OPINIONS, HYPOTHESES, DISCUSSION ISSUES

DOI: https://doi.org/10.17816/PED11455-68

THE ASSOCIATION OF NEUROPSYCHIATRIC DISORDERS AND ENDOCRINE PARAMETERS IN HASHIMOTO THYROIDITIS

© P.A. Sobolevskaia [1], B.V. Andreev [2], A.N. Gvozdetckii [1], A.A. Dolina [1], A.M. Stepochkina [1, 3], Y.I. Stroev [1], V.J. Utekhin [1, 4], T.V. Fedotkina [1, 4], L.P. Churilov [1, 5]

[1] Saint Petersburg State University, Saint Petersburg, Russia;

[2] St. Petersburg State Budgetary Healthcare Institution "Psychiatric Hospital No. 1 named after P.P. Kashchenko", Nikolskoe, Leningrad Region, Russia;

[3] Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, Saint Petersburg, Russia;

[4] St. Petersburg State Pediatric Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia;

[5] St. Petersburg Scientific Research Institute of Phthisiopulmonology of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia

For citation: Sobolevskaia PA, Andreev BV, Gvozdetckii AN, Dolina AA, Stepochkina AM, Stroev YI, Utekhin VJ, Fedotkina TV, Churilov LP. The association of neuropsychiatric disorders and endocrine parameters in Hashimoto thyroiditis. *Pediatrician (St. Petersburg)*. 2020;11(4):55-68. https://doi.org/10.17816/PED11455-68

Received: 10.06.2020 Revised: 09.07.2020 Accepted: 26.08.2020

Hashimoto thyroiditis is the most common thyroid disease. This form of pathology has a diverse clinical picture, including neuropsychiatric disorders. There are frequent cases of comorbidity of autoimmune thyroiditis and psychiatric forms of pathology, along with such a nosological entity as Hashimoto's encephalopathy (aka: Steroid-responsive encephalopathy of autoimmune thyroiditis), characterized by an increased level of antithyroid autoantibodies and various mental disorders, with still unclear pathogenesis. The question arises, how to regard patients with psychiatric disorders and Hashimoto thyroiditis — either as patients having autoimmune thyroiditis, comorbid with psychiatric forms of pathology, or as patients with Hashimoto's encephalopathy? We studied groups of patients with autoimmune thyroiditis free from any psychiatric disorders, autoimmune thyroiditis comorbid with psychiatric forms of pathology, and a group of healthy donors similar as regards to their age and sex. We also studied medical history, clinical manifestations of the disease, instrumental data and the serum levels of thyrotropin, thyroid hormones, various antithyroid autoantibodies, and prolactin. We analyzed the correlation of laboratory and instrumental parameters and clinical data in all groups of patients. There was a significant relationship ($p < 0,05$) between various psychiatric symptoms and a decreased level of free thyroxine, an increased level of thyroid stimulating hormone (TSH), an increased level of prolactin and an increased volume of a thyroid gland. A significant relationship ($p < 0,05$) was also found between various symptoms of hypothyroidism and a decreased level of free triiodothyronine (FT3), an increased level of antibodies to thyroglobulin (anti-TG Ab), and an increased level of antibodies to thyroid peroxidase (anti-TPO Ab).

Keywords: autoimmune thyroiditis; Hashimoto thyroiditis; Hashimoto's encephalopathy; hypothyroidism; euthyroidism; phobias; psychiatric symptoms; antithyroid autoantibodies; thyroid hormones.

