Medicine

Thyroid Dysfunctions and Schizophrenia

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Abstract	**Review Article**

This abstract provides an overview of a comprehensive study investigating the intricate relationship between thyroid dysfunctions and schizophrenia. It explores the influence of neurotransmitters on this connection and delves into the underlying pathophysiological mechanisms. This research offers insights into the complex interplay between these two conditions, with potential implications for both clinical practice and future research directions.

Keywords: Thyroid dysfunctions, schizophrenia, hashiomoto disease, basdow disease, neurotransmitter, pathophysiological mechanisms.

INTRODUCTION

In autoimmune thyroid diseases, autoimmunity has led to dysfunction of the thyroid gland, and changes in the morphology of the gland can be revealed through ultrasound. Autoimmune thyroid disease can be associated with hypothyroidism (as in Hashimoto's thyroiditis [HT]) or hyperthyroidism (as in Graves' disease) [1].

A recent meta-analysis reported that autoimmune thyroid diseases and hypothyroidism are associated with depression and anxiety disorders in the general population [2]. Other psychiatric disorders are also suspected to be linked to autoimmune thyroid diseases. In a study conducted by William W. Eaton, Ph.D., et al. in 2006 using the Danish national registers to create a dataset including all individuals in Denmark diagnosed with schizophrenia from 1981 to 1998 and their parents, as well as a matched sample of comparison subjects and their parents, schizophrenia was nonsignificantly linked to patients with thyroiditis and was significantly associated with thyroiditis in the subjects' parents [3].

In another study by Vikas Menon *et al*., in 2019, the most common psychiatric diagnosis preceding Hashimoto's thyroiditis was acute psychosis (26.1%), followed by depressive disorders (23.9%), dementia (10.9%), and schizophrenia (2.2%), which were less common presentations. Antithyroid peroxidase antibodies were elevated in all patients, but not antithyroglobulin antibodies [4].

By combining the results of these studies, it appears that autoimmune thyroid dysfunctions, especially Hashimoto's thyroiditis, could be linked to a broad spectrum of psychiatric disorders, including schizophrenia. This complex relationship deserves to be explored in more detail to better understand the underlying mechanisms and enhance clinical management strategies.

The aim of our work is to discuss the association between thyroid dysfunctions and schizophrenia through a literature review.

Schizophrenia, Thyroid, and Neurotransmitters

Thyroid hormones play a crucial role in the development of the adult brain. Fluctuations in thyroid hormone levels at any stage of development can lead to the manifestation of psychiatric disorders and can respond to treatment (Santos *et al*., 2012) [5]. Undoubtedly, there exists a relationship between the hypothalamus-pituitary-thyroid axis and the major signaling systems implicated in the pathophysiology of schizophrenia. Roca et al. [4] suggested that most hyperthyroid patients exhibited psychosis (a positive symptom of schizophrenia), while hypothyroid patients showed depression and reduced motivation. Thyroid hormones modulate crucial neurotransmitter systems in the brain, including the dopaminergic, serotonergic, glutamatergic, and GABAergic systems. Additionally, they also contribute to brain myelination and inflammatory processes [5].

Regarding the dopaminergic system, it is now known that antipsychotic medications that block dopamine D2 receptors mitigate hallucinations and delusions [6]. Thyroid hormones regulate dopamine receptor levels [7] and the activity of tyrosine hydroxylase, a rate-limiting step in the catecholaminergic pathway [8]. Another hypothesis in the context of schizophrenia involves serotonin, suggesting that increased serotonergic signaling, particularly through the serotonin 2A receptor, is implicated in the pathophysiology of schizophrenia [9]. Similarly, deficient central 5HT function could underlie certain negative symptoms of schizophrenia [10]. Cleare *et al*., [11] proposed that 5HT activity is diminished in hypothyroid patients.

