Review Article

Adult hypothyroidism and its neurological complications

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ABSTRACT

Hypothyroidism is a clinical entity very commonly encountered in clinical practices. Untreated hypothyroidism can lead to hypertension, dyslipidemia, infertility, cognitive impairment, neurological and neuromuscular involvements. Neurological complications include reversible cerebellar ataxia, dementia, peripheral neuropathy, psychosis, coma, encephalopathy (Hashimoto's encephalopathy), neuromuscular disorders. The disease identification in the initial stage remains difficult as it presents with a large number of clinical features. Neonatal screening protocols in all patients of hypothyroidism can help in the timely detection as well as treatment. Most of the neurological manifestations can be reversed on timely administration of levothyroxine which works well even in reversing of the symptoms as it reverses the metabolic abnormalities. It is important to evaluate every patient with hypothyroidism or with the suspicion of the disease for any neurological abnormalities.

Keywords: Hypothyroidism, Myopathy, Neuropathy, Hashimoto's encephalopathy, Ataxia

INTRODUCTION

Disorders of thyroid gland are among the most common endocrine disorder of which hypothyroidism is the most common.

Over all thyroid hormones have a critical influence on cellular metabolic activities and the integral growth, development and functioning of the central nervous system.

The clinical presentation of hypothyroidism depends upon the age of onset ex: cretinism leads to irreversible cerebral damage while hypothyroidism in adults can be controlled or even reversed with adequate hormone (thyroxine) replacement therapy, Adult hypothyroidism is usually caused by primary thyroid gland disorders like autoimmune thyroiditis, radiological or surgical ablation of thyroid gland, iodine deficiency, thyroid gland tumors or even drug induced.

Being more common in females, hypothyroidism may clinically present with a variety of symptoms like constipation, fatigue, cold intolerance, weight gain, hair loss, bradycardia, etc. It can present with a wide range of neurological complications like peripheral neuropathies, cerebellar ataxia, emergencies like Hashimoto's encephalopathy, neuropsychiatric symptoms as well as myopathies. It becomes imperative and extremely essential to identify the disease at an early stage as well as early identification of emergencies to reduce any complications, especially the neurological complications of the disease.1
EFFECT OF HYPOTHYROIDISM ON NERVOUS SYSTEM

Thyroid hormone deficiency during the critical period of nervous system development may lead to permanent deficit in learning, intelligence and sensory-motor functioning. The overall impact is determined by age of onset, severity, rate of development of deficiency and the co-existing other hormonal deficiencies. There is an extensive interconnection between thyroid hormones, acetylcholine nerve growth factors and hippocampal function as the thyroid hormone affects the maturation of specific neurons in the brain.

NEUROPSYCHIATRIC MANIFESTATIONS

Considering the relationship of thyroid axis and psychiatric symptoms various neurological manifestations like impaired attention, lethargy, poor concentration, psychomotor retardation and even dementia are common in adult hypothyroidism.

A condition known as 'myxedema madness' describe the symptoms of irritability, hallucination, delusions and paranoia is associated with long standing hypothyroidism in adult.2

It has been found that patients with subclinical hypothyroidism often have poor concentration, irritability, slow learning in comparison to normal subjects. It has been studied that the values of thyroid function tests can be valuable in the treatment of depression as well as bipolar disorders. Thyroid hormone affects the brain both in the neonatal period as well as throughout life. Patients of mood disorders have shown variations in the levels of Thyrotropin releasing hormone and TSH, whereas T3 and 14 were usually normal. There is a lot of data that suggests that the hypothalamic pituitary axis in involved in the pathogenesis of depression and mood disorders.3

HEADACHES IN HYPOTHYROIDISM

A nonspecific type of headache of continuous, non-pulsatile in nature; in patients of hypothyroidism, responding well to hormone replacement therapy is a known clinical entity. At times underlying hypothyroidism exacerbates the headache.4,5

CEREBELLAR DEGENERATION AND ATAXIA

Almost one third cases of hypo-tyroidism develop cerebellar ataxia which is reversed in some of the patients with restoring euthyroid status. The occurrence of non-familial adult-onset cerebellar degeneration presenting as gradually progressive ataxia indicate generalized autoimmune disorder like, auto immune or Hashimoto's thyroiditis with advancement of disease the brainstem, ocular, extrapyramidal and peripheral nervous system manifestations develop which further complicates the clinical diagnosis. As the disease advances, the effect of thyroxine on reversibility of ataxia gradually decreases.6,7

DEMENTIA

An uncommon but potential reversible dementia of subcortical nature, commonly presenting as apathy and cognitive slowing is seen in adult hypothyroidism of long-standing nature. Even after adequate replacement by levothyroxine the cognitive function does not improve to the expected level. The longer the dementia remains undiagnosed, the worse the outcome.8 It has been postulated that additional etiological factors may also be implicated in its etiology.