ВЗАИМОСВЯЗЬ ПСИХОНЕВРОЛОГИЧЕСКИХ НАРУШЕНИЙ И ЭНДОКРИННЫХ ПАРАМЕТРОВ ПРИ АУТОИММУННОМ ТИРОИДИТЕ ХАСИМОТО

© П.А. Соболевская [1], Б.В. Андреев [2], А.Н. Гвоздецкий [1], А.А. Долина [1], А.М. Степочкина [1, 3], Ю.И. Строев [1], В.И. Утехин [1, 4], Т.В. Федоткина [1, 4], Л.П. Чурилов [1, 5]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный университет», Санкт-Петербург;

[2] Санкт-Петербургское государственное бюджетное учреждение «Психиатрическая больница № 1 им. П.П. Кащенко», Ленинградская область, с. Никольское;

[3] Федеральное государственное бюджетное учреждение науки «Институт эволюционной физиологии и биохимии им. И.М. Сеченова» Российской академии наук, Санкт-Петербург;

[4] Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения Российской Федерации, Санкт-Петербург;

[5] Федеральное государственное учреждение «Санкт-Петербургский научно-исследовательский институт фтизиопульмонологии» Министерства здравоохранения и социального развития Российской Федерации, Санкт-Петербург

Для цитирования: Соболевская П.А., Андреев Б.В., Гвоздецкий А.Н., Долина А.А., Степочкина А.М., Строев Ю.И., Утехин В.И., Федоткина Т.В., Чурилов Л.П. Взаимосвязь психоневрологических нарушений и эндокринных параметров при аутоиммунном тиреоидите Хасимото // Педиатр. – 2020. – Т. 11. – № 4. – С. 55–68. https://doi.org/10.17816/PED11455-68

Поступила: 10.06.2020 Одобрена: 09.07.2020 Принята к печати: 26.08.2020

На сегодняшний день аутоиммунный тиреоидит Хасимото является наиболее распространенной формой патологии щитовидной железы. Данное заболевание имеет разнообразную клиническую картину, включая психоневрологические нарушения. Нередки случаи коморбидности аутоиммунного тиреоидита и психиатрической патологии, наряду с этим существует такая нозологическая единица, как энцефалопатия Хасимото (синоним: стероид-чувствительная энцефалопатия аутоиммунного тиреоидита), характеризующаяся повышенным титром антитироидных антител и различными ментальными нарушениями, патогенез которой еще недостаточно изучен. Возникает вопрос, как расценивать пациентов с имеющимися психиатрическими расстройствами и тиреоидитом Хасимото — как аутоиммунный тиреоидит, коморбидный с психиатрической патологией, или как пациентов, страдающих энцефалопатией Хасимото? Нами были обследованы группы пациентов с аутоиммунным тиреоидитом без психических нарушений, аутоиммунным тиреоидитом и сопутствующими психиатрическими формами патологии, а также сопоставимая по полу и возрасту группа здоровых лиц. Изучены жалобы, анамнез и клиника заболеваний, данные инструментальных исследований, исследованы сывороточные уровни тиротропного гормона, тироидных гормонов, различных антитироидных аутоантител, пролактина. Изучена корреляция лабораторно-инструментальных параметров и клинических данных во всех группах пациентов. Выявлена достоверная связь ($p < 0,05$) между различными психиатрическими симптомами и пониженным уровнем свободного тироксина, повышенным уровнем тиротропного гормона, повышенным уровнем пролактина, увеличенным объемом щитовидной железы. Также выявлена достоверная связь ($p < 0,05$) между различными симптомами гипотиреоза и пониженным уровнем свободного трииодтиронина (FT3), повышенным уровнем антител к тироглобулину, повышенным уровнем антител к тиропероксидазе.

Ключевые слова: аутоиммунный тиреоидит (тиреоидит); тироидит (тиреоидит) Хашимото (Хасимото); гипотиреоз (гипотиреоз); эутиреоз (эутиреоз); энцефалопатия Хасимото (Хашимото); фобии; психиатрические симптомы; антитироидные (антитиреоидные) аутоантитела; тироидные (тиреоидные) гормоны.

INTRODUCTION

Thyroid gland (TG) pathology currently ranks first in terms of vulnerability and morbidity among all endocrinopathies. Chronic Hashimoto autoimmune thyroiditis (AIT) is the most common disease among thyropathies, which is sometimes considered to occur with Graves–Basedow disease as a single autoimmune TG disease [10]. Untreated AIT results in hypothyroidism. Clinically overt hypothyroidism occurs in 0.2%–2% and subclinical hypothyroidism occurs in 10%–12% of the general population [1]. Due to the ubiquitous nature of thyroid hormone receptors in all body cells, hypothyroidism can disguise as various somatic forms of pathology, including neuropsychiatric disorders [9]. In 1949, Richard Asher gave the classic description of "myxoedematous madness," revealing its direct relationship with hypothyroidism [18].

