VOLUME - 11, ISSUE - 09, SEPTEMBER - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Clinical Research

NEUROLOGICAL ESSENCE OF HYPOTHYROIDISM

Dr. Ansh Chaudhary — Department Of Medicine Bharati Vidyapeeth Hospital & Research Centre, Pune

Dr. (prof.) Bhupendra Chaudhary — FRCP (Glasgow), FRCP (Ireland), FACP (Philadelphia) FAAN (USA), DM (Neurology), MD (Medicine), MBBS Senior Consultant Neurologist Director and Head, Deptt. of Neurosciences, Jaswant Rai Speciality Hospital, Meerut (U.P.)

ABSTRACT Thyroid disease commonly affects nervous system which can be easily recognized when there are frank signs of thyroid dysfunction. The clinical spectrum of hypothyroidism ranges from sub-clinical hypothyroidism to frank myxoedema coma in severe hypothyroidism. It is necessary to consider thyroid diseases in differential diagnosis when neurological manifestation express itself as unexplained encephalopathy, progressive cerebellar degeneration, polyneuropathy, psychosis or progressive cognitive decline and even dementia. Due to protean non-specific diverse manifestations, hypothyroidism may remain undiagnosed for many years hence proactive search and early replacement therapy helps in better therapeutic outcome. Congenital Hypothyroidism is potentially preventable and correctable form of metabolic cerebral disease and mental retardation necessitating neonatal screening for early detection and treatment.

KEYWORDS : Hypothyroidism, Myxoedema, Myopathy, Neuropathy, Cretinism.

INTRODUCTION

Disorders of the Thyroid glands are among the most common endocrine maladies. Hypothyroidism is the most prevalent form of thyroid disease. Thyroid hormones have a critical influence on cellular metabolic activity and also is integrally involved in growth, development and function of the central nervous system (CNS). There appears to be extensive inter-reliance between thyroid hormones, acehylcholine, nerve growth factor and hippocampal function, since the thyroid hormones dramatically affect the maturation of specific neuronal populations. The absence of these hormones during the period of active neurogenesis leads to irreversible mental retardation and is accompanied my multiple morphological alterations in the brain. Low thyroid hormone levels cause slowing of various metabolic processes. Adult onset hypothyroidism is usually caused by primary thyroid gland disorders like autoimmune thyroiditis, surgical or radiological ablation of the thyroid gland, iodine deficiency, thyroid gland tumors or as a result of various medications such as para-amino salicylates, iodides and thiocynates. Hypothyroidism can also be secondary to pituitary dysfunction, causing impaired release of thyroid stimulating hormone (TSH).

The clinical manifestation of hypothyroidism depends on the age of onset eg. cretinism (severe hypothyroidism during intrauterine life or postnatally) leads to irreversible brain damage where in adults it can be reversed with adequate replacement therapy.[1-3]

Being more common in females, hypothyroidism may clinically present with marked psychomotor retardation, weight gain, fatigue, cold intolerance, bradycardia or sub-normal temperature. Other features include headache, weakness, dry skin, brittle hair, constipation, menstural irregularities and lipid abnormalities.

EFFECT OF HYPOTHYROIDISM ON NERVOUS SYSTEM

Thyroid hormone deficiency during the critical period of neural differentiation produces permanent and severe alterations in the morphology and function of the nervous system leading to permanent deficit in intelligence, learning and sensory motor functions. The clinical manifestations depend on the age of onset of hypothyroidism, severity, and rate of development of deficiency, and presence of other hormonal deficiencies.[2,3]

1. NEUROCOGNITIVE IMPAIRMENT

Insufficiency of thyroid hormones in the adulthood causes a wide range of cognitive dysfunctions, including deficits in learning, memory and apathy.

Adult-onset hypothyroidism is associated with neurological changes which may be related to alterations of synaptic plasticity manifesting as diminished attention span, poor recent memory, impaired abstract thinking, slowness in comprehension and difficulty in word fluency. Most patients improve substantially when treated.

