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Overview on Neurological Manifestations of Thyroid Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Hypothyroidism and hyperthyroidism are both prevalent medical conditions that are frequently accompanied with neurologic and neuromuscular dysfunction. Triiodothyronine (T3) and thyroxine (T4) hormones are produced by the thyroid gland and play a crucial role in tissue formation and metabolism. Both of these hormones have a variety of impacts on the brain and neuromuscular system. Specially in children, because brain development can be effected by any disturbances in Thyroidal hormones level. And thus, conditions like Allan-Herndon-Dudley Syndrome & Benign

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Hereditary Chorea is considered genetic thyroidal diseases both will be discussed in this review. hypothyroidism can have serious consequences for neuropsychiatric function. The pathophysiological processes underlying the neurological symptoms of hypothyroidism and hyperthyroidism are likely to be multifactorial, in this review we will be looking at multiple neurological as well as psychiatric manifestations related to thyroidal hormones disorders.

Methods: We used the phrases "hypothyroidism," "hyperthyroidism," "neurological problems," "neuropathy," "myopathy," "congenital hypothyroidism," and "encephalopathy" in a PubMed search, google scholar and google search engines. Case series, individual case reports, systematic reviews, retrospective analyses, and randomized controlled trials were among the papers examined. Classification of thyroidal dysfunction has been made depending on the thyroidal hormones level. The neurological consequences of congenital hypothyroidism were examined, as well as the clinical aspects of hypothyroidism and hyperthyroidism-related neuromuscular disorders, as well as other autoimmune illnesses. Hashimoto encephalopathy's evidence and pathophysiological issues were also examined.

Conclusion: Thyroid is critical organ due to role of its thyroidal hormones, both hypothyroidism and hyperthyroidism induce some serious neurological and phycological disorders, some of which is genetic, hypothyroidism can impact the development of child and thus regular thyroidal hormones testing is recommended in children who demonstrates any signs of neurological psychiatric or cognitive disease.

Keywords: Neurological; Hypothyroidism; hyperthyroidism; neuromuscular dysfunction psychiatric manifestations hormones disorders.

1. INTRODUCTION

Hypothyroidism and hyperthyroidism are both prevalent medical conditions that are frequently accompanied with neurologic and neuromuscular dysfunction. Some of these related conditions are well-known to doctors, but others are not. All of these neurologic symptoms are significant since they might serve as vital indicators to a thyroid disorder's diagnosis. They are also frequently linked to the patients' presenting concerns. Furthermore, they are frequently reversible with the restoration of the patient to a euthyroid state, much like other indications of thyroid disease [1].

Triiodothyronine (T3) and thyroxine (T4) hormones are produced by the thyroid gland and play a crucial role in tissue formation and metabolism. Both of these hormones have a variety of impacts on the brain and neuromuscular system. Hypothyroidism can generate a variety of neurological indications and symptoms as a result. Muscle weakness, weariness, physical and mental sluggishness, weight gain, constipation, and cold sensitivity are all common symptoms of hypothyroidism. Neuromuscular dysfunctions were shown to be common in thyroid diseases, ranging from 20% to 80% [2,3,4].

Hypothyroidism is often classified into two types. Overt hypothyroidism is characterised as a high serum TSH level combined with a low free T4 (fT4) level, whereas moderate or "subclinical" hypothyroidism is described as a high TSH along with a normal fT4. Although these symptoms are all part of a larger picture of hypothyroidism, they will be explored separately. Subclinical hypothyroidism is especially important since it is frequent, especially among the elderly with cognitive problems [5].

Sensory neural hearing loss and ophthalmopathy are two symptoms of cranial nerve involvement in thyroid disease. Patients with hypothyroidism were found to have hearing loss in about 37% of cases. The brainstem auditory evoked potential (BAEP) is a technique for determining the functional integrity of the thalamocortical projections to the primary and association cortex. Even with asymptomatic hypothyroidism, several investigations have found that central and peripheral conduction latencies are prolonged [2].

The pathophysiological processes underlying the neurological symptoms of hypothyroidism and hyperthyroidism are likely to be multifactorial, (1) autoimmune mechanisms such as Hashimoto's encephalopathy (thyroid peroxidase, thyroglobulin or thyroid microsomes). Thyroid autoantibodies, associations with autoimmune disorders (thyrotropin receptor antibodies) and thyroid dysfunction associated with myastenia gravis; (2) "channelopathy" seen in periodic paralysis of thyroid toxicity. (3) Adrenalinergic hypersensitivity associated with hyperthyroidism;

(4) Ischemia in vascular attacks in patients with hyperthyroidism and atrial fibrillation [6].

thyroid function has become one of the "regular bloods" in neurology practise. Other symptoms of potential significance in terms of thyroid disease may be overlooked in the busy general neurology clinic, or abnormal thyroid tests may be assumed to be incidental, even though conditions such as carpal tunnel syndrome prompt thyroid testing despite no clear evidence for this approach [7].