The neuropsychiatric symptomatology of hypothyroidism is often diagnosed as a psychiatric disorder; and in such cases, patients with an unrecognized endocrine disease can be monitored by psychiatrists for years [19].

With hypothyroidism, thyroid hormone levels, namely, free triiodothyronine (FT3) and free thyroxine (FT4), are decreased in the blood, and the levels of thyroid-stimulating hormone (TSH) and prolactin (hyperprolactinemia, due to the prolactin-releasing hormone effect of compensatory thyroliberin production) are increased. Therefore, the prolactin level in the blood must be controlled in such patients [28]. Prolactin promotes the development of autoimmunity and autoimmune pathology as a systemic and paracrine immunostimulant; therefore, hyperprolactinemia can be an immunopathogenic factor contributing to the emergence and progression of AIT according to the vicious cycle principle [13].

Thyroid hormones control both differentiation and functions of neuronal networks and neuroglia; therefore, hypothyroidism is characterized by neuropsychiatric abnormalities such as drowsiness, asthenia, loss of interest in the environment, decreased memory and cognitive decline, delirium and delirium–hallucinatory conditions, anxiety and depressive disorders, and panic attacks [2, 5, 8, 11, 14, 15, 29].

Psychiatric disorder also occurs in euthyroid AIT, when no deficiency of thyroid hormones are noted, hence the occurrence of neuropsychiatric disorders in such patients can not be explained by hypothyroidism.

Perhaps not all of these disorders are due solely to a lack of thyroid hormones. Other immunoendocrine mechanisms associated with various serum bioregulators (autoantibodies, other hormones, and autacoids) may be involved in the pathogenesis of these disorders.

In 1966, Hashimoto's encephalopathy (HE), a new nosological unit, was described, although its etiology and pathogenesis have not been studied yet [19]. HE is believed to be an autoimmune inflammatory disease of the brain, also known as steroid responsive encephalopathy associated with autoimmune thyroiditis [20, 23, 25]. HE can occur with various clinical manifestations, such as tremors, transient aphasia, epileptic seizures, paranoid, visual hallucinations, and behavioral disorders. Historically, the first descriptions were associated with cerebellar symptoms [3, 6, 21, 22–24]. Generally, in case of HE, an increase in the level of autoantibodies to thyroperoxidase (aTPO) is noted, but the etiology and pathogenesis remain a subject of debate, since HE is also associated with autoantibodies against other autoantigens, including extrathyroid ones, and with the vasculitis of cerebral vessels and the effects of TSH excess on the brain.

HE is most often considered an autoimmune cerebral vasculitis or a result of an autoimmune cross-reaction of antithyroid antibodies against antigens present on brain cells. However, the role of autoantibodies towards neuronal α-enolase and/or other autoantigens of the brain is not excluded [4, 21, 26]. According to the literature, HE can be registered in patients with various thyroid states, for example, 35% of the patients have subclinical hypothyroidism, 20% have clinically pronounced hypothyroidism, 30%–40% have euthyroidism, and 10% have hyperthyroidism. Therefore, the relationship of HE and thyroid hormone level is considered ambiguous, and it should not be reduced to myxedematous brain damage only [22].

In 2019, we first proposed a synthetic concept of HE pathogenesis (Fig. 1) [23].

