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Could the Thyroid Gland Dominate the Brain in Obsessive-Compulsive Disorder?

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Abstract
Thyroid hormones have an essential role in brain maturation and neuronal functioning. The comorbidity of thyroid disorders and several mental disturbances is frequently reported. We aimed to evaluate the literature on the potential relationship between thyroid disorders and obsessive-compulsive disorder (OCD) and obsessive-compulsive symptoms (OCS). We searched the literature using PUBMED, ProQuest, Google Scholar, and PsycInfo electronic databases for original studies (cross-sectional, case series, case report) on the association between thyroid dysfunctions and OCD and OCS between 1977 and 2021. Eleven studies met the inclusion criteria. Despite some methodological limitations, the OCD rates in patients with autoimmune thyroid disorders were found to be higher than the normal population in two studies. The findings on thyroid dysfunction in OCD patients were inconclusive. In the light of available data, it could be proposed that there might be a possible association between thyroid disorders and OCD. Some shared immunological mechanisms could play a role in the pathophysiology of both thyroid diseases and OCD. New research is needed to confirm this association and elucidate the underlying common mechanisms between these disorders.

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by anxiety-provoking thoughts (obsessions) leading to repeated, time-consuming behaviors (compulsions) that may or may not provide temporary relief [1]. The prevalence is approximately 2–3% in the general population. OCD is a debilitating disorder that can significantly affect the patient's life in different aspects [2].

It is believed that OCD has a complex etiopathogenesis. Although an important number of attempts have been performed on exploring the pathogenesis of OCD, the exact pathophysiology of the disorder is not clear yet. Different neurobiological, immunological, genetic, behavioral, cognitive, and environmental factors have been proposed to explain the underlying causes of OCD [3, 4]. The stud-

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ies in the literature have uncovered a great amount of knowledge about its genetics and neurobiology.

Neurobiology of OCD

There are many neurobiological studies conducted to determine the etiology of OCD. Among them, neurotransmitter, genetics, brain metabolism, and immunological studies are predominant [5, 6].

Neurotransmitter Abnormalities in OCD

Serotonin. Several studies revealed that the hypothesis of serotonergic (5-HT) dysfunction is located in the center of the pathophysiology of OCD [3, 7]. This hypothesis is supported by the results of observations regarding the treatment response of OCD to serotonergic reuptake inhibitors. While selective serotonin reuptake inhibitors (SSRIs) are found to be efficacious in treating OCD, selective noradrenergic drugs are not effective. The more selective serotonergic psychotropic agents are found to be efficacious in alleviating obsessive and compulsive symptoms (OCS) [8].

Additionally, different pharmacological, genetic, and imaging studies also indicate that the serotonin receptor serves a role in OCD. Genetic research suggested that OCD is associated with polymorphisms in some serotonin-system-related genes [9]. Recently, SPECT studies on molecular imaging also showed decreased availability of serotonergic transporters in the thalamus and midbrain [10]. Thus, it is proposed that the anti-OCD effect is mainly mediated by serotonergic mechanisms [3, 4].

Dopamine. In addition to serotonin, current findings suggest a role for dopaminergic dysfunction in the etiology of OCD. Several studies established altered dopamine levels in different parts of the brain [11]. While depletion of dopamine was observed in the orbitofrontal cortex (OFC) [12], an enhancement of dopaminergic activity was also shown in the nucleus accumbens [13].

Dopaminergic D1, D2, and D3 receptors were claimed to be crucial in the manifestations of OCS. The behavior of rats treated chronically with the dopamine agonist, quinpirole, meets the ethological criteria of compulsive checking in OCD [14]. Trials of combined SSRI and typical or atypical antipsychotic treatment suggest that dopamine receptor antagonism may further reduce OC symptom severity in SSRI-refractory OCD patients, particularly those with comorbid tic disorders [3]. It may be claimed that some forms of OCD could be associated with dysregulated dopaminergic function.

Glutamate. According to some studies, OCD is considered to be a hyperglutamatergic state involving prefrontal brain regions. Modulation of glutamate may play a role in the amelioration of OCS by SSRIs and clomipramine [15]. Moreover, several psychotropic agents that modulate glutamate (e.g., topiramate, riluzole, D-cycloserine) have been demonstrated to be useful in treatment-resistant OCD [3].

Molecular biology and neuroimaging studies also support glutamatergic dysfunction in OCD. The glutamate transporter SLC1A1 gene that codes for the excitatory amino acid carrier (EAAC1), has been shown to cause altered glutamatergic neurotransmission and is implicated in the pathogenesis of OCD [16]. Additionally, in a magnetic resonance spectroscopy study, glutamatergic dysfunction in the caudate nucleus has been stated in OCD patients. The decrease in glutamate concentration and OCD symptoms were also observed after SSRI treatment [17].

Neurochemical Brain Imaging Studies in OCD

Functional magnetic resonance imaging and positron emission tomography studies have shown increased metabolic activity in the brain circuit involving the OFC, the head of the caudate nucleus, and the thalamus. Furthermore, provocative stimuli that induce OCD symptoms increase regional cerebral blood flow in the OFC and the head of the caudate nucleus. A successful treatment (pharmacological or behavioral) is associated with a normalization of their metabolic activity [18, 19].

Genetic Studies in OCD

There are several studies in the literature investigating the genetic basis of OCD. Family studies reported higher rates of OCS in the relatives of OCD patients [20]. It is stated that certain genotypes increase the risk and severity of OCD in individuals. There is evidence that sequence variation in SLC1A1 is associated with susceptibility to OCD, particularly in males [16]. Changes in some glutamate NMDA receptor subunit genes, which are GRIN2A, GRIN2B, and GRIA2, were reported to have an important role in the clinical presentation of OCD [21]. However, some other studies failed to find any single nucleotide polymorphisms that achieved a genome-wide threshold of significance [4]. These findings point out the need for examining the genetics of OCD in a new way, perhaps by focusing on epigenetic expression rather than genotypes.

Immunological Studies in OCD

Besides these neurochemical and genetic abnormalities, there is accumulating evidence that implicates hu-

moral and cellular immunity dysfunctions and inflammation in the pathogenesis of OCD. It was first proposed that an autoimmune response to group A beta-hemolytic streptococcal infection can induce neuroinflammation in the basal ganglia, which resulted in PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) [22]. It is suggested that such patients may respond to specific immunologic interventions, such as plasmapheresis or intravenous immunoglobulin therapy [23]. Furthermore, a high rate of *Toxoplasma gondii* seropositivity was established in patients with OCD [24].

