Review

Depression and autoimmune thyroiditis - their relationship and the effects of treating psychiatric and thyroid disorders on changes in clinical and biochemical parameters including BDNF and other cytokines.

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Abstract: Various autoimmune diseases, including autoimmune hypothyroidism (AHT), are associated with a higher risk of developing mood disorders throughout life. Depression is accompanied by the changes in the levels of inflammatory and trophic factors, including interleukines (IL-1beta, IL-2, IL-6), interferon alpha (IFN-alpha), tumor necrosis factor alpha (TNF-alpha), C-reactive protein (CRP) and brain derived neurotrophic factor (BDNF). Similar disturbances in the cytokine profile are seen in AHT patients and their relatives. Disclosure of the relationship between the coexistence of depression and autoimmune subclinical thyroiditis indicates that the pathomechanism of depression may be related to the changes in the immune system, it is possible that both conditions may be caused by the same immune processes. The above hypothesis is indirectly supported by the observations that the treatment with both antidepressants and levothyroxine leads to a decrease in the levels of proinflammatory cytokines with an increase in BDNF concentrations, simultaneously correlating with an improvement in the clinical parameters. However, so far there are no long-term studies determining the causal relationship between depression, thyroid autoantibodies, and cytokine profile, which could bring us closer to understanding the interrelationships between them and facilitate the use of an adequate pharmacotherapy, not necessarily psychiatric. We consider the above issues insufficiently investigated but of great importance. This article is an overview of the available literature as well as an introduction to our research project.

Keywords: depression, chronic autoimmune thyroiditis; BDNF

1. Introduction

The relationship between thyroid function and depression has been known for a long time [1-3]. It was first described in 1825 by Parry, who noted an increased number of "nerve strokes" in thyroid disease. Seagull in 1873 showed a link between myxoedema and psychosis, which was confirmed in 1888 by the Committee of the Clinical Society. In 1949 Asher introduced the term "myxedema madness" to describe mental state changes in patients with hypothyroidism [4]. It is currently well known that thyroid dysfunction can significantly affect the mental state, including emotions and cognitive functions. Both the excess and the deficiency of thyroid hormones can cause mood disorders, including depressive disorders, which can be usually resolved with an appropriate treatment of dysthyreosis. Depression may, in turn, be accompanied by various degrees of thyroid dysfunction. An overt hypothyroidism is present in 1-4% of patients with affective disorders, while subclinical hypothyroidism occurs in 4-40% of this population. According to Boswell, the frequency of depressive symptoms in patients with hypothyroidism reaches 50% [5], while depression of significant clinical severity occurs in over 40% of people suffering from hypothyroidism [6]. What is practically very important, and what prompted us to

undertake the research, the depressive states associated with broadly understood thyroid dysfunction are usually at least partially resistant to antidepressive treatment, with the causal treatment being the key here. Thyroid hormones are also usually recommended as an adjunctive therapy in the treatment of depression in treatment algorithms [7].

2. Autoimmune hypothyroidism (AHT) and depression

AHT is a progressive disease of the thyroid gland. Dense lymphocytic infiltration covering the gland is involved in the pathogenesis of this type of chronic thyroiditis [8]. Activated B cells produce antibodies against several major thyroid antigens. AHT is characterized by a combination of typical clinical features (please see table) [9], increased serum TSH levels, decreased fT4 levels, presence of antibodies to thyroid antigens, and decreased ultrasonographic echogenicity of the thyroid parenchyma [10].