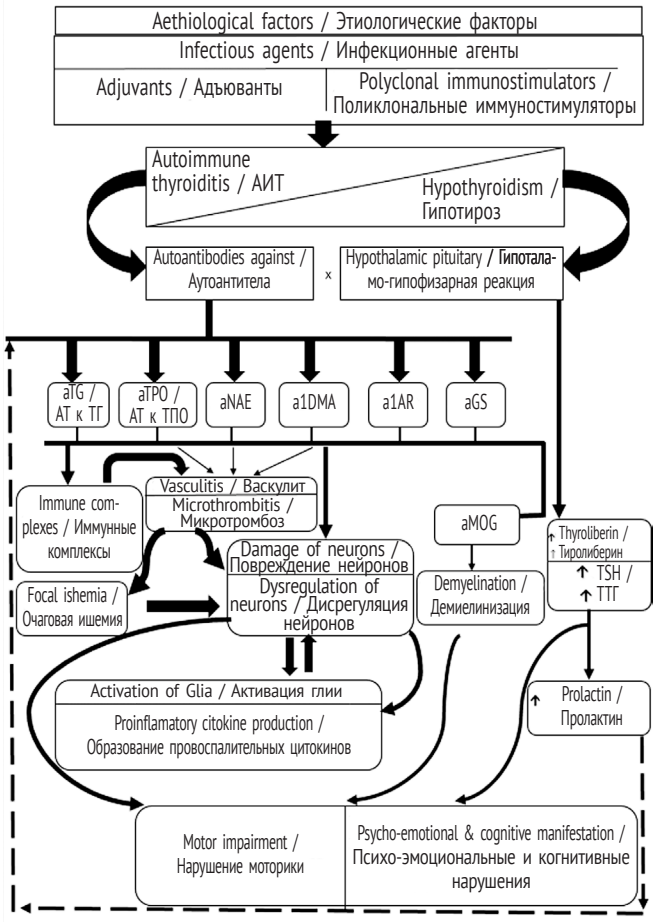

Fig. 1. Scheme of pathogenesis of Hashimoto's encephalopathy. Abbreviations: aTG – autoantibodies against thyroglobulin; aTPO – autoantibodies against thyroid peroxidase; aNAE – autoantibodies against N-terminal peptide of alfa-enolase; a1DMA – autoantibodies against 1-dimethylarginase; a1AR – autoantibodies against 1-aldoreductase; aGS – anti-ganglioside autoantibodies; aMOG – autoantibodies against myelin-oligodendrocyte glycoprotein; TSH – thyroid stimulating hormone

Рис. 1. Схема патогенеза энцефалопатии Хасимото. АИТ — Аутоиммунный тироидит; АТ к ТГ — антитела к тироглобулину; АТ к ТПО — антитела к тиропероксидазе; aNAE — антитела к N-терминальному пептиду альфа-енолазы; a1DMA — антитела к 1-диметиларгиназе; a1AR — антитела к 1-альдоредуктазе; aGS — антиганглиозидные антитела; aMOG — антитела к миелин-олигодендроцитарному гликопротеину; ТТГ — тиротропный гормон

Nowadays, AIT and HE are considered two non-identical nosological entities; in both cases, there is an increase in the level of antithyroid antibodies, but they have different clinical manifestations. However, a fair practical question arises, i.e., should patients with AIT criteria (including diagnostic titers of the corresponding autoantibodies) and various psychiatric diagnoses be treated as having AIT alone, AIT with psychiatric disorder, or as patients with HE? This question is not speculative and is not related only with the perfectionism of the diagnosticians. Modern antipsychotics, having a dopaminolytic effect, aggravate hyperprolactinemia in most cases [16].

At the same time, for AIT, hyperprolactinemia is one of the key pathogenetic links. Therefore, clarification of the origin of psychiatric manifestations for such patients may imply the need for pathogenetic variations in antipsychotic therapy.

MATERIALS AND METHODS

We examined three groups of patients:

• AIT group with psychiatric disorder ($n = 17$), which included 16 women (94.1%) and one man (5.9%), with the average patient age of 50.4 ± 15.5 years.

• AIT group without psychiatric disorder ($n = 21$), which included 19 women (90.5%) and two men (9.5%), with an average age of 51.3 ± 13.7 years.

• Control group of healthy individuals ($n = 20$; in this group, the average age was 42.0 ± 14.9 years, which included 18 women (90%) and two men (10%).