Regarding the glutamatergic pathway, Mohn *et al*., [12] suggested that a reduction in the NMDA receptor (glutamate receptor) leads to symptoms similar to those of schizophrenia. Later, Mendes [13] studied the role of T3 in the central nervous system (CNS), particularly in glutamate uptake. In 2002, researchers treated male rats with glutamate receptor agonists and found that they developed an increase in blood TSH with an antagonistic decrease in serum TSH and TH levels [13]. An upregulation of postsynaptic GABA-A receptors has been described in schizophrenia by Akbarian *et al*., [14]. Thyroid hormones have an effect on enzymes involved in the synthesis and metabolism of GABA and glutamate, on the release and reuptake of GABA, and on GABA receptors [15]. Hypothyroidism is associated with delayed myelination in several brain regions [16].

Researchers have also observed a downregulation of myelin-related genes in the post-mortem brains of schizophrenic individuals, including cyclic nucleotide phosphodiesterase, myelin-associated glycoprotein, transfer gene, and viral oncogene homolog 3 of erythroblastosis virus B-2 [17], all of which are regulated by thyroid hormones. Katsel *et al*., [18] noted changes in cell cycle-related genes through a microarray analysis of schizophrenic patients, showing that two genes, cyclin D1 and cyclin-dependent kinase inhibitor 1C (P57), which are part of the cell cycle genes regulated early after exposure to thyroid hormones, are crucial for oligodendrocyte differentiation [19, 20].

In neurological or psychiatric brain disorders, abnormalities in myelin are often accompanied by inflammation. In schizophrenia, for example, the high expression of cytokines could play a pathological role. Elevated expression of IL-6 and TNF-α is observed in the cerebrospinal fluid (CSF), along with altered expression of creatine kinase and creatine kinase receptors [21, 22]. Their induction in immune and glial cells such as astrocytes and microglia plays an important role in neural cell homeostasis, particularly in oligodendrocyte functions and myelination [23].

Normally, thyroid hormones play a crucial role in regulating deiodinase activity, but other regulatory mechanisms can also influence thyroid hormone metabolism under certain pathophysiological conditions. These mechanisms can intersect with those known to be relevant in the development of schizophrenia [24]. There is an interrelation between schizophrenia, thyroid hormones, and inflammation, as seen in local inflammation sites with increased type 3 deiodinase activity and local degradation of T3 [25].

The role of thyroid hormones in the pathophysiology of schizophrenia becomes clearer when considering the possible function of thyroid hormone as a neurotransmitter. This hypothesis of the neurotransmitter role of T3 was put forward in the 1970s [26]. T3 plays a significant role in the brain as it promotes astrocyte differentiation, mediation of cerebellar astrocytes, neuronal proliferation, and organization of extracellular matrix molecules by astrocytes [13, 27]. A similar neurotransmitter function of 3-iodothyronamine, a product formed during the decarboxylation of T4 or reverse T3 (rT3), has been reported [28].

Hashimoto's encephalopathy (HE) is a rare neuropsychiatric syndrome, more common in women. The term Hashimoto's encephalopathy was first used by Brain et al, and since then, it has been considered an important differential diagnosis of encephalopathy of unknown origin. There is typically serological evidence of the presence of anti-thyroid antibodies in the patient's blood [29]. The onset of the disease is usually acute and is accompanied by episodes of cerebral ischemia, seizures, and psychosis, or it can present with depression, cognitive decline, myoclonus, tremors, and fluctuations in consciousness [29]; [30]. The relationship between HE and Hashimoto's thyroiditis (HT) is not yet clear as there is no evidence that thyroid autoantibodies react with brain tissue and affect neuronal functions. Similarly, the level of circulating antibodies does not correlate with the severity of symptoms or response to treatment. The good response to steroids and the association with other autoimmune diseases indicate that it could be an inflammatory or immunological dysfunction [30]; [29]. Some authors suggest that despite HE, it could be termed steroid-responsive encephalopathy associated with autoimmune thyroiditis [31-33]. They reviewed all published HE cases since its initial description. They reported that HE has a variable clinical spectrum, making the diagnosis and early treatment of the disease challenging. The age of disease onset is also highly variable, but they found it most commonly presents between the fifth and sixth decades of life. The most common manifestations in all these cases were cognitive deficits and generalized seizures [33]. The pathogenesis of the disease involves autoimmune cerebral vasculitis, the toxic effects of TSH on the CNS, and antibody-mediated neuronal reactions. They further indicated that 86% of patients