The association of OCD with immunity is not limited to infectious diseases; it is also comorbidly present with different autoimmune disorders. Some studies proposed that almost 40% of OCD patients have an autoimmune disease. OCD is commonly seen with different neurological disorders (Guillain-Barre syndrome, multiple sclerosis), gastrointestinal disorders (celiac disease, Crohn's disease, ulcerative colitis), rheumatological disorders (Sjögren's syndrome, idiopathic thrombocytopenic purpura), and endocrinological disorders (type 1 diabetes mellitus, Hashimoto's thyroiditis) [25, 26].

The Association of OCD with Physical Diseases

Increasing evidence has shown that mental disorders frequently co-occur with physical diseases. It is revealed that obsessive and compulsive symptoms are correlated with higher prevalence rates of specific physical diseases. Those symptoms are found to be associated with migraine headaches, respiratory diseases, allergies, malignities, and thyroid diseases [27, 28].

Thyroid gland diseases are one of the main groups of disorders that are found to be associated with OCD. It is stated that OCS is more common in patients with thyroid diseases than in the general population [28, 29]. There is an association shown between papillary thyroid cancer and subthreshold OCS [27]. A common immune and inflammatory pathway, genetics, and some certain effects of thyroid hormone (TH) in the central nervous system (CNS) may explain the high degree of association between OCD and thyroid diseases.

Actions of Thyroid Hormones in the Brain

The THs play a crucial role in the development and physiological functioning of the CNS. Their receptors are widely distributed in the CNS. THs have been known to be important for normal neonatal brain development [30]. It is demonstrated that fetal THs play an essential role in neuronal processing and integration, glial cell proliferation, myelination, and the synthesis of key enzymes required for neurotransmitter synthesis [31]. Thyroid deficiency during the perinatal period results in irreversible morphological and cytoarchitecture abnormalities, disorganization, and maldevelopment in the brain [30, 32]. Thyroid dysfunction is claimed to cause alterations of neurotransmitters and disturbance in the GABA, adenosine, and pro/antioxidant systems in the CNS and to give rise to neuronal distortion and mental retardation [31].

Besides neonatal brain development, THs also have a crucial role in mature brain functions. THs receptors are highly expressed in the mature brain. Nuclear receptors for T_3, the TH with the highest biological activity, are widely distributed in the brain [33]. These receptors are present in higher densities in the amygdala and hippocampus, which are the phylogenetically younger parts of the brain, while they are poorly expressed in the brain stem and cerebellum [34]. Not only is the THs receptor expression significant, but also the THs concentrations have been detected relatively high (nanomolar) in the cortical tissue [35]. In contrast to peripheral tissue, where the less active form of TH T_4 concentrations usually far exceed those of T_3, in the brain T_4 and T_3 concentrations are in an equimolar range [36].

THs levels are believed to have an impact on several neuronal circuits in the CNS, although the interrelationships between THs and neurotransmitters are complex. Some studies have suggested that changes in thyroid status likely affect 5-HT neurotransmission and thus the hypothalamic-pituitary-thyroid axis [34, 37]. In rat models, it was shown that serotonin metabolism is positively correlated to T_3 levels and that serum serotonin level rises in hyperthyroidism [38]. Some studies suggested that 5-HT responsiveness is reduced in patients with hypothyroidism, and it is reversible with thyroid replacement therapy [39, 40]. Other experimental studies also showed that TH administration might desensitize autoinhibitory 5-HT_{1A} receptors and increase cortical 5-HT levels [41].

THs also appear to play an important role in regulating central adrenergic function, and it has been suggested that thyroid dysfunction may be linked with abnormalities in central noradrenergic (NA) neurotransmission [35]. Some studies stated that the T_3 hormone serves as a co-transmitter with NA and influences the axonal transport of noradrenergic stimulus [42]. Hyperthyroidism is claimed to increase dopamine levels in various parts of the brain, including the hypothalamus, midbrain, striatum, and hippocampus [43]. Similarly, it is revealed that

antithyroid medications decrease the serum concentrations of dopamine and NA [44]. THs also appear to regulate the beta-adrenergic receptor response to catecholamines by increasing their ability to receive stimulation [45].

Besides the influence of THs on neurotransmitters, THs are proposed to have a role in neuroprotection in the adult brain by decreasing glutamate excitotoxicity, thus oxidative stress. T_3 hormone was shown to activate genomic and nongenomic antioxidant defense mechanisms in neurons and glial cells [46, 47].

Thyroid Functions and Mental Disorders

Thyroid gland disorders are frequently associated with severe mental disturbances. Maternal hypothyroidism during pregnancy could result in psychiatric disorders such as mental-motor retardation, autism spectrum disorders, and attention deficit hyperactivity disorder (ADHD) in children [48].

The relationship between psychiatric disorders and thyroid diseases is not limited to early neuropsychiatric problems. THs are believed to have an important effect on modulating mood and behavior in adults. Therefore, thyroid dysfunctions are associated with depression, mania, acute psychosis, and cognitive decline [49, 50]. Although there are some controversial studies, the prevalence of major affective disorders is found to be higher in patients with thyroid diseases [32, 51]. Major depressive disorder, panic disorder, and generalized anxiety disorder have been shown as the most common psychiatric disorders accompanying hypothyroidism [52]. An increased risk of affective disorders is stated following the diagnosis of hyperthyroidism [53]. Even the relationship of depression with subclinical hyperthyroidism has been demonstrated [54]. Both hypothyroidism and hyperthyroidism are demonstrated to be related to cognitive impairment and dementia [50].

In addition to these common psychiatric and thyroid disorder comorbidities, it is claimed that thyroid dysfunctions often accompany OCS and OCD. The incidence of OCD is shown to be high in patients with thyroid diseases [55]. OCD was more common in patients with Hashimoto thyroiditis (HT) [29]. Moreover, subclinical OCS was observed in some cases with papillary thyroid cancer [27]. This review aimed to better explain the relationship between OCD and thyroid dysfunctions and the possible evidence of common pathophysiological etiology of thyroid diseases and OCD.