The AIT group with psychiatric disorder included patients with a diagnosis of AIT confirmed by the criteria of the Japanese Thyroidological Association in combination with various psychiatric diagnoses verified in a psychiatric hospital [18]. Schizophrenia was diagnosed in 14 patients (82.4%), Alzheimer's disease was registered in one patient (5.9%), and dementia (5.9%) and obsessive–compulsive disorder (5.9%) were identified with one case each (Fig. 2).

Research methods step by step included the following: history taking; physical examination and blood sampling; ultrasonography (US) of the TG with an assessment of the location, anatomical shape, echogenicity of the parenchyma, echo structure of the parenchyma, TG volume, mass lesions, type of formations (node, cyst), and characteristics of peripheral lymph nodes; and immune enzyme assay for blood serum levels of TSH, FT3, FT4, aTPO, aTG, and prolactin. Studies were performed on an Epoch 2 plate spectrophotometer (BioTek Instruments Inc., USA).

Collected laboratory data (TSH, FT3, FT4, prolactin, aTPO, and aTG levels) were analyzed statistically. Given that the study presented a heterogeneous sample of patients (sex, age, cycle phases, etc.), the use of standard statistical methods for comparing parameters within a group as well as between groups was impossible. Therefore, we applied the method of standardization of parameters, followed by the calculation of the decimal logarithm and the use of a logistic regression model.

RESEARCH RESULTS

In the AIT group, symptoms of neuropsychiatric disorders were assessed regardless of the presence and type of psychiatric diagnosis. In the AIT group without psychiatric disorder, phobias were detected in four (19%) patients and sleep disturbances in the form of hypersomnia were registered in four (19%) patients (Fig. 3).

In the AIT group with psychiatric disorder, the psychiatric symptoms were as follows: delirium

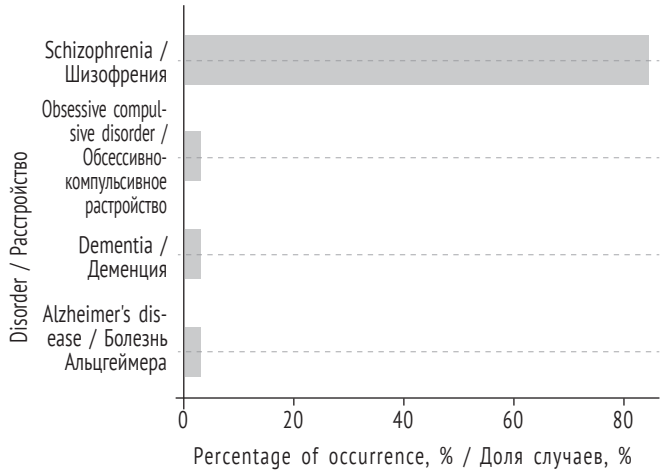

Fig. 2. The structure of psychiatric diagnoses in the autoimmune thyroiditis group in comorbidity with a psychiatric disorder
Рис. 2. Структура психиатрических диагнозов в группе с аутоиммунным тиреоидитом в коморбидности с психиатрическим расстройством