had positive serum anti-thyroid peroxidase (TPO) antibodies, while 48% had anti-thyroglobulin (Tg) antibodies. [34] reported that anti-TPO antibodies might be sufficient to trigger the disease by interacting with CNS tissues, although the pathogenic role of other antibodies cannot be ruled out.

Numerous reports have elucidated the psychiatric consequences of hypothyroidism. Pfeiffer included hypothyroidism among the 29 medical causes of schizophrenia. According to this report, around 10% of individuals with schizophrenia exhibited hypothyroidism. The mental state includes perceptual changes such as auditory and visual hallucinations, thought disturbances like obsession, paranoia, and mood swings. All these symptoms fall within the category of schizophrenia [35]. It has been reported that thyroid hormones improve recovery rates in most schizophrenic patients. In many studies, it has been found that if thyroid hormone treatment was maintained, many schizophrenic patients were relieved of signs and symptoms. This holds true not only for periodic catatonics but also for other schizophrenics without regular periodicity [35]. In his review, Hoffer reported the case of a 16-year-old girl who was a classic adolescent schizophrenic, with perceptual changes, thought disturbances, inappropriate affect, and activity. She was treated with different modes of therapy such as ECT (electroconvulsive therapy), penicillamine, and nicotinic acid, but she did not recover. Finally, when she was administered high doses of thyroid and nicotinic acid, while closely monitoring her pulse, she almost completely recovered and began to lead a normal social life. Keeping these dramatic results in mind, twelve other schizophrenics started receiving high doses of thyroid hormones and nicotinic acid. In this group of 12, only 3 did not improve and one of them discontinued the treatment. Out of the other 9, 6 improved considerably and 3 recovered as the dose of thyroid hormones was increased [35]. Therefore, he concluded that all schizophrenic patients should be screened for hypothyroidism. In case of symptoms, high doses of thyroid hormones should be added to the treatment regimen. Low TSH can sometimes be misleading: patients can have low T3 despite low TSH. This can be due to decreased peripheral conversion of T4 to T3 [35]. Hypothyroidism is a disorder with varying presentations. That is why Heinrich and Grahm [36] reviewed literature describing the relationship between hypothyroidism and various psychiatric presentations. In one of their articles, they describe the case of a 75-year-old woman who suddenly began experiencing episodes of visual and auditory hallucinations without any medical history. The examination by the general practitioner revealed she had a normal thyroid but dry skin and brittle nails. On neurological examination, she exhibited a delay in the relaxation phase of the deep tendon reflex. The patient was admitted to the hospital and laboratory tests revealed elevated TSH and low T3 and T4 levels. When she began low-dose thyroid replacement therapy (TRT) along with risperidone, she slowly started recovering, and after 2 to 3 weeks of treatment, she no longer had hallucinations. Subsequently, she herself stopped risperidone, but no recurrence of symptoms was observed with a maintenance dose of TRT.

Schizophrenia, Thyroid, and Pathophysiology
The genetic etiology of schizophrenia is undeniable. The heritability of schizophrenia is generally Mendelian, and the risk of developing the disease is higher in monozygotic twins. Therefore, the onset of the disease may depend on the presence of other risk factors in genetically susceptible individuals [37]. Previous studies have explained some factors associated with psychosis. These include obstetric and perinatal complications, viral infections before and after birth, and head injuries [37, 38].

