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Vestibular System Dysfunction in Patients with Hashimoto's Thyroiditis

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Abstract:

Hashimoto's thyroiditis (HT), an autoimmune thyroid disorder, is the most common cause of hypothyroidism. While its impact on metabolic, cardiovascular, and neuropsychiatric systems is well-documented, emerging evidence suggests a possible association between thyroid autoimmunity and vestibular dysfunction. However, the vestibular implications of HT remain underexplored. This article was designed to highlight vestibular system affection in HT.

Keywords: Hashimoto's thyroiditis, vestibular system, dizziness, autoimmunity.

Introduction:

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disorder and a leading cause of hypothyroidism globally. It is characterized by chronic lymphocytic infiltration of the thyroid gland and the presence of circulating anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, ultimately leading to progressive thyroid dysfunction **(1).** While HT is traditionally associated with metabolic, cardiovascular, and neuropsychiatric manifestations, its potential effects on vestibular function are not yet fully understood.

The vestibular system is essential for maintaining balance, gaze stability, and spatial orientation. Dysfunction in this system can lead to symptoms such as vertigo, dizziness, and imbalance complaints frequently encountered in patients with thyroid dysfunction, particularly hypothyroidism **(2).** Thyroid hormones are known to influence both central and peripheral nervous system activities, including inner ear function and the vestibular nuclei in the brainstem **(3).** In addition, autoimmune mechanisms in HT may trigger neuroinflammatory responses or microvascular alterations affecting vestibular structures.

Recent research has pointed to a possible association between HT and vestibular system dysfunction, even in patients with normal thyroid hormone levels. Objective testing methods such as videonystagmography (VNG), vestibular evoked myogenic potentials (VEMP), and posturography have revealed subclinical abnormalities in balance and inner ear function among HT patients **(4).** Therefore, the aim of the present study is to explore the potential relationship between thyroid autoimmunity in HT and vestibular impairment.

Vestibular dysfunction in HT

The vestibular system plays a crucial role in space orientation, at rest and in movement, as well as in professional activity, social adequacy, and working capacity of the person **(5)**. The vestibular organs provide information from peripheral receptors (at the otolith organs and the semicircular canals [SCCs]) to the central nervous system, together with visual and somatosensory information, so that a person becomes conscious of body position **(6)**.

Patients report vertigo when a dysfunction occurs at any part of the vestibular organs **(7)**. Peripheral vertigo originates from the vestibular apparatus in the inner ear or the vestibular nerve **(8)**. In contrast, central vertigo arises from lesions in the brainstem or cerebellum **(9)**.

Thyroid hormones play a crucial role in regulating vestibular functions. They directly influence the neuronal circuits involved in the vestibular compensation process. These hormones stimulate the production of myelin, neurotransmitters, and axon growth in the brain, enhancing the body's overall functionality. This support helps the body better cope with postural and motor alterations caused by vestibular pathologies **(10)**.

The presence of both types of thyroid hormone receptors (TRα and TRβ) and the iodothyronine type II deiodinase enzyme in the vestibular nuclei (VN) indicates that thyroid hormones can exert a local effect within these brain regions **(11)**. This suggests that LT4 can act locally within the VN to influence vestibular function. Additionally, LT4 treatment modulates the glial response by reducing the number of microglia and oligodendrocytes in the brainstem vestibular secondary neurons three days after unilateral vestibular neurectomy, while also promoting cell proliferation **(10)**.

In HT, low thyroid hormone levels, as seen in the hypothyroid phase of HT, can negatively impact vestibular function, leading to symptoms such as dizziness, imbalance and vertigo **(10)**. Additionally, antibodies or immune cells attacking the inner ear may cause autoimmune inner ear disease, leading to a health condition characterized by progressive hearing loss and/or dizziness **(12)**.

A) Peripheral vestibular dysfunctions in HT

The relationship between peripheral vestibular dysfunction and HT has been investigated **(13)**. One of the most common causes of inner ear diseases is related to the autoimmune process, where the cochleo-vestibular system might be affected by autoimmune diseases. Patients with positive anti-TPO Abs had a higher risk of developing balance disorders, which was confirmed by the objective assessment of the vestibular functions **(11, 14)**.

