

Review Article

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The link between thyroid autoimmunity, depression and bipolar disorder

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Abstract: Depression and bipolar disorder are two major psychiatric illnesses whose pathophysiology remains elusive. Newly emerging data support the hypothesis that the dysfunction of the immune system might be a potential factor contributing to the development of these mental disorders. The most common organ affected by autoimmunity is the thyroid; therefore, the link between autoimmune thyroid disorders and mental illnesses has been studied since the 1930s. The aim of this review is to discuss the associations between thyroid autoimmunity, depression and bipolar disorder.

Keywords: thyroid peroxidase antibodies; Thyroid autoimmunity; Depression; Bipolar disorder

1 Introduction

Newly emerging data support the link between autoimmunity and mental illnesses which has been examined since the 1930s, when a schizophrenia patient was tested positive for autoantibodies [1,2]. The thyroid is the most common organ affected by autoimmunity [3], with up to 5% of the general population suffering from autoimmune thyroid diseases [4]. Thus, several studies have been conducted with the aim to discover whether there is a role for thyroid autoimmunity in psychiatric disorders. One of the

main clinical manifestations of thyroid autoimmunity is Hashimoto's thyroiditis (HT). Thyroid peroxidase antibodies (TPOAb) are considered to be the best serological marker of HT because about 95% of HT patients are TPOAb positive and false positive results are uncommon, whereas thyroglobulin antibodies (TGAb) are less sensitive and less specific compared with TPOAb [5]. Thyroid sonogram results and a combination of clinical features are required along with antibody positivity for the diagnosis of HT, however, the prevalence of increased TPOAb titers with no clinical manifestation is high and may reach up to 15% among females [5,6]. In this review we focus on the association between thyroid autoimmunity (both HT and asymptomatic elevated TPOAb levels) and two major psychiatric conditions: depression and bipolar disorder.

2 Major depressive disorder

Major depressive disorder (MDD), also referred to as clinical depression, is diagnosed when a distinct change of mood characterized by sadness or irritability occurs for at least 2 weeks, interferes with work and family relations and is accompanied by several psychophysiological changes (e.g., disturbances of sleep and appetite; suicidal thoughts; slowing of speech and action) [7]. MDD is associated with elevated risk of onset, persistence and severity of numerous secondary disorders (e.g., stroke, diabetes, coronary artery disease, certain types of cancer), increased suicide probability and many other issues (e.g., low education, marital disruption, unstable employment) [8]. A cross-national comparison from population-based surveys in 10 countries concluded that the lifetime prevalence of MDD varies substantially across countries and ranges from 3.0% in Japan to 16.9% in the US [9]. A specific form of MDD is postpartum depression (PPD) which is a major depressive episode with its onset within 4 weeks after delivery [10]. The prevalence of PPD is 10-15% in Western countries, but globally it ranges from almost 0% to nearly 60% [11]. PPD affects not only the mother's

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health, but also puts the offspring at risk by impairing their cognitive, social and emotional development [12].

In 1996 The World Health Organisation projected that by 2020 depression would be the second leading cause of disability worldwide [13], thereby encouraging further research concerning the causes of depression. However, due to the heterogeneity of MDD, its pathophysiology has been difficult to explain [14]. Newly emerging data indicate that the immune system may be a potential factor contributing to the development of depression [15]. Increased inflammatory cytokine levels in blood and cerebrospinal fluid as well as elevated acute phase protein concentrations in peripheral blood have been discovered in patients with MDD [16,17] and treatment with selective serotonin reuptake inhibitors has been reported to decrease serum levels of interleukin 6 [18]. It is hypothesized that the dysfunction of the immune system may lead to the reduction of monoamine synaptic availability, which is considered a fundamental mechanism in the pathophysiology of depression [15]. One of the first studies to show the connection between autoimmune thyroid disorders and depression was conducted in 1998 and included 583 perimenopausal women; after adjustment for psychosocial factors it was concluded that women with elevated TPOAb levels (≥ 100 IU/ml) are at risk for depression [19]. Afterwards the association between MDD and thyroid autoimmunity

was further examined in different studies; some of them aimed to reveal the link between HT and depression (see Table 1), while others focused on the connection between increased TPOAb levels and depressive symptoms among the general population (see Table 2).