Table. Autoimmune hypothyroidism - symptoms, assessment and diagnostic findings

Symptoms	Assessment Findings	Diagnostic Findings
Depression	Dry, coarse skin	Hyponatremia
Fatigue	Reduced body and scalp hair	Macrocytic anemia
Weight gain	Dull facial expression	Decreased memory
Constipation	Bradycardia	Hyperprolactinemia
Muscle cramps, arthralgias	Goiter	Elevated creatine kinase level
Menorrhagia	Macroglossia	Pituitary gland enlargement
Infertility	Ascites	Delayed bone age
Sexual dysfunction	Galactorrhea	Hypercholesterolemia
Cold intolerance	Slow relaxation of tendon reflexes	
Carpal tunnel syndrome	Nonpitting edema of lower extremities	
Sleep disorders	Hoarseness	

AHT is the most common organ autoimmune disorder, with an estimated prevalence at approximately 2%, women suffer more frequently. Thyroid peroxidase (TPO) is the main autoantigen, and antibodies to TPO (Anti-TPO) are present in almost all AHT patients and may precede onset of the clinical phase by up to several years. Subclinical AHT (with the presence of Anti-TPO, elevated TSH and normal fT4 levels) is more frequent and affects approximately 9% of general population [10].

Depression, including severe depression, is more common in patients with euthyroid chronic AHT comparing to subjects without this condition [8]. Frequent simultaneous presence of depressive and anxiety disorders in patients with Hashimoto's disease (over 90% of AHT) in the euthyroid stage has also been confirmed [11]. A large Danish epidemiological study has shown that various autoimmune diseases, including AHT, are associated with a higher occurence of mood disorders throughout life [12]. It has been shown that it is not only the decreased level of thyroid hormones that determines the occurrence of mood disorders, we also know that even in patients with normal thyroid function and elevated Anti-TPO antibodies, their presence correlates with a higher risk of anxiety and mood disorders [13]. An increased levels of anti-thyroid antibodies has been documented in 20% of patients with depression, while the incidence in the general population ranges from 5 to 10% [14,15]. In patients with bipolar disorder, regardless of the use of lithium (having "anti-thyroid" properties), the presence of Anti-TPO and AHT is also more frequent [16,17]. Also, the offspring of people with bipolar disorder have a higher incidence of Anti-TPO, even if they do not have mental disorders [18,19]. There are also data showing an increased level of Anti-TPO and antibodies blocking the TSH receptor in patients

with depressive disorders without thyroid dysfunction, but who were resistant to antidepressant treatment [20]. Several hypotheses are proposed to explain the above observations. Decrease in the secretion of thyroid hormones is interpreted as a result of dysregulation of TSH secretion circadian rhythm (physiologically TSH levels are higher at night). This suggests that some depressed patients may have central hypothyroidism (pituitary and hypothalamus dependent - secondary and tertiary, respectively). Moreover, sleep deprivation used in the treatment of depression leads to the restoration of the nocturnal rise in TSH levels and, consequently, an increase in fT3 and fT4 levels. According to another hypothesis, autoimmune thyroid diseases are associated with the hypothalamic-pituitary-adrenal axis and are mediated by changes in the concentration of pro-inflammatory and anti-inflammatory cytokines. TNF-alpha, IL-1 and IL-6 (all pro-inflammatory agents) increase the release of CRH (corticoliberin) and AVP (arginine vasopressin) leading to increase of glucocorticosteroids (GCS) secretion from the adrenal cortex. Chronic high GCS levels induce receptor resistance to GCS, subsequently causing further increase in their secretion and also disturbances in the functioning of the hypothalamic-pituitary-adrenal axis increasing the susceptibility to autoimmune processes and depression [21,22]. Next hypothesis connects the frequent postpartum recurrence of depression with the end of immune tolerance present in pregnancy [23,24]. Unfortunately, currently there are no studies showing a relationship between postpartum thyroiditis and postpartum depression and convincingly explaining the etiopathogenetic relationships but indicate the existence of common elements of the immune pathogenesis of both AHT and mood disorders.

The results of the summary [25] on depression, anxiety and AHT indicate, that in the United States the prevalence of AHT is 4-13%, AHT more often affects women, its occurrence increases with age reaching 20% in the group of older women. Prevalence of depression reached 6.6%, and anxiety disorders 18.1% in this study. It was also found that depression occurs in 16.8% of patients suffering from AHT, while the criteria for anxiety disorders were met by 35.7% of patients.