Methods

Search and Selection Strategies

We conducted a literature search using PUBMED, ProQuest, Google Scholar, and PsycInfo electronic databases, covering the period of 1977–2021. We also manually searched the works of relevant authors and the reference lists of identified articles. The search terms included a combination of (1) OCD, obsessive-compulsive symptoms (OCS) and (2) thyroid dysfunctions, thyroid disorders, and thyroid autoimmunity. Two independent authors for the eligibility at the title and abstract level first screened each study. For relevant studies, the full text of the articles was analyzed. Disagreements between the authors were resolved through consensus.

Observational studies (cross-sectional, case series, case report) presented information on the association between thyroid dysfunctions and OCD/OCS and used standardized diagnostic criteria or validated rating scales, and standardized hormonal and immunologic investigation methods were included. There was no restriction applied during the study selection regarding language, age, gender, date, or publication status. The studies that did not provide data for OCD separately were excluded.

Data Collection

Two authors performed data extraction independently. For each study identified, the information about study characteristics (authors, publication year, sample size, study design), sample characteristics (e.g., gender, age, psychiatric diagnosis, and thyroid pathology), assessment methods of OCD (e.g., structured interview, using rating scales), assessment methods of thyroid functions (e.g., TH levels, thyroid autoantibody positivity, postoperative specimen) and study outcome were extracted.

Results

A total of 708 abstracts were identified. Following the secondary screening process, 11 studies met inclusion criteria and were included in the present review, with publication dates ranging between 1991 and 2020 (Table 1).

OCS and OCD in Thyroid Diseases

Four of 11 studies investigated OCS and OCD in patients with different thyroid diseases. The OCD prevalence was found to be higher in patients with thyroid diseases than in the normal population [29], although one study did not reveal a statistically significant difference in OCD prevalence in euthyroid, subclinical hypothyroid, and hyperthyroid cases [56]. One study without a control group reported a higher rate of OCD in a group of patients with heterogeneous thyroid diseases such as Grave's disease, multinodular goiter, adenoma, and thyroid cancer than expected in the general population [55]. There is also a case report with 3 patients that shows comorbidity of OCS and papillary thyroid cancer [27].

Table 1. Studies examining the relationship between thyroid diseases and OCS/OCD

Author	Sample size	Study design	Sample characteristics	OCD symptom/diagnosis assessment	Assessment of thyroid functions	Main findings
Obsessive-compulsive disorder in thyroid diseases						
Placidi et al. [55]	47 Patients with Graves' disease (GD), 30 patients with multinodular goiter (MNG), 10 patients with adenoma, 5 patients with thyroid cancer, 1 patients with iatrogenic hyperthyroidism	Cross-sectional	Age, gender (female [f], male [m]) GD:47 (38 f, 9 m) MNG:30 (24 f, 6 m) Adenoma:10 (6 f, 4 m) Thyroid cancer:5 (3 f, 2 m) Iatrogenic hyperthyroidism:1 (f)	Clinical interview by a psychiatrist based on DSM-III-R Upjohn Version (SCID-UP-R)	The two endocrinologists reviewed all thyroid function test abnormalities and classified the patients as GD, MNG, thyroid cancer and iatrogenic cases.	OCD was observed in 7.4% of all cases. OCD was more common in autoimmune thyroid diseases (GD) compared to non-autoimmune thyroid diseases ($p = 0.0119$).
Giynas Ayhan et al. [29]	51 Cases with Hashimoto thyroiditis (HT), 45 cases with endemic/nonendemic goiter, 68 healthy controls	Case-control Cross sectional	Age HT: 35.10±7.75 Goiter: 35.47±6.74 Control: 33.82±6.07 Gender (% female) HT: 96.1 Goiter: 91.1 Control: 94.1	Clinical interview by a psychiatrist based on SCID-I	TSH, fT_3, fT_4, TPO-Abs, TG-Abs and thyroid USG	OCD was observed in 7.3% of all cases. OCD was more common in HT group (15.7%) compared to controls (1.5%) ($p < 0.05$). No significant difference was found between endemic/nonendemic goiter and control groups in terms of OCD comorbidity ($p = 0.299$).
Bensenor et al. [56]	12,437 Euthyroid cases, 193 cases with subclinical hyperthyroidism, 784 cases with subclinical hypothyroidism	Case-control Cross sectional	Age Euthyroid: 51.5±9 Sub. Hyperthyroid: 53.3±9.1 Sub. Hypothyroid: 54.1±9.1 Gender (% female) Euthyroid: 51.7 Sub. Hyperthyroid: 63.7 Sub. Hypothyroid: 54	Clinical interview by a psychiatrist based on clinical interview schedule – revised (CIS-R) and grouped according to the ICD-10	TSH, fT_4	There was no statistically significant differences in OCD prevalence between 3 groups ($p = 0.90$)
Caykoylu et al. [27]	3 Cases	Case report	3 Papillary thyroid cancer patients (age 22, 26 and 50 year-old) (2 female, 1 male)	Clinical interview by a psychiatrist based on DSM-IV criteria	Thyroidectomy operation	Subclinical obsessive and compulsive symptoms were observed all 3 patients diagnosed with papillary thyroid cancer.
Thyroid dysfunctions in obsessive-compulsive disorder						
Hantouche et al. [59]	17 Patients with OCD	Cross sectional	Article in French	Clinical interview by a psychiatrist based on DSM-III criteria	TSH	Basal values of THs and TSH were normal, except one case with GD. 12.5% showed a blunted delta TSH (less than 5 mUI/L).