CEREBRO VASCULAR ACCIDENTS (CVA)

Hypothyroid state with its associated factors like diastolic hypertension, increased level of homocysteine, LDL affects the endothelial functions and coagulation profile at times increases the risk of stroke mainly ischemic. The cause and relationship are although weak in most of the cases.

PERIPHERAL NERVOUS SYSTEM ABNORMALITIES

In hypothyroidism, polyneuropathy is less common them mononeuropathy (especially entrapment neuropathy). In many instances an associated B12 deficiency further aggravate the symptoms.

Entrapment mono neuropathy (carpal tunnel syndrome)

Around 30% of hypothyroid individuals (especially females) develops symptoms of median nerve entrapment across the wrist typically as numbness, tingling, paresthesia’s in median nerve distribution area in hands. It usually starts as unilateral but gradually becomes bilateral. A retrograde pain in forearm radiating up to arm at times mimics the C6 cervical radiculopathy. The etiology is related to accumulation of myxoedematous tissue with reduced space in flexor retinaculum at carpal tunnel or swelling of the synovial membrane around the tendons in the carpal tunnel but the former a more appropriate and considerate etiology.9 The Phalen's test on clinical assessment and the evidence of thenar atrophy coupled with weakness in thumb opposition and abduction further help in diagnosis. A nerve conduction study is the gold standard in assessment of carpal tunnel syndrome on laid electrophysiological criteria. The axonal degeneration generally shows delayed and incomplete recovery justifying the need of early diagnosis and treatment. In good number of cases replacement therapy with levothyroxine may produce considerable improvement in 6-8 weeks durations.10

In advanced cases surgical decompression of median nerve may be required. At times hypothyroid state may be related
to other less common entrapment mononeuropathies like tarsal tunnel syndrome and meralgia paresthetica.

**Polyneuropathy**

Though less common hypothyroidism is associated with a large fiber neuropathy manifestation as reduced vibration and proprioception, distal paresthesia and objective distal sensory loss along with sensory symptoms like painful dysesthesias in the hands and feet and lancinating pains. Weakness is a common complaint but objective evidence of this is rarely found. Deep tendon reflexes may be diminished and ankle jerk typically show delayed relaxation. The slow relaxation is the result of disturbances in energy transfer within muscle rather than slowing within neural pathways. Overall, the nerve conduction velocities are slowed. Usually, the protein in cerebrospinal fluid is increased, believed to be a reflection of increased serum protein in hypothyroidism.

There is evidence of dysfunction of both the Schwann cell (leading to demyelination and slowed nerve conduction) and axon (leading to axonal degeneration). The mechanism by which lack of thyroid hormone produce these changes is poorly understood.

**CRANIAL NERVE ABNORMALITIES**

Accumulation of myxomatous tissue around the eighth cranial nerve and fluid in inner ear produces a reversible sensory neural hearing loss with or without tinnitus in a good no. of long-standing hypothyroid cases. Similar myxoeidematous deposition in larynx and tongue results in slurred and thick speech. In untreated primary hypothyroidism, the pituitary gland enlarges and produces compression over optic chiasm with variable field defects. Many times, these effects can be minimized with attainment of euthyroid state.

**MUSCLE DISORDERS**

Muscle involvement is a common complication of adult-onset hypothyroidism. Hypothyroid myopathy ranges from asymptomatic CK elevation to overt muscle complaints like myalgia, severe muscle weakness, cramps. Polymyositis like syndrome, rhabdomyolysis and acute compartment syndrome may be the manifestations of thyroid affection to muscle tissue.

**Thyroid myopathy**

The frequency of myopathy in hypothyroidism ranges from 30-50%, the major symptoms related are muscle cramps, myalgia and proximal muscle weakness. Muscle hypertrophy and wasting are seen infrequently and generally evolve over a longer period of time. It itself can present as a sole manifestation, hence in every unexplained subacute myopathy, thyroid function test (TFT) should be evaluated. Examination reveals proximal muscle weakness (lower limbs more than upper limbs) and delayed relaxation of tendon reflexes.

Adult patients with myopathy associated with acute transient hypothyroidism is also described. Usually, the patients present with severe muscle aches and cramps, stiffness and spasms. Muscle enzymes were markedly elevated but histological changes are generally absent in muscle biopsy. The clinic reversal is attained with euthyroid state. A rare association is Hoffman's syndrome, which is characterized by muscular pseudohypertrophy, weakness, and slowness of movement in adults, while muscle enlargement and apparent hypertrophied calf muscles are described in infants known as Kocher-Debre-Semelaigne syndrome. The unique look has been called as "infant Hercules" because of increase in muscle bulk without increasing muscle power.

