HYPERTHYROIDISM: LOOKING BEYOND PHYSICIAN'S PERSPECTIVE

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Abstract
Hyperthyroidism with its excess circulatory thyroid hormones commonly presents with systemic features like palpitation, weight loss and heat intolerance. This hyperadrenergic, hypermetabolic state with its peripheral and central nervous system affection produces protean neurological manifestations which are generally overlooked by internists. Features of neuropsychiatric nature, cognitive impairment, and dementia movement disorder like tremors or chorea may be presentation of undetected hyperthyroidism. Affliction for muscles presents with proximal myopathy with or without myalgia in 50-70% of long standing hyperthyroid state. Similarly thyrotoxic periodic paralysis due to low serum potassium in adult male is often misdiagnosed as Guillain-Barré syndrome, however replacement of potassium drastically reverse the condition. There is a strong association between autoimmune thyroiditis and ocular myesthenia which post difficulties in clinical diagnosis. Despite of so much variability in clinical presentation attainment of euthyroid state coupled with beta blocker in many situations is helpful to resolve most of the issues.

Keywords: Hyperthyroidism, Grave's, Tremors, Myopathy, Periodic paralysis.

Introduction:
Thyroid disorders are one of the most common endocrinial disorders. Both hypo & hyper thyroid state has a specific prediliction for nervous tissue although thyroid hormone receptors are widely distributed in the body like liver, heart, kidney, skeletal muscles, pancreas and placenta. The excess circulatory thyroid hormone produces a hyper metabolic state. The most common cause of hyperthyroidism is grave's disease but can also be due to toxic adenomas, toxic nodular goitre, destructive thyroiditis, excess thyroid hormone supplementation or even post viral. Apart from common systemic presentations like weight loss, palpitations heat intolerance, number of peripheral and central nervous system manifestations may occur in conjunction with systemic features in hyper thyroidism.[1]

The common neurological complications of hyper thyroid state are Encephalopathy

Cognitive impairment with associated features of confusion, dementia & seizures complicates the hyperthyroid state. Seizure activity is not as usual feature of thyroid disorder but leads to delay in suspicion and diagnosis of hyperthyroidism. Beta blocker therapy help in improvement of cognitive & behavioral dysfunction suggesting a role of hyperthyroid induced hyper adrenergic system. Seizure semiology varies from partial or complex partial seizure to generalised tonic clonic one. New onset of seizure in a child or adult raises the suspicion of underlying hyperthyroidism. seizures in hyper thyroid state are treated by thyroid lowering drugs while antiepileptics are used as a temporary measure till attainment of euthyroid state.[2]

Movement Disorders
The commonest movement disorder in hyperthyroidism is fine tremoss (esp: action tremor) of high frequency and low amplitude manifesting on out strecthed hands. It can also involve head, face and even extremities. These tremors resemble an exaggerated physiological tremors and respond well to Beta blockers (propranolol) so these are indicative of heightened beta-adrenergic state associated with hyperthyroidism. Other less commonly encountered movement disorders are chorea, choreoathetoid movement, myoclonus & even ballismus. In addition to lowering of circulating thyroid levels, dopamine antagonists like haloperidol and even reserpine are helpful.[3,4]

Neuropsychiatric Manifestations
Increased sympathetic stimulation in hyperthyroidism can present as anxiety, agitation, irritability, emotional lability mostly in young patients. Depression is another manifestation of hyperthyroidism seen mostly in elders.[5]

Encephalopathy associated with hyperthyroidism may have delusion, paranoia, psychosis & delirium associated with high fever, vomiting, atrial fibrillation, congestive heart failure mostly in younger individuals. There is also inconclusive evidence suggesting that mild hyperthyroidism may be a risk factor for dementia (both vascular & degenerative) because of neuronal injury produced and hasten by oxidative stress.[6]
Cardiogenic embolic Cerebral Infarction (CVA) & Cerebral Venous Thrombosis

Hyperthyroid induced Atrial Fibrillation (AF) may lead to cerebral infarction in 10-15% cases mostly in men and its prevalence increases with age. The atrial embolisation is high risk factor in hyperthyroidism & justify the use of antithrombotic or oral anticoagulant for secondary prevention. Similarly such hypercoagulable state possibly due to increased factor VIII activity coupled with elevated fibrinogen and decreased protein ‘c’ activity, in hyperthyroidism may predispose to cerebral venous thrombosis. Altered hemodynamics or dehydration induced by thyrotoxicosis & venous stasis may directly affect vascular smooth muscle and endothelium thus altering the vascular reactivity. Though rare but cerebral venous thrombosis in presence of thyrotoxicosis carry high morbidity & mortality.[7]

Peripheral Neuropathy

Ranging from a distal symmetrical sensory polyneuropathy to more pronounced Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy attributed to high titres of circulating thyroid hormones is seen in 5-10% individuals.[8] The symptoms of these neuropathy reverse to some extend with return of euthyroid state.