The study of the relationship between morphological changes in the central nervous system in AHT patients with hypothyroidism using positron emission tomography (PET) did not show any direct relationship between specific changes caused by AHT and the development of depressive disorders [2,26].

3. Inflammatory processes, growth factors and cytokines

Common etiological basis for both thyroid autoimmunity and mood disorders are also seen in similar changes of growth and differentiation in the hematopoietic and neuronal system cells and similar changes in the cytokine profile [10]. Numerous studies indicate that depression activates the inflammatory response system through increased production of pro-inflammatory cytokines such as IL-1beta, IL-2, IL-6, IFN-alpha, TNF-alpha and their receptors (IL-6R, IL-1RA) [27]. Stress induces production of pro-inflammatory cytokines leading to neuroendocrine and neurotransmitter changes resembling symptoms of depression. IFN-alpha immunotherapy (e.g., used in hepatitis C) often causes depressive symptoms and autoimmune thyroid disorders with the appearance of anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (anti-TG) antibodies [28].

The presence of acute phase proteins and cytokines may be associated with inflammation within the brain. Peripherally produced cytokines can cross the blood-brain barrier [29,30], and after crossing it, they are able to participate in stress response modulation and regulation of neurogenesis [28]. One of their potential mechanisms of action on mood is the attenuation of neurogenesis within hippocampal neurons, which is believed to be a key mechanism in the pathophysiology of depression and its treatment [31-33]. The weakening of neurogenesis may, over time, contribute to the reduction of the gray matter volume in hippocampus, often observed in depression [34]. It is still unclear whether the presence of acute phase proteins may be the cause, consequence or only accompanying

the depression.

A study conducted in patients with hypothyroidism after thyroidectomy due to cancer showed increased levels of the pro-inflammatory cytokines IL-6, IL-10. IL-17, TNF-alpha and CRP. Levothyroxine therapy (used in hypothyroidism) resulted in a decrease in the level of these cytokines, but their levels were still higher than in healthy subjects [35]. In patients treated with levothyroxine, a simultaneous reduction in the level of pro-inflammatory cytokines and an increase in the levels of anti-inflammatory cytokines has been also demonstrated [36]. Interestingly, primary AHT is characterized by increased values of pro-inflammatory cytokines such as IL-2, IL-6, IL-15, TNF-alpha and CRP [7,36-38]. During treatment with levothyroxine, a significant decrease in the levels of IL-1, IL-2, IL-6, IL-12, IFN-gamma, TNF-alpha and a significant increase in IL-10 (anti-inflammatory cytokine) was observed [7,36]. In the Polish study the incidence of mild and moderate depression among patients with hypothyroidism was initially 57%. After 6 months of levothyroxine therapy and achieving euthyroidism nearly half of the group (42%) remitted depressive symptoms [7].