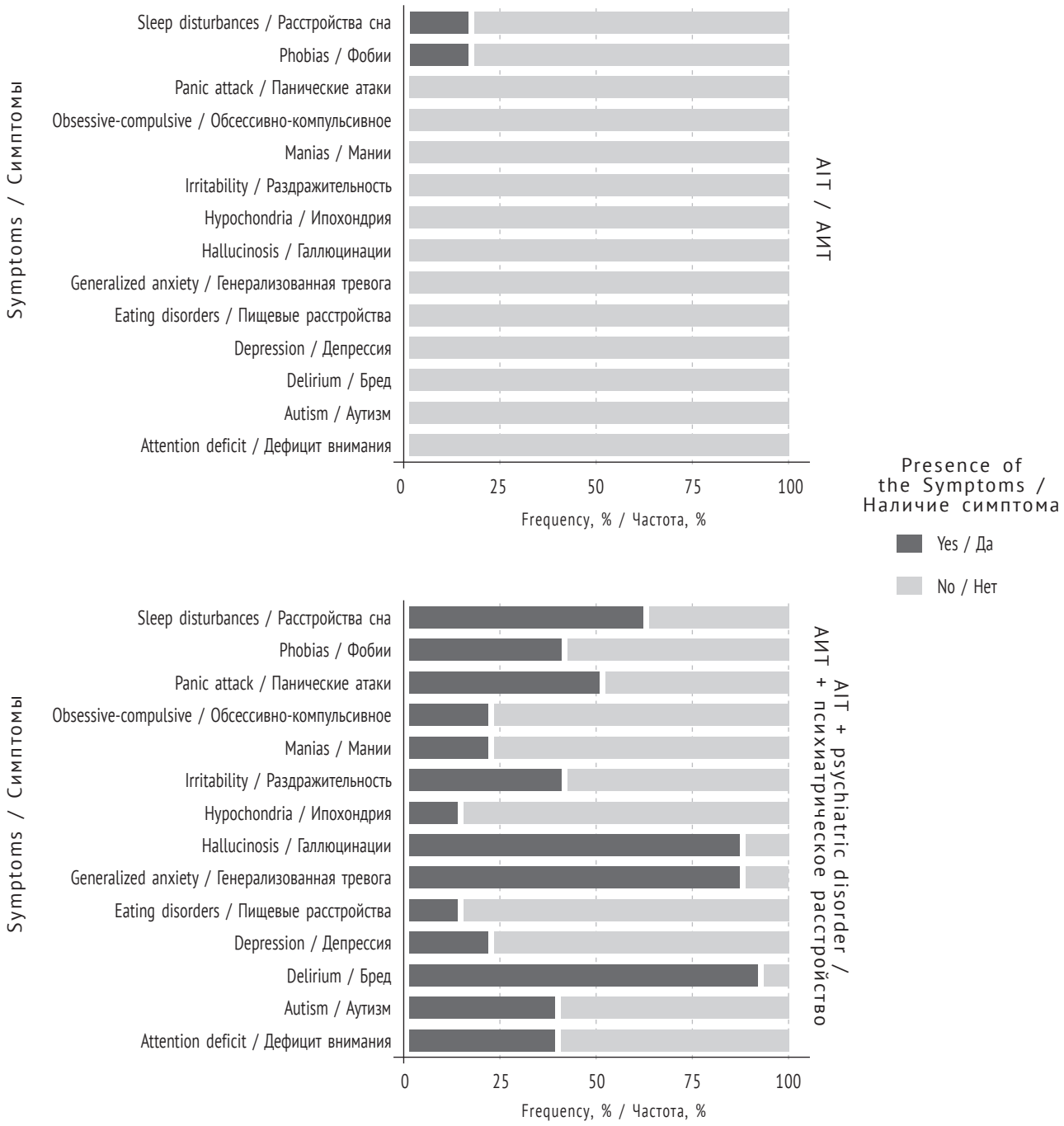

Fig. 3. Structure of psychiatric symptoms in groups of patients with autoimmune thyroiditis (AIT)
Рис. 3. Структура психиатрических симптомов в группах пациентов с аутоиммунным тироидитом (АИТ)

(*n* = 16, (94.1%), hallucinations (*n* = 15, 88.2%), generalized anxiety (*n* = 15, 88.2), panic attacks (*n* = 9, 52.9%), phobias or irritability (*n* = 7, 41.2%), hypochondria (*n* = 2, 11.8%), depression (n = 4, 23.5%), mania (*n* = 4, 23.5%), sleep disturbances as insomnia (*n* = 7 patients, 41.2%) or hypersomnia (*n* = 4, 23.5%), and attention deficit (*n* = 6, 35.3%). Eating disorders were noted in two patients (11.8%) (Fig. 3).