Though uncommon acute severe paraplegia or Quadriplegia associated with areflexia known as 'Basedow's Paraplegia' which occur in setting of severe thyrotoxicosis or thyroid storm is also described.[9] Similarly there is marginal risk of development of Carpal Tunnel Syndrome (CTS) but less as compared to hypothyroidism in patients with long standing untreated hyperthyroidism.[10]

Myopathy

Skeletal muscles are one of the key areas of thyroid function action. 50-70% of untreated patients develops predominantly proximal muscle weakness and myalgias with or without muscle atrophy. This muscle involvement is seen more frequently in individuals after the age of 40 and is progressive in nature.[11] Thyrotoxicosis although seen mostly in women, myopathy is commonly seen in males. Increase in hormone levels result in increased catabolic action on muscles which leads to imbalance between myofibril synthesis and it degradation process, decrease in muscle carnitine levels, increased cellular metabolism & energy utilization, all contributes to pathogenesis of myopathy. The clinical presentation of myopathy may be:

- Acute thyrotoxic myopathy with severe proximal and distal weakness and rarely with bulbar or respiratory muscle involvement.
- Chronic thyrotoxic myopathy (more common) develop is around two-thirds of patients and begins with proximal limb girdle weakness after several weeks to months of development of hyperthyroid state.[12] It may be associated with myalgias.

Both these types of myopathies are not associated with muscle atrophy and a rise in serum creatine kinase. Unlike usual myopathic disorder, the deep tendon reflexes (esp: knee & ankle) are increased or normal due to shortened relaxation phase of muscle contraction. Thyrotoxic myopathy is generally uncommon in pediatric populations. Electromyography (EMG) may be normal but sometime demonstrates myopathic features of low amplitude, short duration, motor unit potentials without any spontaneous activity.[13] Treatment of hyper thyroid condition is usually sufficient to treat the myopathy.

Thyrotoxic Periodic Paralysis (TPP)

It represents an acquired form of hypokalemic periodic paralysis in which attacks of generalised weakness occur. The attacks are generally triggered by strenuous exercise, high carbohydrate meal or less commonly by alcohol, infection, trauma, emotional stress or even menstruation.[14] Asian males in their second to fourth decades have high chances of developing such periodic paralysis. Clinically the muscle weakness is presented with symmetric ascending paralysis with decreased deep tendon reflex and prodromal symptoms of aches, cramps and muscle stiffness. Ocular, bulbar and respiratory muscles are generally spared with no alteration of consciousness. There is a massive shift of potassium in to the cells due to increase in Na⁺–K⁺–ATPase pump activity (in skeletal muscles, liver and kidney) because of excess thyroid hormones, beta adrenergic catecholamines & insulin levels along with extra renal loss of potassium.[15] The severity of weakness is directly proportional to decrease in potassium level. With potassium replacement and use of beta blockers the paralysis reverses in order of its appearance in 24 to 36 hrs. TPP in pediatric population is rare.[16]

Myasthenia Gravis (MG)

An epidemiological link exists between myasthenia gravis and hyperthyroidism (Particularly Grave's disease) due to shared autoimmunity of HLA B, HLA DQ3 and genetic susceptibility. Myasthenia gravis in all forms of thyroid disease comes around 25-30% but reverse of this is pattern is seen in cases of autoimmune thyroiditis, where incidence of myasthenia gravis is less than 1%. Overall ocular MG is more commonly associated with auto immune thyroid disease as compared to MG without thyroid or thymic disease or acetylcholine receptor antibodies.[17] The association between ocular MG and Grave's disease may reflect immunological cross reactivity against common auto immune targets in eye muscles. Ocular features in form of intermittent ptosis and diplopia may preceed or follow the features of hyperthyroidism. Grave's ophthalmopathy and ocular MG despite having overlap symptoms can be distinguished clinically as weakness of orbicularis oculi and ptosis suggest ocular MG while restricted extra ocular movement, lid retraction, lid lag, proptosis and periorbital edema suggest the Graves ophthalmopathy. More than half of the patients demonstrates parallel disease activity with worsening of
both diseases over a similar time period.\textsuperscript{[18]} The treatment and prognosis of MG is almost similar in patients with or without hyperthyroidism and consists of acetylcholinesterase inhibitors, immunosuppressive therapy and thymectomy. Treatment of hyperthyroidism alone does not usually affect MG. Thymectomy appears to have no influence on hyperthyroidism.\textsuperscript{[19]}

Very rarely hyperthyroidism may be associated with motor neuron disease (ALS) with features of both upper and lower motor neuron features, pseudobulbar palsy or features of pure corticospinal tract involvement.\textsuperscript{[20]}

**Conclusion**

The diverse neurological manifestations affecting the central and peripheral nervous systems, muscles & myoneural function are common in hyperthyroidism. A close look over new onset or deteriorating neurological states should raise a suspicion of underlying hyperthyroid state as correction of thyroid hormone levels and achieving euthyroid state can resolve most of the issues.

**References**