The inner ear conditions associated with HT and responsible for peripheral vestibular dysfunction include: benign paroxysmal positional vertigo (BPPV), Meniere's disease (MD), and vestibular neuronitis **(15)**.

I. Benign paroxysmal positional vertigo (BPPV)

BPPV disease is characterized by a short-term spinning sensation upon changes in body position. The attacks are of short duration (30 seconds to several minutes) and not accompanied by any auditory sensation such as hearing loss or tinnitus **(16)**. This type of vertigo is due to abnormal stimulation of the cupula by free-floating otoconia (canalolithiasis) or otoconia that have adhered to the cupula (cupulolithiasis) within any of the three SCCs **(17)**.

In canalolithiasis BPPV, otoconia (crystals of calcium carbonate and calcium phosphate embedded in the gelatinous layer covering the cilia of the utricular sensory cells) are detached from the utricular macula. The otoconia become free to move in the endolymph to the semi-circular ducts of the membranous labyrinth. This phenomenon is most commonly observed in the posterior semicircular duct, in nearly 95% of cases **(13)**.

On the other hand, the cupulolithiasis theory suggests that otoconia become dislodged and stick to the cupula in the SCCs, most commonly the posterior canal. However, when otoconia attach to the cupula, they make it heavier, creating a density imbalance. This difference causes the cupula to move in response to gravity, even when the head isn't moving, leading to abnormal stimulation of the hair cells, contributing to balance disturbances **(18)**.

Otoconia can become detached due to several factors, including head trauma, viral infections, middle ear surgery or the use of ototoxic drugs. Autoimmunity is also suspected to be involved in this phenomenon **(19)**. Research has shown elevated levels of anti-TPO Abs and anti-TG Abs in patients with positional vertigo, suggesting that these antibodies may trigger immune reactions in the inner ear structures due to the inflammatory nature of HT. These antibodies can access the endolymphatic sac and the inner ear structures

through the blood vessels, leading to impaired endolymphatic flow. This impairment stimulates vestibular sensory cells and can result in the attacks typically associated with positional vertigo **(13)**.

Another reason why these two diseases (BPPV and HT) are interconnected is related to a vitamin D metabolism disorder. Vitamin D is a specific immunomodulator and has anti-inflammatory activity. It is also involved in many immune-related processes **(13)**. Deficiency of vitamin D is a risk factor for HT **(20)**. A decreased level of vitamin D can be observed in HT due to an elevated TSH level caused by hypothyroidism **(21)**. It was confirmed that vitamin D supplementation in therapeutic doses reduced the level of anti-TG Abs in patients with HT **(22)**.

Persistently low levels of vitamin D increase the risk of many diseases, including osteoporosis. This condition results in reduced bone mass and a decrease in trabecular bone and may raise the risk of positional vertigo **(23, 24)**. Additionally, it may stem from structural changes in otoconia that could elevate the chance of otoconia detachment from the utricular macula. Research has confirmed that low levels of vitamin D and disorders of bone mineralization (potentially due to HT) increase not only the risk of BPPV, but also the likelihood of recurrence of the condition **(13)**.

II. Vestibular neuritis

The condition is manifested by sudden, severe vertigo (spinning sensation), resulting from sudden unilateral weakness or loss of labyrinth function **(25)**. The vertigo attack usually lasts from 12 to 24 hours **(26)**. It is not associated with any auditory sensations such as hearing loss or tinnitus **(25)**. Although an acute attack usually lasts for several days, postural instability (unsteadiness) may accompany the patient for many weeks **(27)**.

The exact etiology of the disease is uncertain **(28)**. It may be caused by a viral infection (adenoviruses, Epstein-Barr virus or human parainfluenza viruses) **(26)** or may result from the adverse effects of ototoxic drugs (e.g., gentamicin or furosemide) **(29)**. In addition, an autoimmune basis of the disease is suspected **(30)**.