2. NEUROPSYCHIATRIC MANIFESTATIONS

The relationship between the thyroid axis and psychiatric symptoms and disease is well established. In myxeodema, psychomotor retardation, lethargy, impaired attention, concentration, and dementia are not unusual. An overlap may exist between depression, dementia & psychosis of hypothyroid state. "Myxeodema madness" has been used to describe the symptoms of irritability, paranoia, hallucinations, and delusions that accompany this state. At the other extreme, severe depression and melancholia are also observed. In about one fourth of rapid cycling severe form of bipolar disorder an underlying hypothyroid status is noted.[4]

3. DEMENTIA

Despite being considered as potentially reversible cause of dementia the overall incidence of hypothyroidism in dementia is actually low. This dementia of thyroid origin is sub-cortical in nature and commonly present as apathy and cognitive slowing and is easily overlooked. Even after adequate replacement the cognitive function does not improve to expected level suggesting the role of some other additional etiological factors. Appropriate treatment with replacement therapy will sometimes improve mental changes, though they are frequently only partially reversible. The longer the condition remains undiagnosed, the worse the outcome.

4. EPILEPTIC SEIZURES

Hypothyroidism perse does not produce seizure except in myxodema coma where other associated metabolic factors like hyponatremia and hypoglycemia plays a major role to produce epileptic seizure.

5. HEADACHE

An association of hypothyroid status (especially in children) and headache is found in one quarter of cases with headache carrying no distinguishing features. It commonly manifest as diffuse, chronic, and recurrent headache.[5]

6. CEREBRO VASCULAR ACCIDENTS (CVA)

An indirect association of CVA and hypothyroid state is attributed to factors like diastolic hypertension, increased low density lipoproteins, increased homocysteine and dyslipidemia which affects endothelial function and coagulation profile hence increasing the risk of stroke.

7. CEREBELLAR DEGENERATION AND ATAXIA

One third of cases of hypothyroidism develop unsteadiness of gait which is reversed in some of the patients with restoring euthyroid which suggests thyroid mediated dysfunction of cerebellum. In others the cerebellar deficit persists or progresses despite thyroid replacement, suggesting different mechanism. The non-familial adult onset cerebellar degeneration presenting as progressive gait ataxia with a euthyroid state indicate generalised autoimmune disorder like Hashimoto's or Autoimmune thyroiditis.[6] As the disease progresses the ocular, motor, brain stem, extra pyramidal and peripheral nerve manifestation gives a picture similar to olivopontocerebellar atrophy with brain image showing mid-line cerebellar atrophy.

8. CRANIAL NERVE ABNORMALITIES

Reversible sensory neural hearing loss with or without tinnitus is seen in three-fourth of long standing hypothyroid individuals due to accumulation of myxoedematous tissue around eighth nerve and accumulation of fluid in inner ear rather than due to neurologic dysfunction. Similarly myxoedematous deposition in tongue and larynx result in thick and slurred speech. The distortion of taste and smell is common and reverses back to normal with attainment of euthyroid status. Night blindness may be caused by deficient synthesis of pigment required for night vision. In long-standing untreated primary hypothyroidism pituitary gland may enlarge leading to compression of optic chiasma and field defects, which reverse back to normal after T4 correction.

9. PERIPHERAL NERVOUS SYSTEMS ABNORMALITIES

Hypothyroidism can have mononeuropathy or polyneuropathy. Generalized neuropathy is less common than mononeuropathy. Associated B12 deficiency may increase the symptoms.

(a) Mononeuropathy – Carpal Tunnel Syndrome (CTS)

Mononeuropathies are frequently seen in hypothyroidism, the most common being carpal tunnel syndrome (CTS) resulting from compression of median nerve as it traverses across the wrist. It occurs in upto 30% of newly diagnosed hypothyroid patients.[7] Typically, patient presents with symptoms like tingling, numbness and pain in sensory distribution of median nerve which worsen at night. Gradually it becomes bilateral. A retrograde pain sensation in forearm and even upto arm, mimics like pain of C_6 cervical radiculopathy.

Carpal tunnel syndrome results from local physical factors like myxedematous tissue accumulation leading to reduced space in the flexor retinaculum. Replacement therapy may produce considerable improvement in 6-8 weeks but on the contrary the individuals with axonal degeneration generally show delayed and incomplete recovery justifying the need of early diagnosis and treatment to avoid long term disability. In cases with severe sensory symptoms and atrophy of thenar musculature, surgical decompression of median nerve may be required.