2. CLASSIFICATION OF THYROIDAL DYSFUNCTION

Some of the disease classified depending on the characteristic of it being hyperthyroidism or hypothyroidism: [9]

1. Diseases characterized by hyperthyroidism:
    A. Basedow-Graves' disease
    B. Plummer's disease
    C. Autonomous nodule (hyperthyroid)
    D. Hashimoto's disease
    E. Thyrotoxicosis
2. Diseases characterized by hypothyroidism:
    A. Primary hypothyroidism which can be adult or neonatal
    B. Secondary: hypothalamic-pituitary hypothyroidism

3. GENETIC DISORDERS OF THYROID METABOLISM

3.1 Allan-Herndon-Dudley Syndrome

The X-linked disorder Allan-Herndon-Dudley syndrome (AHDS) is characterised in males by neurologic observations (hypotonia and feeding difficulties in infancy, developmental delay / intellectual disability varies from minor to profound) and later-onset pyramidal signs, extrapyramidal findings (dystonia, choreoathetosis, paroxysmal movement disorder, hypokinesia, masked facies), and seizures, which are often drug resistant Dysthyroidism (which manifests as poor weight growth, decreased muscle mass, and fluctuating cold sensitivity, sweating, high heart rate, and irritability) and pathognomonic thyroid test results are other possible findings [10].

In 1944, William Allan, Nash Herndon, and Florence Dudley published a six-generation North American pedigree with 24 afflicted boys who had a specific mix of dysmorphic traits, intellectual incapacity, and neurological abnormalities. After the discovery of several family male cases with identical clinical characteristics and additional thyroid hormone abnormalities, Allan-Herndon-Dudley syndrome was recognised as a separate X-linked intellectual impairment disease [6].

Diagnosis/testing: AHDS is diagnosed in a male proband with suggestive signs and a hemizygous SLC16A2 pathogenic variation revealed by molecular genetic testing, and in a female proband with a heterozygous SLC16A2 pathogenic variant detected by molecular genetic testing. [10] Increased blood lactate concentrations, perhaps representing a hyperthyroid metabolic myopathy, and increased serum sex hormone-binding globulin concentrations, likely reflecting a thyroid hormone impact on the liver, are two less specific test abnormalities. In certain people, higher ferritin levels and lower cholesterol levels have been found [6].

Treatment: Treatment with antiepileptic medications by a neurologist with experience. Thyroid hormone replacement treatment in children offers little benefit and may even be harmful by exacerbating dysthyroidism. Assess developmental progress and educational needs in children every six months until they are four years old, then once a year: neurologic examination for new manifestations (e.g., seizures, changes in tone, movement disorders); spine for scoliosis and hips for dislocation; mobility and self-help skills. L-T4 or L-T3 administration alone can aggravate elevated serum T3 levels and the consequent hypermetabolism [10].

3.2 Benign Hereditary Chorea (Brain-Lung-Thyroid Disease)

Benign hereditary chorea (BHC) is an autosomal dominant condition characterised by nonprogressive chorea that develops early in life. BHC is distinguished from Huntington disease by its early start and benign history. [11] NKX2-1-related illnesses include choreoathetosis, congenital hypothyroidism, and infant respiratory distress, among others. The hallmark of NKX2-1-related illnesses, childhood chorea, may or may not be linked to respiratory distress syndrome or congenital hypothyroidism. Chorea usually begins in early infancy or around the age of one year (in

Table 1. Classification form Biochemical perspective. [8]

Condition	TSH level	Thyroidal Hormone
Overt hyperthyroidism	<0.1 mIU/L or undetectable	Elevated T4 or T3
Overt hypothyroidism	>4.5 mIU/L	Low T4
Subclinical hyperthyroidism	<0.1 mIU/L	Normal T4 and T3
	0.1 to 0.4 mIU/L	Normal T4 and T3
Subclinical hypothyroidism	4.5 to 10 mIU/L	Normal T4
	≥10 mIU/L	Normal T4

most cases), or later in childhood or adolescence, and persists until the second decade, after which it remains static or remits. The second most prevalent symptom is pulmonary illness, which includes respiratory distress syndrome in newborns, interstitial lung disease in young children, and pulmonary fibrosis in the elderly. generally speaking, BHC individuals have normal IQ, and dementia is not present, as it is in HD patients. Early start of symptoms, usually before the age of one year, indicates a developmental problem. Choreic motions seem to reduce in certain BHC families as they become older. Harper observed an almost full penetrance in men and a 0.75 penetrance in females (1978). The condition is less common than HD. [11].