The onset and development of schizophrenia can be determined by the presence of prior brain trauma, such as head injury or substance abuse, or prior brain injury [37]. Several studies have been conducted on individuals at high risk of developing schizophrenia. These studies have shown that certain childhood issues such as delayed neuromotor development and attention deficit [39] are associated with the later development of schizophrenia. In a survey by [37] of 100 consecutive patients admitted for the first time with a diagnosis of schizophrenia according to DSM-III-R, they did not find an increased risk of schizophrenia following childhood head injuries. Hall [40] reported that psychosis occurs in 1 to 15% of patients with hypothyroidism. In patients with acute hypothyroidism, anxiety disorders appear in 30 to 40% of them. Patients with acute myxedema typically develop progressive anxiety accompanied by restlessness. They may also experience disorientation (which worsens over time), delusional hallucinations, and alternating lethargy with restlessness. In extreme cases, patients may complain of auditory and visual hallucinations, increased sexual activity, irritability, delusion, lack of concentration, and decreased memory, all of which are signs of acute thyroid disease. Increased fatigue, psychomotor slowing, and chronic anxiety are more likely to be due to a progressive change in thyroid hormone levels in these patients. Elderly patients and patients whose thyroid hormone levels change rapidly exhibit more severe mental symptoms [40].

At the beginning of treatment, the initial symptom, which is anxiety, disappears within a few days or months, but the main effect of hypothyroidism can only be eliminated after 2 to 12 months of successful treatment. Sleep disturbances and growth hormone levels during sleep take weeks to months to normalize and are related to the complete recovery of anxiety in these patients [40]. Trepacz *et al.*, [41] reported a higher rate of anxiety in patients who did not receive any treatment for Graves' disease. In the brain,

there is a system of behavioral inhibition in which neuroanatomical circuits modulate the response to stress stimuli. If these systems are overstimulated, a state of persistent anxiety appears in humans. One of these systems is the septo-hippocampal system, whose discharge increases excitement. Noradrenergic and serotonergic stimulation of this system sends many impulses to the limbic system and the prefrontal cortex. Medical conditions that alter the hypothalamo-pituitary axis or that modify neurotransmitter levels in the brain can lead to anxiety.

Wells *et al.*, [42] examined 2,554 patients suffering from one of eight chronic illnesses and estimated that significant anxiety is present in 10 to 20% of patients. They also noted that over 11% of patients with chronic illnesses have experienced a recent episode of anxiety disorder. They found that 10 to 40% of anxious patients have an organic cause for their psychiatric symptoms [42]. He also suggested that among the various psychiatric disorders, anxiety disorders are those with a strong association with chronic illnesses. It has been reported that patients with common anxiety problems have higher plasma catecholamine levels than controls. Their catecholamine receptors are downregulated, reducing the sensitivity of the adrenergic nervous system receptors [43]. In another report, it was found that patients with generalized anxiety disorder have a reduced growth hormone response to clonidine stimulation (a partial alpha-2 agonist), suggesting a decrease in the sensitivity of alpha-2 receptors, which again might be due to increased catecholamine levels in these patients [44]. Wu *et al.*, [45] reported that in patients with generalized anxiety disorders, there is an increased relative metabolic rate in the occipital, temporal, and frontal lobes, as well as in the cerebellum. They also noted a decrease in absolute metabolic activity in the basal ganglia, cingulate gyrus, temporal lobe, amygdala, and hippocampus of patients. Popkin [46] stated that endocrine disorders manifesting as anxiety are due to dysfunction of the adrenal glands, Cushing's syndrome, pancreatic tumors, pheochromocytomas, and thyroid disorders (hyperthyroidism, hypothyroidism, and thyroiditis) [46].

A similar study was conducted on 711 patients from the Harvard Brawn Anxiety Disorders Research Program (HARP), where it was found that patients with anxiety disorders, along with panic disorders and depression, had higher rates of reported illnesses such as peptic ulcers, angina, and thyroid disorders. In the current study, about two percent of men were included, and among them, around nine percent of women had a thyroid disorder [47]. Subsequently, Sherbourne et al. [48] studied a group of 2,494 patients with hypertension, heart disease, and diabetes, and assessed them for depression, panic disorders, generalized anxiety disorders, and phobias. They found that medically depressed patients had a higher incidence of