**Pseudo myotonia**

Pseudo-myotonia with delayed relaxation of muscle may occur with a prolonged tendon reflex relaxation time, myoedema, the "mounding phenomenon", may be elicited in some hypothyroid patients on direct percussion of the muscle or tapping with reflex hammer. This mounding typically relaxes slowly and lasts for seconds to minutes.

Hypothyroidism is also a risk factor for statin-induces myopathy (SIM) and even spontaneous myopathy. Muscle aches, cramps and weakness are the typical clinical features irrespective of the precipitant like heavy exercise, pre-existing renal failure and hypolipidemic drugs. Rhabdomyolysis, the most feared and potentially fatal complication of SIM, is also rarely caused by isolated hypothyroidism. When this is seen, it is usually characterized by a moderate rise in creatine phosphokinase (CPK) because of these associations, patient's thyroid status should always be considered before initiating lipid-lowering medications and for patients receiving statin therapy. Thyroid function should be assessed whenever myopathic symptoms or resistance to therapy is noted.

Increased serum activities of enzymes of muscle origin (MM), particularly the creatine kinase isoenzyme, are found in hypothyroidism whether or not muscle symptoms are present. Serum myoglobin concentrations are also raised.

Electromyogram (EMG) examination of proximal muscles may reveal short duration, low-amplitude, polyphasic motor unit action potentials (myopathic units) without spontaneous activity. There is electric silence in myoedema. Routine histopathological studies show non-specific findings, but histochemical studies have shown atrophy and reduced frequency of type 2 fibers.

**COMA IN HYPOTHYROIDISM**

**Myxoedema coma**

Myxoedema coma is a rare life-threatening complication of long-standing untreated hypothyroidism occurring in <1% of elderly females. This medical emergency is characterized by marked impairment of the central nervous...
system and cardiovascular functions and is responsible for higher mortality rate of 20-30%.

Common precipitating factors for myxoedema coma are exposure to cold, concurrent infection, trauma congestive heart failure, stroke and drugs like sedatives, antidepressants, hypnotics and anesthetics etc.

Patient shows overt signs of hypothyroidism like dry skin, bradycardia, swelling over body along with hypothermia, hypotension, hypoventilation, bradycardia, etc. Hypothermia is present in almost three-fourth of patients. It is an indicator of high mortality. Patients having core body temperature of <90°F have poor prognosis. Neurological features of myxoedema coma usually include depressed mental status, cerebellar signs and seizures in some patients. Here also, thyroid hormone supplementation has been found to be useful, along with glucocorticoids and supportive cardiopulmonary measures. Prompt initiation of treatment with thyroid hormone therapy is extremely necessary if there is a high suspicion of myxoedema coma, as delay in initiation of the treatment can lead to high morbidity and mortality.14

**HASHIMOTO ENCEPHALOPATHY**

Hashimoto encephalopathy (steroid-responsive encephalopathy) associated with autoimmune thyroiditis is a potentially fatal condition manifesting as myoclonus, altered conscious state, seizures, stroke like episodes, rapid cognitive decline, and neuropsychiatric symptoms, including psychosis, hallucinations, and abulia. It is an important differential diagnosis of rapidly progressive dementia. It is also an important cause of potentially reversible dementia because with prompt and appropriate treatment its symptoms can be completely reversed. Controversially, Hashimoto encephalopathy can present in the absence of thyroid function abnormalities, even though it is associated with high titres of antithyroid peroxidase and antithyroglobulin antibodies.16

The Hashimotos encephalopathy can present as an acute encephalopathy, chronic psychiatric form, cerebellar ataxic form. It can be commonly associated with cerebellar ataxia, truncal ataxia, which is reversed on giving steroids. It is more of a treatable ataxia. Hashimoto's encephalopathy shows slowing on EEG and a noticeably decreased amplitude over left hemisphere. There was seen to be a considerable amount of improvement on the administration of intravenous steroids, with respect to the slowing of EEG waves, which could also correlate to the clinical findings.17,18

Common differential diagnosis of Hashimoto’s encephalopathy can be Creutzfeld Jakob disease, rapidly progressive dementias, paraneoplastic limbic encephalitis. It responds well to high doses of corticosteroids. Plasmapheresis has been also found effective.

**CONCLUSION**

Thyroid disorders are common and often associated with neurological manifestations. However, high index of suspicion is needed when neurological symptoms are presenting features. In such cases, proactively doing thyroid function tests and antibody testing is necessary as treatment may lead to complete recovery. Appropriate and timely administration of thyroid replacement therapy works for most of the neurological complications of hypothyroidism, except Hashimoto’s encephalopathy; which responds best to steroids. However, it becomes extremely crucial to treat every patient of hypothyroidism as a potential case of neurological complications; hence early and prompt administration of levothyroxine can be of utmost value in the prevention of neurological, neuropsychiatric as well as neuromuscular disorders associated with hypothyroidism.

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