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Table 1 (continued)

Author	Sample size	Study design	Sample characteristics	OCD symptom/diagnosis assessment	Assessment of thyroid functions	Main findings
Aizenberg et al. [60]	10 Patients with OCD, 10 controls	Case-control Cross sectional	Age OCD: 28.9±7.6 Control: 28.4±6.9 Gender (% female) OCD: 80 Control: 80	Clinical interview by a psychiatrist based on DSM-III-R	TSH	There was a significant difference in blunted responses of TSH to TRH among OCD patients in comparison to control group. Seventy percent of OCD patients demonstrated a blunted TSH response (TSH <5 IU/mL), compared to 20% of control group ($p < 0.035$).
Black et al. [61]	13 Patients with OCD	Cross sectional	Age: 40±15 Gender: 46.1% female Adult or childhood onset-OCD	Clinical interview by a psychiatrist based on DSM-III criteria	Tg-Abs, thyroid microsomal antibodies	One patient with elevated thyroid microsomal antibodies with not known thyroid disease (titer 1:400) One patient had thyroid microsomal antibodies with the history of resected papillary thyroid cancer (titer 1:1,600) There was not Tg-Abs antibody seropositivity in any case.
McCracken and Hanna [58]	16 Pediatric patients with OCD, 13 controls	Case-control Cross sectional	Age: OCD: 13.6 Control:13.1 8 weeks clomipramine treatment were administered to OCD group.	Clinical interview by a psychiatrist based on DSM-III criteria and CY-BOCS scores were compared between pre and after-treatment.	TSH, total T_3, and total T_4 levels	Serum TSH, T3, and T4 levels were greater in OCD groups ($p < 0.002$, $p < 0.0006$, $p < 0.0004$ respectively) Clomipramine treatment was associated with significant decreases in TSH and T_3 levels ($p < 0.0.05$, $p < 0.0.02$). Pre-treatment TSH and T_4 levels were correlated with reductions in CY-BOCS after 8 weeks clomipramine treatment ($p < 0.0.05$, $p < 0.0.01$).
Maina et al. [62]	74 Patients with OCD, 44 patients with major depression (MD)	Case-control Cross sectional	Age OCD: 35.3±12.7 MD: 56.0±16.8 Gender (% female) OCD: 41.9 MD: 31.8	Clinical interview by a psychiatrist based on DSM-IV criteria (Y-BOCS > 16)	TPO-Abs, Tg-Abs, TR-Abs	No significant difference in antibody parameters was found between the two groups ($p > 0.05$ for all).

Table 1 (continued)

Author	Sample size	Study design	Sample characteristics	OCD symptom/diagnosis assessment	Assessment of thyroid functions	Main findings
Witthauer et al. [28]	3,571 Cases without OCD, 371 case with OCS, 239 cases with subthreshold OCD and OCD	Cross-sectional	Evaluating the comorbidity between DSM-IV OCD and subthreshold forms (OCS) and physical diseases in the general population (age 18–65), based on the data of German Health Interview and Examination Survey and its Mental Health Supplement (GHS-MHS)	Clinical interview by a psychiatrist based on M-CIDI/DIA-X interview	A self-report questionnaire and a standardized computer-assisted medical interview by a general practice physician, and laboratory results are evaluated to make a diagnosis of thyroid diseases	Significantly higher prevalence was found for thyroid diseases in subjects with OCS (OR 1.4; 95% CI: 1.01–2.0) compared to the no OCS group.
Mermi and Atmaca [57]	40 Patients with OCD, 40 controls	Case-control Cross sectional	Age OCD: 36.92±12.19 Control: 35.50±8.18 Gender (% female) OCD: 70 Control: 60	Clinical interview by a psychiatrist based on DSM-IV criteria	TSH, fT_3 and fT_4 levels	TSH levels were not statistically different between groups ($p = 0.11$) Reduced fT_3 and fT_4 levels in OCD patients ($p < 0.02$)

CY-BOCS, Children's Yale Brown Obsessive Compulsive Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; fT_3, free T_3; fT_4, free T_4; M-CIDI/DIA-X, Munich-Composite International Diagnostic Interview; OCD, obsessive-compulsive disorder; OCS, obsessive-compulsive symptoms; SCID-I, Structured Clinical Interview for the DSM IV Axis I Disorders; TSH, thyroid stimulating hormone; USG, Ultrasonography; Y-BOCS, Yale Brown Obsessive Compulsive Scale.

Based on limited studies, there may be an association between thyroid diseases and OCD. However, the association needs to be interpreted in the context of some limitations, including modest sample size, the limited number of studies, and their design.

Thyroid Dysfunctions in OCD

Seven studies examine the thyroid dysfunctions in OCD. In a large sample study investigating the relationship between OCS/OCD and physical diseases, a significantly higher prevalence was found for thyroid diseases in subjects with OCS compared to the group without OCS [28]. Thyroid function test results varied in different studies. One study showed a reduced level of fT_3, fT_4 [57], while another study with pediatric OCD cases demonstrated higher T_3 and T_4 [58]. Although two studies demonstrated normal TSH levels in OCD patients [57, 59], blunted TSH response was a significant result of two studies [59, 60].

In a study with pediatric OCD cases, higher TSH and T_3 levels decreased after clomipramine treatment. Moreover, it has been suggested that the decrease in TSH and T_3 levels with treatment correlates with the decrease in OCD symptoms [58]. Given the limited number of studies and conflicting results in the literature, the thyroid dysfunctions in OCD are inconclusive.

Autoimmune Thyroid Diseases and OCD

In two studies investigating the OCD rates in thyroid diseases,0 OCD seems more common in autoimmune thyroid diseases (e.g., HT, GD) than in other thyroid disorders [29, 55]. There are also cases reporting OCD comorbidity in papillary thyroid cancer, which is thought to have strong immunological factors in its etiology [28].

There were two studies assessing the thyroid autoantibodies in OCD. In one study with a limited number of participants, only 2 patients (15.4%) had positive thyroid microsomal antibodies, although only one of them had known thyroid diseases. There was no TG-Abs seropositivity found in any of the OCD cases [61].

Another study that compares thyroid autoantibodies in patients with OCD and major depression did not show any significant difference in levels of TPO-Abs, Tg-Abs, or TR-Abs between the two groups [62]. According to the available data, there is potential evidence for a linkage between autoimmune thyroid disorders and OCD. However, the evidence comes from a small number of studies and relatively small clinical samples.

Discussion

This is the first review that investigated the potential link between thyroid dysfunctions and OCD. The results of the study demonstrated a possible association between thyroid autoimmune disorders and OCS. The conclusions of our review are restricted by both scarcity of the studies and their methodological design. There was a broad spectrum of heterogeneity in the study designs regarding age groups, subgroups of thyroid dysfunctions, selection of OCD patients, and control groups. Additionally, the evaluation tool of thyroid dysfunctions was very limited. While some of the studies only assessed TSH or postoperative clinical diagnosis [27, 28, 55, 59, 60], only a few studies used a larger tool including TSH, fT_3, fT_4 and thyroid autoantibodies [29, 57, 58, 61].