The results of one study showed a higher prevalence of MDD among euthyroid HT patients and the findings of another one indicated that HT may increase the predisposition to depression [20,21]. Even though HT patients have been reported to be at higher risk for depression, l-thyroxine (T4) treatment for more than one year was found to reduce the chance of MDD [22]. Robert Krysiak with colleagues [23] hypothesized that the development of depression in patients with HT may be linked to decreased sexual function. They observed more impaired sexual function among females with autoimmune subclinical hypothyroidism than among those with non-autoimmune subclinical hypothyroidism or euthyroid HT. Sexual dysfunction also correlated with the severity of depressive symptoms. It was concluded that both subclinical hypothyroidism and HT may have a negative effect on female sexual function and might contribute to the development of depressive symptoms [23]. The study on males with autoimmune hypothyroidism led to the conclusion that even mild forms of autoimmune hypothyroidism are followed by sexual

Table 1: Studies assessing the association between Hashimoto's thyroiditis and depression

Author (year)	HT group		Characteristics	Control group		Results
	Sample size	Age (years)		Sample size	Age (years)	
Giynas Ayhan et al. (2014) [20]	51	Mean (SD) 35.10 (7.75)	Euthyroid, no T4 treatment	68	Mean (SD) 33.82 (6.07)	Higher current prevalence of MDD among HT patients compared with controls (29.4% vs 4.4%, $p=0.000$)
Yalcin MM et al. (2017) [21]	93	Mean 42.0 Range 29.0-52.0	Euthyroid, 44 with T4 treatment, 49 without T4 treatment	31	Mean 39.5 Range 27.0-55.0	Higher Beck Depression Inventory scores among HT patients compared with control subjects (7.5 vs. 5.0, $p=0.008$) 1. Greater overall incidence of depression among HT patients in comparison with the non-HT cohort (8.67 vs 5.49 per 1000 person-years; crude HR= 1.58, 95% CI =1.18– 2.13) 2. T4 treatment for more than one year decreased the risk of depression (adjusted HR=1.02; 95% CI=0.66– 1.59)
Lin I-C et al. (2016) [22]	1220	Mean (SD) 42.7 (13.8)	533 with T4 treatment 687 without T4 treatment	4880	Mean(SD) 42.5 (14.1)	

CI =confidence interval, HR =hazard ratio, HT =Hashimoto's thyroiditis, MDD =major depressive disorder, SD =standard deviation, T4 =l-thyroxine

Table 2: Studies assessing the link between increased thyroid antibody levels and depressive symptoms among the general population

Author (year)	Sample size	Age (years)	TPOAb+ threshold level (IU/ml)	Threshold level of elevated TPOAb (IU/ml)	Results
Delitala AP <i>et al.</i> (2016) [26]	3138	Mean 49,7	≥35	-	1. No association between depressive symptoms and TPOAb+ (TPOAb+ vs. TPOAb-: OR=1.40, 95% CI=0.75-2.60, p=0.126) 2. No association between depressive symptoms and TPOAb titer (OR=1.00, 95% CI=0.66-3.95, p=0.300)
Medici M <i>et al.</i> (2014) [27]	1503	Mean (SD) 70.6 (7.3)	>10	-	No association between incident depressive syndromes and TPOAb+ (OR=1.12, 95% CI=0.49-2.56, p=0.79) 1. No association between TPOAb+ and MDD in the 12 months preceding the examination (RR=1.78, 95% CI=0.56-5.74) 2. Increased TPOAb levels were associated with MDD in the 12 months preceding the examination (RR=2.88, 95% CI=1.47-5.65)
Itterman T <i>et al.</i> (2015) [25]	2142	Range 20-79	>200	≥60 among males ≥100 among females	3. No association between TPOAb+ and recurrent MDD (RR= 1.47, 95% CI=0.55-3.92) 4. No association between increased TPOAb levels and recurrent MDD (RR=1.18, 95% CI=0.60-2.34)

CI =confidence interval, MDD =major depressive disorder, OR =odds ratio, RR =relative risk, SD =standard deviation, TPOAb =thyroid peroxidase antibodies, TPOAb- =thyroid peroxidase antibody negativity, TPOAb+ =thyroid peroxidase antibody positivity

function impairment and depressive symptoms, both of them were reduced after T4 treatment [24].

Only one general population study showed a possible link between thyroid autoantibodies and depression (see Table 2): Itterman *et al.* [25] revealed that increased TPOAb levels were associated with MDD in the 12 months preceding the examination. However, that was not confirmed for TPOAb positivity (TPOAb+) and no connection was found between recurrent depression and TPOAb titer or TPOAb+. Thus, the authors concluded that it may be just a chance finding.

To our knowledge, a single study has provided an insight on the effect of thyroid autoimmunity on the response to antidepressants. In order to examine the connection, Eller and colleagues [28] compared the response to escitalopram treatment for MDD between TPOAb+ (>100 IU/ml) and TPOAb negative (TPOAb-) individuals. Although no significant differences were found, the non-responder group showed a trend for a higher prevalence of TPOAb+ compared with responders.