Other mononeuropathies related to hypothyroid state are tarsal tunnel syndrome and meralgia paresthetica secondary to compression of posterior tibial nerve and lateral cutaneous nerve of thigh respectively.

(b) Polyneuropathy

Hypothyroidism may rarely be associated with a large fibre neuropathy with reduced vibration and proprioception, distal paresthesias and objective distal sensory loss alongwith sensory symptoms like painful dysesthesias in the hands and feet and lancinating pains.[8] Weakness is a common complaint but objective evidence of this is rarely found. Reflexes may be diminished and ankle jerk may show delayed relaxation. The slow relaxation is the result of disturbances in energy transfer within muscle rather than slowing within neural pathways. Nerve conduction velocities are slowed. The cerebrospinal fluid protein is usually increased, believed to be a reflection of increased serum protein in hypothyroidism.

There is evidence suggesting dysfunction of both the Schwann cell (leading to demyelination and slowed nerve conduction) and axon or neuron (leading to axonal degeneration). The mechanism by which lack of thyroid hormone produce these changes is not clear. The cases in which marked axonal degeneration has occurred, the recovery will be delayed and incomplete.[7]

10. MUSCLE DISORDERS

Muscle involvement in a variety of forms is a common complication of adult-onset hypothyroidism. Hypothyroid myopathy spans a clinical spectrum that includes a number of different manifestations. Ranging from asymptomatic CK elevation to overt muscle complaints like myalgia, severe muscle weakness, cramps, polymyositis like syndrome, rhabdomyolysis and acute compartment syndrome can be the manifestations of thyroid affection to muscle tissue.

The frequency of myopathy in hypothyroidism ranges from 30-80%, the major symptoms related are muscle cramps, myalgia and proximal muscle weakness. It itself can present as a sole manifestation, hence in every unexplained subacute myopathy thyroid function test (TFT) must be done.

Examination reveals proximal muscle weakness (lower limbs more than upper limbs) and delayed relaxation of tendon reflexes.

Pseudomyotonia with delayed relaxation of muscle may occur and a prolonged tendon reflex relaxation time is typical. 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.

Muscle weakness, aches and cramps, stiffness and delayed tendon jerk relaxation are usual features of hypothyroid myopathy (30-80%), while muscle hypertrophy, myoedema and wasting are occasionally seen. They evolve gradually over a long period of time.

A rare association is Hoffman's syndrome, which is characterised by muscular pseudohypertrophy, weakness, and slowness of movement, 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.

Adult patients with myopathy associated with acute transient hypothyroidism is also described. Patients presented with severe muscle aches and cramps, stiffness and spasms. Muscle enzymes were markedly elevated but histological changes are generally absent in muscle biopsy, probable because of the short duration of metabolic disturbance. The myopathy subsided promptly when the hypothyroid state is reversed.

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 characterised by a moderate rise in creatine phosphokinase (CPK) because of these associations, patients 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 myglobin 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 fibres.

11. COMA IN HYPOTHYROIDISM

Myxoedema Coma

Myxoedema coma is a complication of long-standing untreated hypothyroidism. The term is largely a misnomer since most patients are not comatose. This condition is characterised by marked impairment of the central nervous system and of cardiovascular function.

It's a severe life-threatening hypothyroidism usually occurring in <1% elderly females. Precipitating factors are exposure to cold, concurrent infection, congestive heart failure, and stroke. Sometimes in undiagnosed hypothyroid patients' drugs such as sedatives, antidepressants, hypnotics, and anesthetics may precipitate coma.

Patient shows signs of hypothyroidism like dry skin, bradycardia, swelling over body. Unique features are hypothermia, hypotension, hypoventilation, bradycardia, and distant heart sound. Hypothermia is present in almost three-fourth of patients. It is associated with high mortality. Patients having core body temperature of <90° Fahrenheit (F) have poor prognosis.

Some patients of primary hypothyroidism can have associated adrenal deficiency (Schmidt's syndrome) leading to Cortisol deficiency. Presence of alopecia and vitiligo should alert the physician about possibility of polyglandular autoimmune deficiency syndrome. In patients with secondary or tertiary hypothyroidism features of secretory pituitary tumor like acromegaly may be seen. Associated Cortisol deficiency must be kept in mind as it needs to be replaced before thyroxine replacement.

