproximal progression, affecting lower limbs first. The severity of the clinical picture relates more to the duration of the disease than to the severity of thyroid hormone deficiency.¹⁵ The other type of neuropathy is the mononeuropathy related to entrapment syndromes. The endocrinal changes make the nerves more susceptible to compressions, due to the mucinous deposits in the tissues. Median nerve entrapment at the wrist is caused by deposition of mucinous material in the tissue. Bilateral symmetrical foot drop may be caused by peroneal neuropathy due to decubitus pressure or glycosaminoglycans deposition in the perineural sheath.

Myasthenia gravis, also an immune disorder, can co-exist with thyroid disorders and the two can be confused, as fatigue is a common symptom of hypothyroidism. But when there is strong diurnal fluctuation and the eyelids or bulbar musculature is affected, additional neuromuscular junction disorder needs to be considered. Patients with myasthenia gravis have an increased incidence of thyroid disorders.¹⁶ It is important to recognize this association, as hypothyroidism may exacerbate the myasthenic weakness and have implications in the management.

HYPERTHYROIDISM

Hyperthyroidism is usually associated with a thyroid adenoma or Grave's disease, which would be accompanied by other sequel of this autoimmune illness, such as ophthalmic symptoms. In addition to the physical symptoms associated with hyperthyroidism, a heterogeneous group of psychiatric symptoms and syndromes may occur.^{17,18} These include anxiety, cognitive difficulties, psychotic symptoms, and even major depression. As with hypothyroidism, treatment of the underlying endocrine disorder commonly leads to resolution of psychiatric symptoms, although further psychotropic intervention is required occasionally.

In patients with hyperthyroidism, 80% have neuromuscular complaints and more than 50% have marked muscle weakness.^{19,20} Women predominate at 3:1 to 4:1, and the mean age of onset is the fifth decade. Weakness is primarily proximal and is usually out of proportion to the amount of muscle wasting; distal weakness develops later and is less severe than the proximal myopathy. Myalgia, fatigue, and exercise intolerance are common. Breathlessness is common, and respiratory insufficiency, requiring ventilatory support can occur. Bulbar muscles and the oesophagus may be involved. Sphincters are spared. Tendon

reflexes are usually normal. Rarely, an inflammatory myopathy occurs with thyrotoxicosis which necessitates corticosteroid therapy.²¹

Thyrotoxic periodic paralysis is a thyroid-related disorder that is manifested as recurrent episodes of hypokalemia and muscle weakness lasting from hours to days. The knowledge of the condition is particularly relevant to us in India as the incidence of the disorder is relatively higher among Asians.²² Many features of this disease are identical to those of familial hypokalemic periodic paralysis. Patients with thyrotoxic periodic paralysis have recurrent muscular weakness affecting mainly the lower extremities. The onset of paralytic attacks usually coincide with the onset of hyperthyroidism, though overt findings of thyrotoxicosis are rarely present with the initial paralytic attack. In some cases, the periodic paralysis is the sole manifestation of the hyperthyroidism. Though thyrotoxicosis is more often seen in women, TPP has a strong predominance in men, with a male-to-female ratio of 11:1.2. A notable early symptom during the initial stage of an attack is a sensation arising in the affected muscles variously described as aching, stiffness, pain, or cramp. Paralysis occurs only when the patient is at rest, preceded by unusually great physical activity and consumption of a high-carbohydrate meal. The attacks of paralysis vary widely in severity and range of weakness of the muscles of the pelvic girdle, lasting several hours, to a total paralysis of all the muscles from the neck downward, lasting up to 48 hours. Proximal muscles are affected more severely than distal muscles. Deep tendon reflexes are either absent or reduced. Recession of the paralysis is usually in the reverse order of its appearance. Although the mechanism of thyrotoxic periodic paralysis remains uncertain, the two main ingredients that produce a paralytic attack are thyrotoxicosis and hypokalemia. Once the paralytic attack has started, administration of potassium is standard therapy, and it hastens the recovery of the periodic paralysis.²³ It is given mainly to prevent cardiac arrhythmias that potentially can be life-threatening. Potassium is usually administered intravenously, even though there is no proven advantage of using this route of administration. The definitive therapy for thyrotoxic periodic paralysis is the management of the thyrotoxic state by medical therapy, surgery, or radioactive iodine therapy. Adrenergic blockade induced by propranolol therapy has resulted in marked relief of the episodes of paralysis and is probably the most useful preventive therapy until euthyroid state is achieved.²³

Thyroid Eye Disease is a common and important manifestation of the neurological involvement. Two types of manifestations may occur in thyroid eye disease, firstly, the functional abnormalities due to hyperactivity of the sympathetic nervous system and secondly, infiltrative lesions involving the contents of the orbit. The infiltrative type has a much more serious prognosis. Infiltrative ophthalmopathy is considered a characteristic and unique feature of Graves' disease. The signs and symptoms are produced by the following related abnormalities. Edema of the orbital contents, protrusion of the globe, infiltration of the extra-ocular muscles and damage to the optic nerve and the retina and increased intraocular pressure are seen. The muscle enlargement can be recognized by ultrasound or, more certainly, by computed tomography (CT) or MRI scanning. The enlargement is almost pathognomonic of Graves' disease. Paralysis, or paresis, of the extra-ocular muscles also occurs. The retina may be injured by venous congestion or