Laboratory tests may reveal thyroid function problems in BHC patients, such as low thyroxine and excessive thyroid-stimulating hormone. Due to the ease with which hypothyroidism may be treated with l-thyroxine, individuals with early onset chorea, as well as other movement disorders and neurodevelopmental delays, should have thyroid function tests performed as part of their initial diagnostic work-up. Patients with mutation-positive BHC should also have their thyroid function tested on a regular basis [6].

Treatment: Tetrabenazine and levodopa have been found to be the most effective therapy in a few individual patients with BHC. Some individuals were given these drugs, but only experienced adverse effects and saw no or little improvement in their hyperkinetic movements. As a result, no results or recommendations can be derived from this or past studies. Physical exercise, physiotherapy, interdisciplinary facilitation at school and at work, and yearly lung and thyroid checks and medication, if needed, are probably still the best treatment choices for most people with BHC [12].

3.3 Psychiatric and Cognitive Effects of Hypothyroidism

Many clinic patients complain of low quality of life and weariness, which are frequently linked to mental co-morbidity and urge a TSH check. If the TSH level is modestly high, the patient and physician presume the symptoms are due to mild hypothyroidism. However, these symptoms frequently do not improve with L-T4 therapy, raising the question of whether they were initially caused by the thyroid abnormalities. Subclinical hypothyroid individuals have been found to have higher rates of depression and anxiety symptoms than the general population [5,13-17]. This is not, however, a general finding. In fact, no changes in sadness or anxiety were detected between euthyroid and subclinical hypothyroid patients in the biggest investigations [5,18,19].

Overt hypothyroidism can have an impact on a variety of cognitive functions. General intellect, attention/concentration, memory, perceptual function, language, psychomotor function, and executive function have all been found to be impaired in studies. Memory is the most consistently impacted domain, with verbal memory losses being the most prominent. Although there may not be total reversal, L-T4 therapy is typically beneficial in correcting these decrements [5].

3.4 Neurologic Complications of Thyroid Dysfunction

In England and Wales, the outpatient "incidence" for thyrotoxicosis was 1.1 per 1,000 in 1955 and 1.7 per 1,000 in 1956. Inpatient "incidence" in the United States in 1971 was 0.16 per 1,000 for thyrotoxicosis and 0.13 per 1,000 for myxedema. In Olmsted County, Minnesota, the average yearly incidence of Graves' illness for females was 30.5 per 100,000 from 1935 to 1967. Clinical evidence of mild or severe muscular weakness can be found in more than half of hyperthyroid individuals. The weakness is usually proximal, and electro-myography and muscle biopsy both show the presence of a myopathic process. Severe muscle weakness with an immediate start is rather uncommon, occurring in only around 1% of hyperthyroid individuals. Patients with ophthalmoplegia and psychosis account for 4%

and 2% of all cases, respectively. Despite its widespread awareness, myasthenia gravis is thought to affect less than 1% of people. TPP is almost non-existent in the West; nevertheless, it is seen in 2 to 8% of hyperthyroid patients in the Orient, and is 20 to 60 times more common in hyperthyroid men than in hyperthyroid women. Myxedema's neurologic symptomatology is more comprehensive, and there is little agreement across the numerous series [20].

3.5 Neurological Manifestations of Hyperthyroidism

Clinical signs of thyrotoxicosis in children and adolescents include tremor, which is commonly noticed in the hands, face, and legs. This result can be noticed in the majority of thyrotoxicosis individuals of any age. Because beta blockers generally give considerable alleviation, tremor is assumed to be due to beta-adrenergic system excitation. It may be viewed at rest as well as with intent. In one research evaluating the prevalence of thyrotoxicosis in children, 58.2 percent of individuals with the disease developed tremor. Tremor is more prevalent in pubertal/postpubertal children than in preschoolers. Choriform movements associated with thyrotoxicosis have been recorded in children and adolescents, however they are rare. Involuntary but seemingly well-coordinated spastic movements like flexing and extending fingers, raising and lowering shoulders, or grimacing may improve with beta blockade, and in youth totally resolve once thyroid function is normalised with appropriate antithyroid medication or definitive treatment like radioiodine ablation or surgical thyroidectomy [21-26].

3.6 Hashimoto Encephalopathy

Shaw , who gathered five cases with comparable symptoms such as seizures, disorientation, recurrent episodes of alternating hemiparesis, elevated protein levels in the cerebral fluid, and electrocardiographic abnormalities, coined the name "Hashimoto encephalopathy" (HE) in 1991. These individuals, however, showed hypothyroidism as well as positive thyroid antibodies. A 63-year-old man with seizures, disorientation, recurrent bouts of alternating hemiparesis, elevated protein levels in the cerebral fluid, electrocardiographic abnormalities, and biopsy-confirmed Hashimoto thyroiditis was documented in 1966. [27].