The findings of studies on TPOAb+ and PPD development are summarised in Table 3. Two of these studies identified an association between TPOAb+ during pregnancy and the development of PPD [29,30], while another one revealed that TPOAb values immediately after delivery do not affect PPD development [31]. Thus, it might

be concluded that the development of PPD is associated with TPOAb values during pregnancy, but not shortly after delivery.

3 Bipolar disorder

Bipolar disorder (BD) is a chronic, relapsing illness characterized by recurrent episodes of manic or depressive symptoms, with intervening relatively asymptomatic periods [32]. The aggregate cross-study estimate of the lifetime prevalence of bipolar disorder is 1.2% [33], with a range of 0.1% in China [34], 1.0% in Germany [35] and up to 3.3% in the United States [36].

The interaction between genetic, environmental and psychosocial factors is believed to lead to the development of BD, but the exact cause remains unknown. Recent evidence suggests that the dysfunction of the immune system is linked to the pathophysiology of BD. A meta-analysis of 30 studies showed increased concentrations of proinflammatory cytokines among bipolar patients compared with healthy controls [37], another one also found some support for immune dysregulation in BD [38]. This data leads to inquirer whether BD may be associated with organ-specific autoimmune disorders, including thyroid

Table 3: Studies assessing the link between thyroid autoimmunity and postpartum depression

Author (year)	Aim	Sample size	TPOAb+ threshold level (IU/ml), assessment time point	Results
Kuijpers JL et al. (2001) [29]	To identify whether the presence of TPOAb+ during pregnancy or postpartum is associated with PPD	291	>50; 12 and 32 weeks gestation 4, 12, 20, 28, 36 weeks postpartum	<ol style="list-style-type: none"> 1. Higher prevalence of PPD among women who were TPOAb+ at one or more time points during gestation and/or postpartum compared with TPOAb- women (59% vs 38%, $p=0.03$) 2. TPOAb+ at 12 weeks gestation was found to be associated with the development of PPD even after the exclusion of women who were depressed at 12 weeks gestation (OR=2.8, 95% CI=1.7-4.5) or after the exclusion of those who had been previously depressed (OR=2.9, 95% CI=1.8-4.3) 3. No association between TPOAb+ at 32 weeks gestation and the development of PPD
Groer MW et al. (2013) [30]	To analyse the relationship between TPOAb status and development of dysphoric moods during pregnancy and postpartum	631	>20; Between 16 and 25 weeks gestation	<ol style="list-style-type: none"> 1. TPOAb+ was associated with higher scores on the POMS depression-dejection subscale at the time of pregnancy measurement compared with TPOAb- (8.5 vs 5.9, $p=0.028$) 2. TPOAb+ was associated with higher depression scores postpartum
Albacar G et al. (2010) [31]	To evaluate whether thyroid function immediately after delivery can predict postpartum depression	1053	>27; 48h after delivery	No link between PPD and TPOAb+ (OR=0.609, 95% CI=0.149–2.486) or TPOAb titer (OR=1.002, 95% CI=0.998–1.006)

CI =confidence interval, OR =odds ratio, POMS =Profile of mood states, PPD =postpartum depression, TPOAb =thyroid peroxidase antibodies, TPOAb+ =thyroid peroxidase antibody positivity, TPOAb -=thyroid peroxidase antibody negativity

autoimmunity. The link between thyroid function and BD is usually explained by the use of lithium and its effect on the thyroid. For more than 60 years lithium has been the gold standard for BD treatment [39,40]. It is now known that lithium definitely affects thyroid function [41], probably by inhibiting T3 and T4 release [42], but the exact mechanism remains elusive. During the first years of treatment, the patients are more prone to develop hypothyroidism, whereas hyperthyroidism and thyroid cancer are uncommon [43]. The association between lithium treatment and thyroid autoimmunity has been studied, but the question whether lithium per se can induce an increase in anti-thyroid antibody titers remains open to discussion [43]. Thyroid autoimmunity has been found to be more prevalent among BD affected individuals, irrespective of treatment. In 2002, Kupka with colleagues [44] reported that 28% of their studied bipolar patients were positive for TPOAb (≥ 10 IU/ml), compared with 3-18% for population and psychiatric controls; this increased prevalence was not associated with lithium treatment. Afterwards a group of researchers conducted three consecutive studies and

concluded that their findings point to a possible increased inherited risk of the co-occurrence of BD and AIT [45–47]. However, their results were contradictory to the ones of another study which showed no familial association between BD and thyroid autoimmunity [48] (see Table 4).