The relationship between vestibular neuritis and HT has not been confirmed yet **(31)**. However, the autoimmune reaction is suggested as a hypothesis for the vestibular neuritis **(32)**. According to this hypothesis, an immune reaction occurs when autoantibodies attack the myelin sheath of the vestibulocochlear nerve, resulting in damage to the myelin sheath and impaired nerve function **(33)**.

III. Meniere's disease (MD)

The disease is characterized by episodes of vertigo (spinning sensation) with unilateral low-frequency hearing loss and simultaneous tinnitus **(13)**. The attack is preceded by the sensation of unilateral ear fullness **(34)**. The typical triad of symptoms lasts from 30 minutes to several hours. Patients between 30 and 50 years of age are mostly affected by the disease **(35)**.

The underlying cause of the disease is a sudden increase in fluid pressure in the inner ear and, consequently, the occurrence of labyrinthine hydrops **(36)**. Attacks of vertigo may occur with varying frequency, and are usually exacerbated by excessive stress, dietary error or post-viral infections **(37)**. The risk of MD is greater in patients with a history of head trauma, including fractures of the skull base, labyrinthitis or syphilis **(38)**. Autoimmune disorders, including HT, remain a potential cause for some cases of MD **(39)**.

Possible mechanisms that support the autoimmune etiology in MD include the increased prevalence of systemic autoimmune diseases in patients with MD than the general population, the elevated levels of immunocomplexes, the association between MD and HLA types and good response to glucocorticoid treatment **(40)**. Research has shown that the blood-inner ear barrier is permeable to antigenic proteins and immunocompetent cells **(13)**.

Hypothyroidism may contribute to increased fluid pressure within the inner ear, potentially leading to the development of endolymphatic hydrops **(41)**. Moreover, the endolymphatic sac turned out to be the organ of the inner ear responsible for immune response **(36)**. Inflammatory diseases (such as HT) could cause a cross-immune cascade reaction against inner ear cells and impair cochlear and vestibular functions **(10)**.

Following this reasoning and considering the inflammatory basis of HT, it is possible to find a relationship between both diseases. Some studies confirmed statistically higher serum levels of anti-TPO Abs and anti-TG

Abs in patients with MD compared to groups of patients with vestibular disorders other than endolymphatic hydrops. Anti-TPO Abs and anti-TG Abs could reach the structures of the inner ear through the blood vessels. Due to the reaction with the cells of the endolymphatic sac, they could increase endolymphatic pressure in the inner ear. Resolution and reduction of vertigo attacks in patients with MD after a three-month treatment with LT4 is postulated to be evidence for a relationship between both diseases **(13)**.

B) Central vestibular dysfunction in HT

Thyroid hormones play a critical role in maintaining the normal function of central vestibular pathways, which involve the brainstem and cerebellum. These central vestibular structures can be significantly affected by both thyroid hormone levels and thyroid-related autoantibodies, particularly in autoimmune thyroid diseases, such as HT (**42**).

In hypothyroidism, decreased hormone levels can slow neural conduction, alter synaptic transmission and impair reflex integration within central vestibular pathways, leading to symptoms such as dizziness, delayed postural responses and poor coordination. Additionally, the cerebellum, a key structure in balance control, may become metabolically impaired, resulting in gait disturbances and unsteadiness **(10)**. Autoantibodies such as anti-TPO and anti-TG may contribute to central vestibular dysfunction through immune-mediated inflammation or potential cross-reactivity with neural tissue **(43)**.

The possible central vestibular lesions associated with HT include vestibular migraine (VM), multiple sclerosis (MS) and transient ischemic attacks (TIAs) (**44)**.

I. Vestibular migraine (VM)

VM is a neurological disorder characterized by episodes of dizziness or vertigo, often accompanied by other migraine symptoms such as headache, nausea, and sensitivity to light or sound **(45)**. It has been noted that patients with VM are positive for TG Abs and TPO Abs at a high rate. Serum anti-thyroid antibodies (including TG Abs and TPO Abs) were found to be positive in 12.9% of VM patients **(46)**. These are specific autoantibodies associated with autoimmune thyroid disease, such as HT. The presence of these antibodies suggests an autoimmune etiology, which may contribute to the patient's vestibular symptoms **(47)**.