Thyroid Functions and OCD

It is indicated in the literature that the influence of THs on monoamines in the adult brain varies with the neurotransmitter and the brain area. Although THs generally enhance the metabolism and activity of 5-HT and catecholamines [35, 63], they have a protective role in glutamatergic excitotoxicity [47].

In the light of this knowledge, it could be expected that thyroid hypoactivity might have a relationship with OCS and OCD. However, studies showed conflicting results regarding the thyroid functions in OCD. While most of the studies revealed blunted TSH response [57, 59, 60] and decreased T_3, T_4 levels, there was also a study that showed hyperthyroidism in OCD cases [58].

Along with similar lines, OCS/OCD incidence in thyroid dysfunctions also varies. Some studies indicate a relationship between OCS/OCD and HT and papillary thyroid cancer [27, 29]; another study did not find a significant difference in OCD incidence between groups with hypothyroidism and hyperthyroidism [56]. Moreover, one study indicated higher OCD rates in patients with GD [55]. In a study that investigated the OCD rates in patients with hypothyroidism, it was found that the incidence of OCD was higher only in cases with autoimmune hypothyroidism compared to the control group. There was no significant difference in OCD rates between patients with non-autoimmune hypothyroidism and the control group [29]. These results might suggest that not only thyroid function status but also thyroid autoimmunity could play a role in OCD.

Autoimmunity, Thyroid Gland, and OCD

Accumulating evidence points out the hypothesis that the dysfunction of the immune system might be a potential factor contributing to the etiopathogenesis of mental disorders. One of the most common organs affected by autoimmunity is the thyroid. About 5% of the general population suffers from autoimmune thyroid diseases [64]. Therefore, the link between autoimmune thyroid disorders and mental illnesses has been studied for a long time [65–67].

Thyroid autoantibodies are circulating antibodies against several thyroid antigens, which are present in most patients with autoimmune thyroid disorders, such as autoimmune hypothyroidism, thyroid malignancies (papillary and follicular thyroid cancers), and Graves' disease (GD) [68, 69]. They can be detected in up to 10% of the general population [70]. The thyroid autoantibodies are widely used in clinical diagnostic laboratories, and these include antibodies to thyroid peroxidase (TPO-Abs), antibodies to thyroglobulin (Tg-Abs), and antibodies directed against the TSH receptor (TR-Abs) [71].

TPO-Abs constitutes one of the major autoantigens involved in autoimmune thyroid diseases [72]. The seropositivity of TPO-Abs is high in HT and GD. The positivity for TPO-Abs and Tg-Abs are found higher in differentiated thyroid cancers consisting of papillary and follicular thyroid cancer [73]. TR-Abs has been found in GD and atrophic thyroiditis. Additionally, the seropositivity of TG-Abs reaches up to 50% in autoimmune thyroiditis and GD [74].

Although several studies show the interrelation between thyroid autoimmunity and affective disorders, few studies investigate the link between thyroid autoimmunity and OCS. One study revealed that TPO-Abs positivity in HT is associated with poorer SCL 90-R results, especially in depression, somatization, obsession, and compulsion subscales [68]. Another study reported childhood-onset OCD cases with a maternal history of thyroid autoimmunity [75].

There is also some strong evidence of the increased prevalence of OCD in autoimmune thyroid disorders. Although there is no clear evidence of an increased level of circulating thyroid autoantibodies in OCD, OCD comorbidity was higher in HT and GD [27, 29, 55].

The relationship between thyroid dysfunctions and OCD might be important in clinical practice. Both changes in the hypothalamic-pituitary-thyroid axis and immunological reactions might play a role in the etiopathogenesis of OCD (shown in Fig. 1). Because of this reason, thyroid dysfunctions and thyroid autoantibodies could