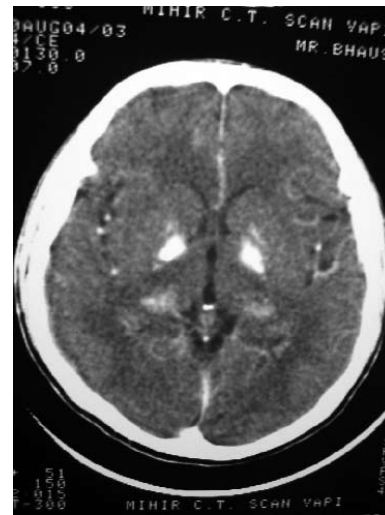


Fig. 1 :

hemorrhages. Field defects are occasionally seen. Papilledema may be present, especially in severe involvement of the eye. If the optic nerve is involved, there may be pallor of the optic disc and a decrease in central visual acuity or field cuts, valuable and ominous signs. Blindness may occur without protrusion of the globe. Increased intraocular pressure occurs in about 25% of patients with TED, especially in those with infiltrative disease. Supportive therapy or no therapy at all is needed for majority of patients.²⁴ Management of thyroid dysfunction, tobacco cessation, reassurance and support, elevation of head of the bed, low-salt diet, diuretics, artificial tears, protective sunglasses and prism in glasses help. Medical management includes oral corticosteroids, pulsed intravenous methyl-prednisone therapy, cyclosporine, intravenous immunoglobulin (IVIG), octreotide, plasmapheresis, and orbital radiotherapy.

Neuromuscular junction disorders like myasthenia gravis may be seen in a proportion of patients with hyperthyroidism. Patients with myasthenia gravis have an increased incidence of thyroid disorders; and 5.7% of myasthenic patients are hyperthyroid.²⁰

PARATHYROID DISORDERS

Hypercalcemic symptoms consist of polyuria, thirst, constipation, lethargy, weakness, and gastrointestinal symptoms and these are seen only in the more severe forms of the disorder. Mild hypercalcemia is often diagnosed during a routine biochemical screening when patients are asymptomatic, although patients with hypercalcemia have significantly more psychiatric symptoms than controls.

Hypercalcemia and hypocalcemia may present with psychiatric symptoms. Such symptoms are insidious and may simulate a bipolar or schizophreniform disorder. There may be no other associated symptoms or signs, making the diagnosis difficult. More over, even the biochemical alterations of calcium may be mild. Seizures are also common in hyper and hypocalcemia. They are usually generalized, but at times begin focally with secondary generalization. Intracranial calcifications are common and are symmetrical, involving the basal ganglia and dentate nuclei of the cerebellum (Fig. 1). The calcium deposition is outside the neurons and hence in spite of the severe abnormalities on neuroimaging, neurological signs may be few. Movement disorders of various types like the chorea, athetosis, and dystonias may be seen in



Fig. 2 :

such patients and at times, they may be the leading symptoms of the parathyroid disease. Occasionally, the patients present with rise of intracranial pressure with papilledema without localizing signs, like benign intracranial hypertension.

Hypocalcemia and hypomagnesemia produce hyperexcitability of nerve fibers with spontaneous and repetitive discharges in them. As a result, patients have perioral and distal numbness and parasthesiae, carpopedal spasm and diffuse muscle cramps.²⁵ Latent tetany can be elicited by hyperventilation, by tapping the facial muscles (Chovstek's sign) or by occluding venous return from arm, resulting in carpopedal spasm (Trousseau's sign). In severe cases laryngeal muscle spasm may develop.

Myopathy is a rare manifestation and may present as progressive proximal limb girdle muscle weakness. Hypoparathyroidism has been observed in several cases of Kearns-Sayre syndrome a non-hereditary multisystem disease.

In primary hyperparathyroidism, patients have symmetrical muscle weakness and atrophy. Bulbar muscles and sphincters are usually unaffected. Muscle cramps are common. Some of these neuromuscular manifestations of hyperparathyroidism resemble motor neuron disease. Patient with increased PTH may present with muscle atrophy and weakness with hyperreflexia and spasticity. Untreated patients tend not to do well and progress much like patient with motor neuron disease.

Secondary hyperparathyroidism is usually the result of osteomalacia or chronic renal failure. Lower extremity weakness predominates but with time all limbs are affected. In patients with chronic renal failure, the myopathy may be associated with dialysis encephalopathy.²⁶ About 33% of patients with osteomalacia have complaints of myalgia and essentially all patients have proximal weakness. The nonspecific manifestations of fatigue, myalgia and general weakness may lead to confusion with fibromyalgia or polymyalgia rheumatica. Because symptoms develop gradually, patients may present with significant weakness before presentation. Bone pain and tenderness are most prominent in the pelvis, the femur, the spine and the ribs.

CONCLUDING REMARKS

Diseases of the thyroid and parathyroid glands are regularly encountered in clinical practice of internal medicine. These

disorders affect all parts of the central and peripheral nervous system in many different ways. When the neurological symptoms are the presenting or the only symptoms, high index of suspicion is required to unearth the underlying endocrinopathy, on which the success of therapy depends.

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