In all patient groups, clinical signs and symptoms of hypothyroidism were assessed. In the AIT group, a positive Stroev's symptom (i.e., habitual biting of the cheeks and tongue) was noted in 9 (42.9%), decreased knee reflexes in 7 (33.3%), brittle nails in 8 (38.1%), dry elbows in 14 (66.7%), positive Chvostek's symptom (i.e., contraction of facial muscles upon tapping on the skin in the area of innervation of the facial nerve)

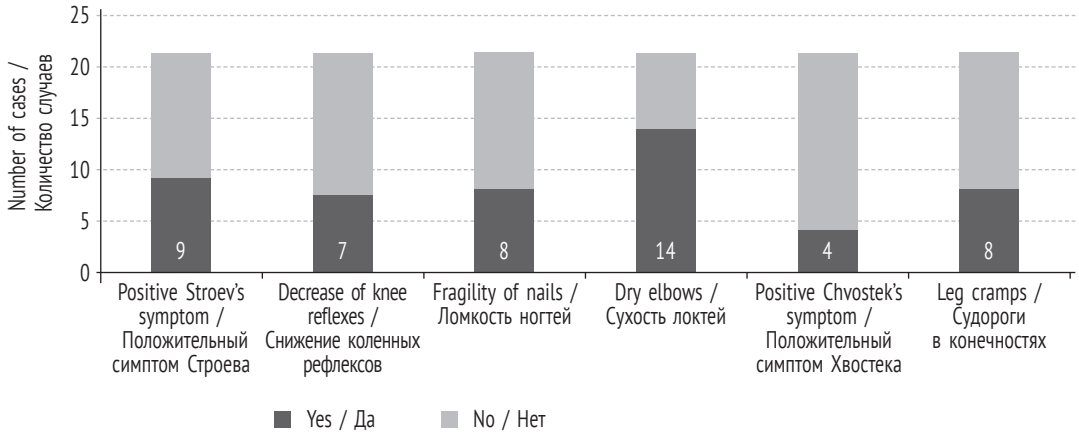

Fig. 4. Structure of psychiatric symptoms in groups of patients with autoimmune thyroiditis
Рис. 4. Структура клинических признаков гипотироза в группе пациентов с аутоиммунным тироидитом

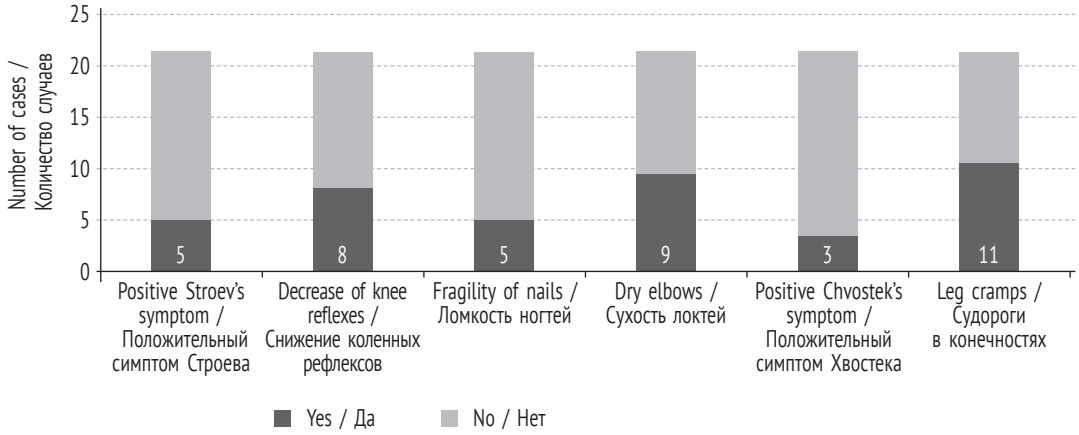

Fig. 5. Structure of psychiatric symptoms in groups of patients with autoimmune thyroiditis and psychiatric disorder
Рис. 5. Структура клинических признаков гипотироза в группе пациентов с аутоиммунным тироидитом в сочетании с психиатрическим расстройством

in 4 (19%), and limb cramps in 8 (38.1%) patients (Fig. 4).