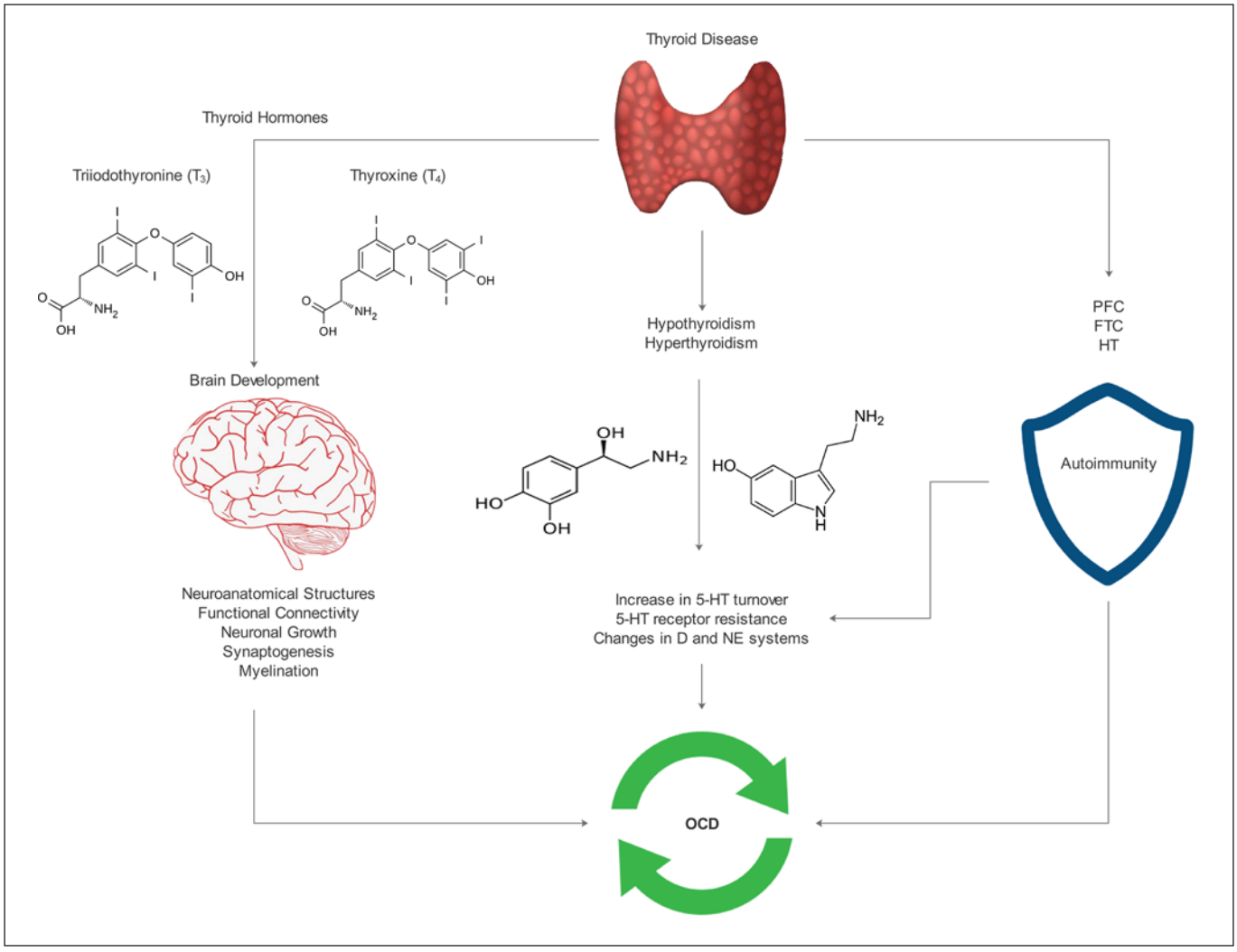

Fig. 1. The possibly related pathophysiological pathways between thyroid diseases and OCD. OCD, obsessive-compulsive disorder; D, dopamine; FTC, follicular thyroid cancer; HT, Hashimoto's thyroiditis; NE, norepinephrine; PTC, papillary thyroid cancer.

be notable risk factors for a group of OCD patients. Thus, a detailed evaluation of thyroid functions could be essential in patients with OCD.

This review has some limitations. First, because the included studies had a cross-sectional design, a causal relationship between thyroid dysfunction and OCD could not be accurately established. Secondly, the main methodological limitations of the studies including the small size of the samples, lack of control groups, and poor usage of psychometric tests restrict our conclusion. Finally, most of the studies evaluated the thyroid functions only with TSH or a limited number of thyroid autoantibodies, which makes it more difficult to provide a broader assessment of the relationship between thyroid functions and OCD symptoms.

Conclusion

There could be an association between thyroid disorders and OCD. However, most of the reviewed studies had some methodological limitations that prevent reaching certain conclusions in the light of the available data. Further studies are needed to elucidate the underlying immunological mechanisms of the possible relationship between thyroid dysfunctions and OCD.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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Author Contributions

Ali Caykoylu: conception and design of the study, literature search, interpretation of data, manuscript preparation, and final approval of the study. Esra Kabadayi Sahin: literature search, interpretation of data, manuscript preparation, and final approval of the study. Mustafa Ugurlu: conception and design of the study, interpretation of data, manuscript preparation, and final approval of the study.

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, DC: American Psychiatric Press Inc.; 2013. p. 237–8.
2 Doshi PK. Surgical treatment of obsessive compulsive disorders: current status. Indian J Psychiatry. 2009 Jul–Sep;51(3):216–21.
3 Ganesan V. Neurobiology of obsessive-compulsive disorder. In: Janardhan Reddy Y, Srinath S, editors. Obsessive compulsive disorder: current understanding and future directions. 1st ed. NIMHANS; 2007. p. 41–85.
4 Lack C, Husky A, Weed D. The etiology of obsessive-compulsive disorder. In: Lack C, editor. Obsessive-compulsive disorder: etiology, phenomenology, and treatment. Ginger Prince Publications; 2015. p. 25–42.
5 Bandelow B, Baldwin D, Abelli M, Altamura C, Dell'Osso B, Domschke K, et al. Biological markers for anxiety disorders, OCD and PTSD – a consensus statement. Part I: neuroimaging and genetics. World J Biol Psychiatry. 2016 Apr 3;17(5):321–65.
6 Karch S, Pogarell O. [Neurobiology of obsessive-compulsive disorder]. Nervenarzt. 2011 Mar 1;82(3):299–307.
7 El Mansari M, Blier P. Mechanisms of action of current and potential pharmacotherapies of obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2006 May 1;30(3):362–73.
8 Rauch S, Whalen P, Dougherty D, Jenike M. Neurobiologic models of obsessive- compulsive disorder. In: Jenike M, Baer L, Minichiello W, editors. Obsessive-compulsive disorders practical management. 3rd ed. St Louis, MO: Mosby; 1998. p. 222–53.
9 Taylor S. Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol Psychiatry. 2013 Jul;18(7):799–805.