Use of selective serotonin reuptake inhibitors (SSRI), our most frequently used group of antidepressants, reduces promoting-depression effect of pro-inflammatory cytokines. Fluoxetine has been shown to reduce the expression of IL-1beta, IL-6, and TNF-alpha, but interestingly subsequently increasing the level of IL-10 [39]. Desipramine (tricyclic antidepressant, TCA) reduces levels of TNF-alpha in the hippocampus and brainstem [40], and its clinical efficacy has been associated with its ability to alter the sensitivity of noradrenergic neurons to TNF-alpha [41]. In conclusion, studies evaluating the effects of SSRIs and other antidepressive drugs indicate that inflammatory factors contribute to the pathogenesis of depression, and that various antidepressants have ability to reduce the release of pro-inflammatory cytokines. It is worth noting, that preliminary data suggest that anti-inflammatory drugs may be useful in mood disorders - it has been reported that in patients treated with rofecoxib and celecoxib, the depressive symptoms improvement was more pronounced than in the group not treated with these drugs [42,43]. This effect at least partially may be related to the analgesic effect of the COX-2 inhibitors, but studies on rats showed that use of rofecoxib leads to serotonin increase in frontal, parietal and temporal cortex, which may indicate their other-than-analgesic mechanism of action [42]. Even if not all depressive states have an inflammatory etiology, according to the available data there is possibly a separate subtype of depression of inflammatory origin or manifestation of inflammatory process is able to clinically mimics depression. Biological anti-inflammatory drugs, including anti-TNF-alpha antibodies as e.g., infliximab, adalimumab and golimumab potentially may be useful to treat those types of depression. Those particles have an ability to reduce severity of inflammation (e.g., in rheumatic diseases, psoriasis and Crohn's disease) very effectively. However, the conclusions from limited depression trials are ambiguous, although patients with high initial levels of pro-inflammatory cytokines may have more benefit with this treatment. [44,45]. Tocilizumab studies show completely different results, this IL-6 receptor blocker exacerbates depressive symptoms in haematological patients [46]. Interestingly, hallucinogens (increasingly studied in depression) and bupropion have the ability to block TNF-alpha or decrease its production [47].

Scarce data from studies concerning the thyroid gland function during use of TNF-alpha antibodies showed also positive results [48]. We need to underline here that depression (also with increased suicidal risk) and thyroiditis (new onset or its exacerbation) are among common side effects of TNF-alpha blockers.

Studies involving relatives of patients with AHT force even deeper reflections about common origin of both ATH and depression. Euthyroid women being relatives of AHT patients have abnormal serum levels of hematopoietic and neural growth and differentiation factors important in etiology of depression – BDNF (Brain-derived neurotrophic factor), IGFBP-2 (insulin-like growth factor binding protein), EGF (epidermal growth factor) and SCF (stem cell factor) [10,49-51].

4. Brain-derived neurotrophic factor (BDNF) and depression, AHT and gender

BDNF needs a broader description as a crucial element in current understanding of development and dynamics of depressive symptomatology. This particle belongs to the group of neurotrophins, proteins synthesized in the cells of the central and peripheral nervous system and involved in the development, function and protection of nerve cells. It regulates many processes in our body, including the development and growth of neurons, inhibiting apoptosis, promoting neurogenesis, neuroregeneration, and stimulating the formation of dendritic connections. BDNF participates in the regulation of neuronal plasticity related to learning and memory processes, influencing the process of synaptic long-term potentiation and long-term depression in the hippocampus. It also influences the development of serotonergic, dopaminergic, noradrenergic and cholinergic neurons. Dopaminergic neurons of the substantia nigra and striatum have been found to be the main source of BDNF secretion. BNDF easily cross the blood-brain barrier [52].