Hashimoto Encephalopathy

Hashimoto encephalopathy, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis is a potentially fatal condition associated with a presentation of myoclonus, altered conscious state, 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 titers of antithyroid peroxidase and antithyroglobulin antibodies.

HYPOTHYROIDISM OF FETAL AND NEONATAL LIFE

Thyroid gland of fetus starts functioning at the end of first trimester. Till that period fetus is dependent on mother for supply of thyroid hormone. Children born to untreated hypothyroid mothers are found to have mean IQ score of 4-7 points below normal. Hence, mothers who are hypothyroid should be treated with L-thyroxine to keep free T4 in upper range of normal and TSH below 2.5 in the first trimester and below 3 in second and third trimester.

Congenital Hypothyroidism

Babies with congenital hypothyroidism may have variable clinical picture ranging from subtle neurocognitive defects to mental retardation in severe untreated cases. The mental retardation would be severe if diagnosis is delayed as thyroid hormone is essential for development, differentiation, and myelination of cortical neurons. Congenital hypothyroidism is a uniquely treatable cause of mental retardation. About 30-40% will be missed clinically, hence neonatal screening of hypothyroidism is necessary. Clinical markers arousing suspicion are post maturity, macrosomia, an open posterior fontanelle, delayed passage of meconium, prolonged neonatal jaundice, and umbilical hernia. The only extra thyroid malformation consistently associated with dysgenesis of thyroid is defects in heart septation.

Neurologic Cretinism

The characteristic features of neurological endemic cretinism are severe mental retardation, squint, deaf-mutism, and spasticity.[9] The posture is typical with hip and knees flexed and trunk tilted forward. The gait is broad-based and knock kneed. The arms are held with shoulders abducted and elbows flexed. The mean IQ is <30, which indicates severe mental retardation. There is excessive laxity of weight-bearing joints. Nearly onethird have squint. In severe cases gait is spastic and ataxic and even standing is not possible. Goiter is common but thyroid functions are normal. Neurological cretinism is due to maternal iodine deficiency (thereby thyroxin deficiency) during second and third trimester of pregnancy. The thyroid hormone is essential for dendritic-axonal development and organization of neurons. As cochlea, cerebral cortex, and basal ganglia neurons are formed during later part of second trimester; they suffer irreversible damage from lack of thyroid hormones. Hence, these effects cannot be corrected by giving thyroid hormone at birth or thereafter. Iodine supplementation to the mother before and during the first trimester of pregnancy is the only way for prevention.[10]

With iodine supplementation in the form of injectable iodized oil, thyroid functions improve only in children < 4 years but not in older patients indicating that thyroid gradually loses its capacity to function. Cretinism can be prevented by maternal iodine prophylaxis.

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.

REFERENCES

1. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology. 12thed. Philadelphia: Elsevier Saunders 2011.
2. Jameson JL,, De Groot LJ. Endocrinology Adult and Pediatric. 6th edn. Philadelphia: Elsevier Saunders 2010.
3. Lavin N. Manual of Endocrinology and Metabolism. 4th edn. Philadelphia: Lippincot, Williams and Wilkins 2009.
4. Harris B, Othman S, Davis A, et al. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. BMJ 1992;305:152-56.

5. Fallah R, Mirouliaei M, Bashardoost N, Partovee M. Frequency of subclinical hypothyroidism in 5 to 15 year old children with migraine headache. J Pediatr Endocrinol Metab 2012;25:859-62.
6. Selim M, Drachman DA. Ataxia associated with Hashimoto's disease: progressive non familial adult onset cerebellar degeneration with autoimmune thyroiditis. / Neurol Neurosurg Psychiatry 2001; 71:81 -7.
7. John P. Neuropathy in diseases of the thyroid and pituitary glands. In: Peripheral Neuropathy Peter D, Thomas PK, eds. ElsevierSaunders 2005:2039-49.
8. Lin KP, Kwan SY, Chen SY et al. Generalized neuropathy in Taiwan an etiologic survey. Neuroepidemiology 1993;12:257-61.
9. Srivastav A, Maisnam I, Dutta I, et al. Cretinism revisited. Indian J Endocrinol Metab 2012;16(Suppl 2);S336-7.
10. Cao XY, Jiang XM, Dou ZH, et al. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Eng / Med 1994:331:1739-44.