II. Multiple Sclerosis (MS)

MS is an autoimmune disease that affects the central nervous system, leading to demyelination in the brainstem and cerebellum and potential vestibular dysfunction. Studies have shown that individuals with autoimmune thyroid diseases, such as HT, may have an increased risk of developing MS. Treg cell dysfunction, shared genetic susceptibility and environmental triggers may explain overlapping neuro-immune pathways in both diseases **(44)**.

III. Transient ischemic attacks (TIAs)

TIAs are precursors to ischemic stroke, characterized by symptoms that typically resolve within one hour. Frequent episodes of TIAs are a common cause of cerebral small vessel disease **(48)**. Clinical hypothyroidism can affect the central nervous system's regulation of blood pressure, blood glucose, blood lipids and other related physical functions. These factors may exacerbate the risk of hypertension, hyperglycemia and hyperlipidemia. Hypothyroidism also increases the occurrence of ischemic stroke and aggravates oxidative stress damage and calcium overload after cerebral ischemia, triggering inflammatory cascades and adversely affecting the prognosis of ischemic stroke **(49)**.

Moreover, some studies have shown that elevated levels of thyroid autoantibodies, such as anti-TPO and anti-TG, are associated with an increased risk of ischemic events. These autoantibodies can contribute to vascular damage, leading to a higher incidence of TIAs **(46)**.

Effect of HT and dizziness on quality of life (QoL)

A) HT and QoL

Thyroid hormones regulate normal growth, development and various homeostatic functions, particularly the production of energy and heat **(50)**. In individuals diagnosed with hypothyroidism, the lack of these hormones or their ineffective action in target organs can result in a wide range of clinical symptoms that can significantly reduce overall health and QoL **(51)**.

These symptoms include fatigue, weakness, increased body weight, distraction, memory problems, hypersensitivity to cold, hair loss, thickening of the voice, constipation, dry skin, menstrual irregularities, and depression **(52)**. The clinical manifestations of hypothyroidism vary depending on the etiology, duration and severity of the disease. It can affect all organs and systems of the body **(53)**.

HT can significantly impact various aspects of a person's life. Beyond the physical symptoms, the condition often affects emotional well-being, cognitive function and overall QoL. Patients with HT frequently experience fatigue and muscle weakness **(54)**. Cognitive impairments, such as memory problems and difficulty concentrating, are also common. These symptoms can hinder daily activities and reduce overall life satisfaction. HT is also associated with higher rates of depression and anxiety, even in patients with normal thyroid hormone levels. Studies have shown that individuals with HT report lower scores in physical functioning, general health, and mental health domains, indicating a diminished QoL **(55)**.

B) Dizziness and QoL

Dizziness is a common self-reported symptom, with a lifetime prevalence ranging from 15% to 36%. Chronic dizziness and balance disorders are well known to not only severely diminish individuals' QoL but also increase the risk of falls **(56)**. Individuals with dysfunction of the vestibular system report symptoms such as disorientation, lightheadedness, disequilibrium, and visual blurring **(57)**. It may be associated with psychiatric comorbidities such as anxiety, depression, and restricted social behavior **(58)**

People experiencing vertigo, dizziness and imbalance encounter numerous challenges in their daily lives. Due to these symptoms, patients often fear falling and tend to avoid activities that require head movement, resulting in a decrease in their physical activity levels. Individuals with dizziness prefer lighter exercises such as light gardening, short walks, and doing light household chores **(59)**.

Dizziness or vertigo and other vestibulopathies can also influence patients' QoL and are associated with psychiatric comorbidities. Psychiatric comorbidities are present in about 30-50% of patients suffering from dizziness or vertigo. One of the most common comorbidities identified is depression, with a prevalence of 4-62%, according to the literature. Impaired QoL often results from vertigo or dizziness. Psychiatric comorbidities may further worsen the QoL of patients experiencing vertigo **(60)**. On the other hand, impairment in QoL, decreased daily activities, and inability to work may lead to psychological distress **(61)**.

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