Preclinical studies show that stress reduces BDNF expression in the rat hippocampus, while a single two-sided direct infusion of BDNF into the rat hippocampus has an antidepressant effect in animal models of depression [53]. In humans, BDNF plays a significant role in the pathophysiology of mental disorders, especially depression, where its key role is undisputable. Patients with severe depressive symptoms show lower levels of BDNF compared to controls. Moreover, BDNF levels are correlated with the reduction of the hippocampal volume [54]. We also know that BDNF expression is lower in the prefrontal cortex and hippocampus of people who died committing suicide compared to the control group matched in terms of sex and age [55]. The use of sertraline, escitalopram and venlafaxine in the study by Matrisciano et al. resulted in significant clinical improvement despite varying effects on peripheral BDNF levels. A relationship was also found between an increase in BDNF serum levels and an improvement in the Hamilton Depression Rating Scale, thus indicating that a higher BDNF level in the blood serum corresponds to recovery [54]. It has been shown that BDNF levels were directly related to antidepressant responses, and people who responded well to treatment (> 50% improvement in the scores of depression severity scales) had higher BDNF levels before treatment than non-responders, indicating that BDNF can be a potential predictor of the antidepressant response [56]. It was also confirmed that the concentration of BDNF and its changes are not rigidly correlated with improvement in depression, but that the level of BDNF generally increases during antidepressant treatment. Studies on rapid-acting antidepressant - ketamine - having different mechanism of action than SSRIs and TCAs, showed that the rapid antidepressant response after its administration is mediated by an increase in BDNF levels [57]. Research directly linking BDNF to thyroid disorders is scarce at present. Rats with early-onset hypothyroidism exhibited lower levels of BDNF in the brain [58]. Preclinical studies conducted by Hung indicate that thyroxine protects against white matter damage by increasing the level of BDNF [59]. In clinical trials, higher TSH levels were associated with a more discrete increase in serum BDNF levels in depressed patients during antidepressant therapy [60], and lower baseline TSH levels correlated with greater improvements after fluoxetine and sertraline [61]. It has also been shown that observed clinical results were better among patients who had lower TSH levels during sertraline and triiodothyronine therapy [62]. On the other hand, the only study evaluating the effect of thyroid hormones on changes in BDNF in serum, plasma and platelets over the 3-month period of treatment with antidepressants in patients without thyroid disease showed that higher TSH levels correlated with a lower increase in serum levels of BDNF during antidepressive treatment. It was additionally indicated that with TSH increase BDNF concentrations decreased throughout the observation period [60]. In patients participating in this study, no such relationship was found between the levels of triiodothyronine (T3), thyroxine (T4), corticotropic hormone (ACTH), cortisol, prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogen and progesterone. A study evaluating similar relationships in patients with hypothyroidism and subclinical hypothyroidism has not

been conducted so far.

Summarizing, it can be hypothesized that thyroid hormones may affect the response to antidepressant therapy through its influence on BDNF, but so far there are no sufficient data to confirm this hypothesis unequivocally.

Due to the epidemiology of depression and AHT, it is worth emphasizing that the relationship between the level of BDNF and depression may depend on gender. It has been shown that reduced BDNF values are more pronounced in women with depression, and long-term antidepressant use selectively raises its concentration in women. Therefore, it is possible that the more frequent occurrence of depression in women may be related to this mechanism and interactions with female sex hormones, especially since it has been shown that BDNF expression can be reduced by exogenous administration of estradiol [56].

5. Summary

People with higher risk of developing mood disorders, including depressive disorders, are at the same time more likely to develop autoimmune thyroid disease and vice versa, what may indicate a common pathogenetic roots. An abnormal profile of haemopoietic and neuronal growth factors, including BDNF, is observed in patients with mood disorders as well as in those at risk of developing ATH. Similar observations apply to the cytokine profile in patients with both diseases, in whom we observe an increase in the concentrations of pro-inflammatory interleukins, e.g., IL-1beta, IL-2, IL-6, and TNF-alpha. From the clinical perspective, the conclusion that seems to be of particular importance is that in euthyroid patients with autoimmune thyroiditis and elevated levels of anti-thyroid antibodies, the incidence and severity of depression is significantly higher [8]. Treatment with both antidepressants and levothyroxine leads to a decrease in the level of pro-inflammatory cytokines, an increase in the level of BDNF, correlating with an improvement in clinical parameters of depression. Hence one of the hypotheses that depression may belong to the spectrum of inflammatory and degenerative disorders [63].

For the above reasons, patients with depression and anxiety disorders should be tested for autoimmune hypothyroidism, and patients with AHT should be screened for psychiatric symptoms [25]. However, it is necessary to conduct long-term studies (as our team is planning now) to determine the causal relationship between depression, thyroid autoantibodies, and cytokine levels, which would help us bring us closer to understanding the interrelationships between them and facilitate the use of adequate pharmacotherapy, not necessarily psychiatric. At the same time, it would be possible to identify groups of higher risk for the occurrence of both frequent and very burdensome diseases, and from psychiatric perspective to help prevent the development of full-blown depression and finally to predict the therapeutic response to particular groups of drugs.

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