panic disorders than medically non-depressed patients. Similarly, phobia and anxiety disorders are 14.6% more prevalent in depressed patients than in non-depressed patients. They found that 14 to 66% of patients in the care unit had received medical care and suffered from at least one anxiety disorder [48]. According to Brawman-Mintzer and Lydiard [49], patients at risk of developing generalized anxiety disorders may have issues with the regulation of the hypothalamo-pituitary axis. These patients are more sensitive than controls in terms of the number and intensity of symptoms. Brawman-Mintzer and Lydiard suggested that several anomalies in cellular structures and regulatory mechanisms could play a significant role in the production of anxiety. In response to stressful stimuli, an inappropriate reaction occurs in the locus ceruleus-norepinephrine sympathetic nervous system, the hypothalamo-pituitary axis, and the cholecystokinin (CCK) system. Anomalies are also observed in the GABAergic and 5-HT systems [49]. Meredith *et al.*, [50] studied 2,189 patients in general medicine and concluded that patients with primary medical conditions associated with anxiety disorders are more likely to receive treatment for their anxiety than patients with primary anxiety disorders. They also found that if anxiety disorder is associated with another condition, such as a medical illness or depression, the patient is more likely to receive counseling or treatment with psychotropic medications.

When it is established that anxiety is most often associated with a medical condition, we should be able to differentiate primary anxiety disorder from anxiety associated with a medical condition; some questions in this regard would be helpful. Is there a link between exacerbation and remission of a medical condition and worsening or improvement of anxiety symptoms? Do anxiety symptoms disappear when the primary illness is treated? Are atypical characteristics of primary anxiety disorders present? For example, the usual age and type of onset, the initial presentation, or the absence of family history. In-depth studies have concluded that neurological and endocrine disorders are responsible for half of the symptoms of medically-originated anxiety. The differences between patients with anxiety disorders and those with medically-originated anxiety disorders are as follows: a) patients with medically-originated anxiety disorders experience fluctuations in the severity and duration of their episodes; b) there is a clear link between the progression of their anxiety condition and their underlying illness; c) medically-originated anxiety disorders manifest before the age of 14 and after the age of 35, and patients generally lack family history or prior episodes. On the other hand, patients with primary anxiety disorders have a history of other psychiatric symptoms such as phobia and conversion symptoms, as well as a history of recent severe psychological stress.

Psychiatric presentations are typically the first sign of hypothyroidism and are considered initial

symptoms in 2 to 12% of reported cases, along with organic mental deficits [51]. The initial symptoms then progress to mental slowing associated with decreased recent memory, speech disturbances, reduced learning, etc. In women aged 40 to 60 years, spontaneous hypothyroidism occurs, presenting with symptoms of weakness, fatigue, cold intolerance, decreased libido, lethargy, dry skin, headaches, and menorrhagia. Signs include thin hair, brittle nails, decreased pulse, pallor, and decreased deep tendon reflexes. Late symptoms include changes in taste, smell, vision, and hearing, weight gain and sweating, pallor, hoarseness of voice, peripheral edema, muscle cramps, angina, and dyspnea. Menstrual irregularities may also be observed. The emergence of severe anxiety disorders in hypothyroid patients is due to the rapid changes in thyroid hormone levels in these patients. Regardless of the cause of hypothyroidism, whether it's due to thyroidectomy, autoimmune disease, or thyroid gland ablation by radioactive iodine due to thyroid cancer, neuropsychiatric symptoms are the same in all cases.

CONCLUSION

There is indeed a relationship between thyroid dysfunction and schizophrenia, as evidenced by the significant family history of thyroid disorders in schizophrenic patients and the interaction between the hypothalamic-pituitary-thyroid axis and the dopamine, serotonin, glutamate, and GABA systems, as well as myelin and the pro-inflammatory response that are strongly implicated in schizophrenic patients. The thyroid profile of all schizophrenic patients should be examined, as thyroid dysfunction is associated with depression (a negative symptom of schizophrenia) and psychosis (a positive symptom of schizophrenia).

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