4 Conclusions

The results of most studies point towards the conclusion that thyroid autoimmunity is associated with both MDD and BD. Euthyroid HT patients have been shown to be more prone to depression, thus, MDD may be linked to the presence of high TPOAb titers among HT patients irrespective of their thyroid function. However, current data show no link between slightly elevated TPOAb levels and depressive symptoms among the general population. TPOAb+ during pregnancy has been linked to PPD development, but the presence of TPOAb shortly after delivery has not been found to be associated with PPD. In addition,

Table 4: Studies assessing the link between thyroid autoimmunity and bipolar disorder

Author (year)	Aim	Study population, antibody positivity threshold level (IU/ml)	Results	Conclusion
Hillegers MHJ <i>et al.</i> (2007) [45]	To study the prevalence of autoimmune thyroiditis among offspring of bipolar patients	140 children (age 12-21 years) of bipolar parents (DBO group); 77 controls; ≥ 25 (TPOAb)	<ol style="list-style-type: none"> 1. Marginally significant higher prevalence of TPOAb+ among the DBO group compared with controls (8.7% vs 3.1%, $p=0.05$) 2. High prevalence of TPOAb+ among the DBO group females compared with females in the control group (15.8% vs 3.9%, $p=0.008$) 	Offspring of bipolar individuals may be more vulnerable to develop thyroid autoimmunity
Vonk R <i>et al.</i> (2007) [46]	To examine whether AIT could be an endophenotype for BD	51 twin pairs (age 18-60 years) with at least one twin suffering from BD; 35 control twin pairs; ≥ 25 (TPOAb)	<ol style="list-style-type: none"> 1. Higher mean TPOAb levels among discordant* twin pairs compared with control twin pairs 2. Higher mean TPOAb levels among bipolar patients compared with control twins 3. Higher prevalence of TPOAb+ among bipolar patients compared with control twins (27% vs 16%) (difference statistically insignificant). 4. Higher prevalence (not statistically significant) of TPOAb+ among monozygotic (discordant*) nonbipolar co-twins (27%) compared with dizygotic (discordant*) nonbipolar co-twins (17%) and with matched healthy control twins (16%) 	AIT, with TPOAb as a marker, might be an endophenotype for BD
Snijders G <i>et al.</i> (2017) [47]	To elucidate whether TPOAb are a trait marker for BD	103 DBO subjects from the study by Hillegers MHJ <i>et al.</i> (2007), 50 controls; 31 bipolar index twins, 32 co-twins, 58 control twins from the study by Vonk R <i>et al.</i> (2007); ≥ 25 (TPOAb)	<ol style="list-style-type: none"> 1. TPOAb+ was stable over 12 years among the DBO group and over 6 years among the bipolar twin group, TPOAb+ was not associated with lithium use 2. Increased prevalence of TPOAb+ among the DBO group compared with controls (10,4% vs 4%) (difference statistically insignificant) 3. Higher TPOAb levels (although difference statistically insignificant) among discordant* nonbipolar co-twins compared with control twins (1.06 IU/ml vs 0.82 IU/ml) 	There is a possible increased inherited risk of the co-occurrence of BD and AIT, but large-scale studies are needed to reveal the connection
Cobo J <i>et al.</i> (2015) [48]	To elucidate if there is an association between thyroid autoimmunity and BD	239 patients affected by BD and 131 their FDR; 108 controls; ≥ 15 (TPOAb) ≥ 100 (TGAAb)	TGAAb and/or TPOAb positivity found among 19.5% of individuals in the BD group, 25.8% in the FDR group and 20.8% of controls (differences statistically insignificant).	AIT is not an endophenotype for BD

AIT =autoimmune thyroiditis, BD =bipolar disorder, DBO =Dutch bipolar offspring, FDR =first-degree relatives, TGAAb = thyroglobulin antibodies, TPOAb =thyroid peroxidase antibodies, TPOAb+ =thyroid peroxidase antibody positivity, *discordant twins – the index twin is affected by BD, but the co-twin does not have BD

further research is needed to assess the effect of TPOAb+ on the response to antidepressants.

Unfortunately, the association between BD and thyroid autoimmunity still remains unclear. The offspring of bipolar parents have shown higher rates of TPOAb+ and

the twin study has led to the theory that BD and thyroid autoimmunity may be a result of the same genetic disturbance, but other scientists report to have found no association between BD and TPOAb levels. Thus, further large-scale research is needed to reach final conclusions.

Abbreviations

AIT: autoimmune thyroiditis
 BD: bipolar disorder
 HT: Hashimoto's thyroiditis
 MDD: major depressive disorder
 PPD: postpartum depression
 TGAbs: thyroglobulin antibodies
 TPOAbs: Thyroid peroxidase antibodies
 TPOAb-: thyroid peroxidase antibody negativity
 TPOAb+: thyroid peroxidase antibody positivity
 T4: l-thyroxine

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