The pathogenesis of Hashimoto encephalopathy, on the other hand, is poorly known, and there is presently no consensus on diagnostic criteria among neurologists and endocrinologists. Although documented cases of the illness improve with thyroid hormone replacement, autopsy investigations in adults reveal lymphocytic infiltration of the central nervous system, results that are comparable to the well-described pathological alterations of thyroiditis found in Hashimoto disease. Furthermore, based on these results, glucocorticoids in anti-inflammatory dosages appear to relieve encephalopathy. [21]

SPECT revealed brain perfusion anomalies in euthyroid patients with Hashimoto's thyroiditis and no signs of neurological illness. The findings of a postmortem or a brain biopsy might be normal or demonstrate perivascular lymphocytic infiltrate. Antineuronal antibodies have recently been discovered in Hashimoto's thyroiditis patients. Patients with Hashimoto's encephalopathy had a high specific reactivity to human alpha-enolase, while it was missing in patients with other neurological diseases and healthy participants. Another subset of Hashimoto's encephalopathy patients had specific antineural antibodies. Ferracci et al. also discovered antithyroid antibodies in the CSF of Hashimoto's encephalopathy patients. [28].

4. DISCUSSION

Hypothyroidism usually affects both the central and peripheral nervous systems. Patients have reflex loss, proximal muscular weakness, numbness, paresthesia, reduced sensations, and slower muscle contraction and relaxation as a result of their peripheral neuropathy. [2] Thyroid diseases affect the general public as well as hospitalised patients. Thyroid illness can manifest with neurological consequences initially, or it can develop alongside other neurological diseases, especially those with an autoimmune origin. As a result, neurologists frequently meet thyroid illness patients. [29] Polyneuropathy has been linked to hypothyroidism in numerous previous studies. Peripheral polyneuropathy is caused by a deficiency in the nerve cell body, axons, or myelin sheath, and it causes reduced nerve conduction velocities and amplitudes. The sural and median nerves are the most usually impacted nerves, as the distal and sensory nerves are affected first. Carpal tunnel syndrome, caused by entrapment of the median nerve, is the most common cause of peripheral nerve injury in hypothyroidism [2].

Graves' disease (GD) is the most prevalent cause of spontaneous hyperthyroidism and is a common

endocrine illness. It has been linked to autoimmune diseases including myasthenia gravis (MG) and type 1 diabetes mellitus. The confluence of ocular myasthenia and GD might be difficult to diagnose since the visual symptoms of both disorders are quite similar. From a therapeutic and prognosis standpoint, the diagnosis is critical. Myasthenia is aggravated by undiagnosed and untreated hyperthyroidism, which can occasionally lead to a deadly myasthenic crisis. [30].

Longer delay and lower amplitude of visual evoked potentials have been linked to hypothyroidism. VEPs are potential changes recorded from the scalp by electrodes in response to visual stimuli. It's a noninvasive, straightforward electrophysiological test for determining the impact of hypothyroidism on the central nervous system (CNS). If electrodiagnostic techniques are to be employed in the early diagnosis of nerve involvement in hypothyroidism, it is necessary to understand the anomalies in VEP [2].

The physiological operation of a wide variety of organ systems, including the brain, is dependent on normal thyroid hormone metabolism. Inherited disorders that affect both normal brain and thyroid development and function (AHDS and BHC, or 'brain-thyroid' disorders) are uncommon but important to recognise because they can mimic a variety of neurological and neuropsychiatric symptoms, including congenital neuromuscular disorders, cerebral palsy, primary movement disorders, certain leukodystrophies, and (X-linked) intellectual disability. Furthermore, while none of these illnesses can currently be treated, supportive measures can help to lessen disease symptoms. More rational therapy techniques are still in the early stages of development, but they may assist patients in the future [6].

Thyroid hormones have a primary target organ in the brain, and adult-onset hypothyroidism can have serious consequences for neuropsychiatric function. Patients with moderate hypothyroidism, on the other hand, may link unrelated symptoms to their thyroid status. This can lead to overtreatment or the use of nonstandard thyroid hormone formulations, both of which have hazards associated with them. In this context, according to a recent research from the United Kingdom, L-T4 is being recommended more frequently and for milder forms of hypothyroidism. This indicates that L-T4 is frequently recommended for minor causes, most of which are neuropsychiatric in origin [5].

5. CONCLUSION

Thyroid is critical organ due to role of its thyroidal hormones, both hypothyroidism and hyperthyroidism induce some serious neurological and phycological disorders, some of which is genetic, hypothyroidism can impact the development of child and thus regular thyroidal hormones testing is recommended in children who demonstrates any signs of neurological psychiatric or cognitive disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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