10 Hesse S, Müller U, Lincke T, Barthel H, Villmann T, Angermeyer M, et al. Serotonin and dopamine transporter imaging in patients with obsessive-compulsive disorder. Psychiatry Res. 2005 Oct 30;140(1):63–72.
11 Perani D, Garibotto V, Gorini A, Moresco R, Henin M, Panzacchi A, et al. In vivo PET study of 5HT(2A) serotonin and D(2) dopamine dysfunction in drug-naive obsessive-compulsive disorder. Neuroimage. 2008 Aug 1;42(1):306–14.
12 Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci. 2014 Jun;15(6):410–24.
13 Nabizadeh M. The role of serotonin and dopamine neurotransmitters in obsessive-compulsive disorder. Shefaye Khatam. 2019 Apr 10;7(2):99–106.
14 Zadicario P, Ronen S, Eilam D. Modulation of quinpirole-induced compulsive-like behavior in rats by environmental changes: implications for OCD rituals and for exploration and navigation. BMC Neurosci. 2007 Dec;8:23.
15 Carlsson ML. On the role of cortical glutamate in obsessive-compulsive disorder and attention-deficit hyperactivity disorder, two phenomenologically antithetical conditions. Acta Psychiatr Scand. 2000 Dec;102(6):401–13.
16 Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. Arch Gen Psychiatry. 2006 Jul 1;63(7):769–76.
17 Moore GJ, MacMaster FP, Stewart C, Rosenberg DR. Case study: caudate glutamatergic changes with paroxetine therapy for pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 1998 Jun 1;37(6):663–7.
18 Nakao T, Okada K, Kanba S. Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. Psychiatry Clin Neurosci. 2014 Aug;68(8):587–605.
19 Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. Dev Psychopathol. 2008;20(4):1251–83.
20 Nestadt G, Grados M, Samuels JF. Genetics of obsessive-compulsive disorder. Psychiatr Clin North Am. 2010 Mar 1;33(1):141–58.
21 Bozorgmehr A, Ghadirivasfi M, Ananloo E. Obsessive-compulsive disorder, which genes? Which functions? Which pathways? An integrated holistic view regarding OCD and its complex genetic etiology. J Neurogenet. 2017 Jul 3;31(3):153–60.
22 Swedo S, Seidlitz J, Kovacevic M, Latimer M, Hommer R, Lougee L, et al. Clinical presentation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in research and community settings. J Child Adolesc Psychopharmacol. 2015 Feb 1;25(1):26–30.
23 Stein DJ. Advances in the neurobiology of obsessive-compulsive disorder. Implications for conceptualizing putative obsessive-compulsive and spectrum disorders. Psychiatr Clin North Am. 2000 Sep 1;23(3):545–62.
24 Sutterland A, Fond G, Kuin A, Koeter M, Lutter R, van Gool T, et al. Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. Acta Psychiatr Scand. 2015 Sep 1;132(3):161–79.
25 Mataix-Cols D, Frans E, Pérez-Vigil A, Kuja-Halkola R, Gromark C, Isomura K, et al. A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders. Mol Psychiatry. 2018 Jul;23(7):1652–8.
26 Pérez-Vigil A, Fernández de la Cruz L, Brander G, Isomura K, Gromark C, Mataix-Cols D. The link between autoimmune diseases and obsessive-compulsive and tic disorders: a systematic review. Neurosci Biobehav Rev. 2016;71:542–62.
27 Caykoylu A, Ugurlu G, Yenilmez D, Caykoylu H, Ugurlu M. Subthreshold obsessive-compulsive symptoms in 3 patients with papillary thyroid carcinoma. Prim Care Companion CNS Disord. 2020 Jan 23;22(1):19l02463.
28 Witthauer C, Gloster T, Meyer A, Lieb R. Physical diseases among persons with obsessive compulsive symptoms and disorder: a general population study. Soc Psychiatry Psychiatr Epidemiol. 2014 Dec;49:2013–22.

29 Giynas Ayhan M, Uguz F, Askin R, Gonen M. The prevalence of depression and anxiety disorders in patients with euthyroid Hashimoto's thyroiditis: a comparative study. Gen Hosp Psychiatry. 2014 Jan 1;36(1):95–8.
30 Porterfield SP, Hendrich CE. The role of thyroid hormones in prenatal and neonatal neurological development: current perspectives. Endocr Rev. 1993 Feb 1;14(1):94–106.
31 Ahmed OM, El-Gareib AW, El-Bakry AM, Abd El-Tawab SM, Ahmed RG. Thyroid hormones states and brain development interactions. Int J Dev Neurosci. 2008 Apr 1;26(7):147–209.
32 Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017 Feb 7;342:68–100.
33 Schroeder AC, Privalsky ML. Thyroid hormones, T3 and T4, in the brain. Front Endocrinol. 2014 Mar 31;5:40.
34 Schwartz HL, Oppenheimer JH. Nuclear triiodothyronine receptor sites in brain: probable identity with hepatic receptors and regional distribution. Endocrinology. 1978 Jul 1;103(1):267–73.
35 Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Mol Psychiatry. 2002 Feb;7(2):140–56.
36 Campos-Barros A, Hoell T, Musa A, Sampaolo S, Stoltenburg G, Pinna G, et al. Phenolic and tyrosyl ring iodothyronine deiodination and thyroid hormone concentrations in the human central nervous system. J Clin Endocrinol Metab. 1996 Jun 1;81(6):2179–85.
37 Cleare AJ, McGregor A, O'Keane V. Neuroendocrine evidence for an association between hypothyroidism, reduced central 5-HT activity and depression. Clin Endocrinol. 1995 Dec;43(6):713–9.
38 Kulikov A, Moreau X, Jeanningros R. Effects of experimental hypothyroidism on 5-HT1A, 5-HT2A receptors, 5-HT uptake sites and tryptophan hydroxylase activity in mature rat brain1. Neuroendocrinology. 1999;69(6):453–9.
39 Altshuler L, Bauer M, Frye M, Gitlin M, Mintz J, Szuba M, et al. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. Am J Psychiatry. 2001 Oct 1;158(10):1617–22.
40 Gur E, Lerer B, Newman ME. Chronic clomipramine and triiodothyronine increase serotonin levels in rat frontal cortex in vivo: relationship to serotonin autoreceptor activity. J Pharmacol Exp Ther. 1999 Jan 1;288(1):81–7.
41 Bauer M, Whybrow PC. Thyroid hormone, neural tissue and mood modulation. World J Biol Psychiatry. 2001 Jan 1;2(2):59–69.
42 Gordon JT, Kaminski DM, Rozanov CB, Dratman MB. Evidence that 3,3',5-triiodothyronine is concentrated in and delivered from the locus coeruleus to its noradrenergic targets via anterograde axonal transport. Neuroscience. 1999 Aug 1;93(3):943–54.
43 Mano T, Sakamoto H, Fujita K, Makino M, Kakizawa H, Nagata M, et al. Effects of thyroid hormone on catecholamine and its metabolite concentrations in rat cardiac muscle and cerebral cortex. Thyroid. 1998 Apr;8(4):353–8.
44 Puymirat J. Effects of dysthyroidism on central catecholaminergic neurons. Neurochem Int. 1985 Jan 1;7:969–77.
45 Whybrow PC, Prange AJ. A hypothesis of thyroid-catecholamine-receptor interaction. Its relevance to affective illness. Arch Gen Psychiatry. 1981 Jan1;38(1):106–13.
46 Lin H, Davis F, Luidens M, Mousa S, Cao J, Zhou M, et al. Molecular basis for certain neuroprotective effects of thyroid hormone. Front Mol Neurosci. 2011 Oct 14;4:29.
47 Losi G, Garzon G, Puia G. Nongenomic regulation of glutamatergic neurotransmission in hippocampus by thyroid hormones. Neuroscience. 2008 Jan 2;151(1):155–63.
48 Thapa D, Upadhyaya T, Subedi S. The study of psychiatric disorders in patients with thyroid disorder at the tertiary care centre in western region of Nepal. J Psychiatr Assoc Nepal. 2013;2(2):29–34.
49 Brownlie B, Rae A, Walshe J, Wells J. Psychoses associated with thyrotoxicosis: "thyrotoxic psychosis." A report of 18 cases, with statistical analysis of incidence. Eur J Endocrinol. 2000 May 1;142(5):438–44.
50 Lass P, Slawek J, Derejko M, Rubello D. Neurological and psychiatric disorders in thyroid dysfunctions. The role of nuclear medicine: SPECT and PET imaging. Minerva Endocrinol. 2008 Apr 4;33(2):75–84.
51 Ittermann T, Völzke H, Baumeister SE, Appel K, Grabe HJ. Diagnosed thyroid disorders are associated with depression and anxiety. Soc Psychiatry Psychiatr Epidemiol. 2015 Sep;50(9):1417–25.
52 Shoib S, Mushtaq R, Maqbool Dar M, Arif T, Shah T, Hussain T, et al. Psychiatric Manifestations in thyroid disorders. Int J Clin Cases Investig. 2013 Oct 1;5(3):84.
53 Thomsen AF, Kvist TK, Andersen PK, Kessing LV. Increased risk of affective disorder following hospitalisation with hyperthyroidism: a register-based study. Eur J Endocrinol. 2005 Apr 1;152(4):535–43.
54 Hong JW, Noh JH, Kim DJ. Association between subclinical thyroid dysfunction and depressive symptoms in the Korean adult population: The 2014 Korea National Health and Nutrition Examination Survey. PLoS One. 2018 Aug 14;13(8):e0202258.
55 Placidi G, Boldrini M, Patronelli A, Fiore E, Chiovato L, Perugi G, et al. Prevalence of psychiatric disorders in thyroid diseased patients. Neuropsychobiology. 1998;38(4):222–5.
56 Benseñor IM, Nunes MA, Sander Diniz MF, Santos IS, Brunoni AR, Lotufo PA. Subclinical thyroid dysfunction and psychiatric disorders: cross-sectional results from the Brazilian Study of Adult Health (ELSA-Brasil). Clin Endocrinol. 2016 Feb;84(2):250–6.
57 Mermi O, Atmaca M. Thyroid gland functions are affected in obsessive-compulsive disorder. Anadolu Psikiyatri Derg. 2016 Jan 1;17(2):99–103.
58 McCracken JT, Hanna GL. Elevated thyroid indices in children and adolescents with obsessive-compulsive disorder: effects of clomipramine treatment. J Child Adolesc Psychopharmacol. 2005 Sep 1;15(4):581–7.
59 Hantouche E, Piketty ML, Poirier MF, Brochier T, Olié JP. [Obsessive-compulsive disorder and the study of thyroid function]. Encephale. 1991;17(5):493–6.
60 Aizenberg D, Hermesh H, Gil-ad I, Munitz H, Tyano S, Laron Z, et al. TRH stimulation test in obsessive-compulsive patients. Psychiatry Res. 1991 Jul 1;38(1):21–6.
61 Black JL, Lamke GT, Walikonis JE. Serologic survey of adult patients with obsessive-compulsive disorder for neuron-specific and other autoantibodies. Psychiatry Res. 1998 Dec 14;81(3):371–80.
62 Maina G, Albert U, Bogetto F, Borghese C, Berro A, Mutani R, et al. Anti-brain antibodies in adult patients with obsessive-compulsive disorder. J Affect Disord. 2009 Aug 1;116(3):192–200.
63 Schwartz M, Spath M, Muller-Bardorff H, Pongratz DE, Bondy B, Ackenheil M. Relationship of substance-P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients. Neurosci Lett. 1999 Jan 15;259:196–8.
64 Hutfless S, Matos P, Talor MV, Caturegli P, Rose NR. Significance of prediagnostic thyroid antibodies in women with autoimmune thyroid disease. J Clin Endocrinol Metab. 2011 Sep 1;96(9):E1466–71.
65 Barbuti M, Carvalho A, Köhler C, Murru A, Verdolini N, Guiso G, et al. Thyroid autoimmunity in bipolar disorder: a systematic review. J Affect Disord. 2017 Oct 15;221:97–106.
66 Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Front Immunol. 2017 May 9;8:521.
67 Waliszewska-Prosół, Bladowska MJ, Budrewicz S, Sąsiadek M, Dziadkowiak E, Ejma M. The evaluation of Hashimoto's thyroiditis with event-related potentials and magnetic resonance spectroscopy and its relation to cognitive function. Sci Rep. 2021 Jan 28;11(1):2480.
68 Müssig K, Künle A, Säuberlich A, Weinert C, Ethofer T, Saur R, et al. Thyroid peroxidase antibody positivity is associated with symptomatic distress in patients with Hashimoto's thyroiditis. Brain Behav Immun. 2012 May 1;26(4):559–63.
69 Xiao Y, Zhou Q, Xu Y, Yuan SL, Liu QA. Positive thyroid antibodies and risk of thyroid cancer: a systematic review and meta-analysis. Mol Clin Oncol. 2019 Sep 1;11(3):234–42.

70 Czarnocka B, Ruf J, Ferrand M, Carayon P, Lissitzky S. Purification of the human thyroid peroxidase and its identification as the microsomal antigen involved in autoimmune thyroid diseases. FEBS Lett. 1985 Oct 7;190(1):147–52.
71 Esfandiari NH, Papaleontiou M. Biochemical testing in thyroid disorders. Endocrinol Metab Clin North Am. 2017 Sep 1;46(3):631–48.
72 Rebuffat SA, Bresson D, Nguyen B, Péraldi-Roux S. The key residues in the immunodominant region 353-363 of human thyroid peroxidase were identified. Int immunol. 2006 July 1;18(7):1091–9.
73 Spencer CA. Clinical review: clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC). J Clin Endocrinol Metab. 2011 Dec 1;96(12):3615–27.
74 Boelaert K, Franklyn JA. Thyroid hormone in health and disease. J Endocrinol. 2005 Oct;187(1):1–15.
75 Jones H, Ho A, Sharma S, Mohammad S, Kothur K, Patel S, et al. Maternal thyroid autoimmunity associated with acute-onset neuropsychiatric disorders and global regression in offspring. Dev Med Child Neurol. 2019 Aug;61(8):984–8.