In the AIT group with psychiatric disorder, a positive Stroev's symptom was noted in 5 (29.4%), decreased knee reflexes in 8 (47.1%), brittle nails in 5 (29.4%), dry elbows in 9 (52.9%), positive Chvostek's symptom in 3 (17.6%), and limb cramps in 11 (64.7%) patients (Fig. 5).

In the control group, no clinical signs of hypothyroidism were found. In the AIT group with psychiatric disorder, the average FT3 level was 3.84 ± 0.23 pmol/L, and the FT4 level was 9.8 ± 4.76 pmol/L, which was lower than the reference values of the norm; the average TSH level was 2.54 ± 2.29 mIU/L, the average aTPO level was above the norm (2040.1 ± 4982.5 IU/ml), and the average aTG level was also above the norm (354.3 ± 836.3 IU/mL). The average prolactin level was 1105 ± 734 mIU/L, which exceeded the reference value of the norm (Table 1).

In the AIT group, the average FT3 level was 3.5 ± 0.3 pmol/L, the FT4 level was 12.4 ± 1.8 pmol/L, the average TSH level was 1.3 ± 1 mIU/L, the average aTPO level was above normal at 230 ± 299 IU/ml, the average aTG level was 95.9 ± 163.2 IU/ml, and the average prolactin level was 472 ± 511 mIU/L.

In the control group, the average FT3 level was 4.2 ± 0.8 pmol/L, the FT4 level was 14.1 ± 2.1 pmol/L, the average TSH level was 1.0 ± 0.7 mIU/L, the average aTPO level was 9.4 ± 12.3 IU/ml, and the average aTG level was 21.8 ± 14 IU/ml. The average prolactin level was 461 ± 420 mIU/L. All indicators in this group were within the normal reference values.

Using a logistic regression model, the FT3 level was not beyond the normal values in all three groups of patients, while it was statistically significantly different between the AIT group and the control group ($p < 0.001$) and between the AIT group and the AIT group with psychiatric disorder ($p < 0.001$). No statistically significant difference in this parameter was found between the AIT group with psychiatric disorder and the control group ($p = 0.598$).

Table 1 / Таблица 1

The average levels of laboratory parameters in patients of all clinical groups in comparison with reference values of the norm
Средние уровни лабораторных показателей у пациентов всех клинических групп в сравнении с референсными значениями нормы

Laboratory parameter / Лабораторный показатель	Patients with AIT + psychiatric disorder / Группа пациентов с АИТ + психиатрическое расстройство	Patients with AIT / Группа пациентов с АИТ	Healthy control group / Контрольная группа здоровых лиц	Reference values / Референсные значения нормы
FT3	3.84 ± 0.23	3.5 ± 0.3	4.2 ± 0.8	2.5–5.8 pmol/l / пмоль/л
FT4	9.8 ± 4.76	12.4 ± 1.8	14.1 ± 2.1	10.0–21.0 pmol/l / пмоль/л
TSH / ТТГ	2.54 ± 2.29	1.3 ± 1.0	1.0 ± 0.7	0.3–4.0 mIU/l / мМЕ/л
antiTPO Ab / АТ к ТПО	2040.13 ± 4982.5	230 ± 299	9.4 ± 12.3	<30 IU/ml / МЕ/мл
antiTG Ab / АТ к ТГ	354.32 ± 836.3	95.9 ± 163.2	21.8 ± 14	<100 IU/ml / МЕ/мл
Prolactin / Пролактин	1105 ± 734	472 ± 511	461 ± 420	Men 60–560 mIU/l / Мужчины 60–560 мМЕ/л Women / Женщины Cycle phases / Фазы цикла: Follicular 60–600 mIU/l / Фолликулярная 60–600 мМЕ/л Luteal 120–900 mIU/l / Лютеиновая 120–900 мМЕ/л Menopause 40–550 mIU/l / Менопауза 40–550 мМЕ/л

Note. AIT – autoimmune thyroiditis; TSH – thyroid stimulating hormone; antiTPO Ab – autoantibodies against thyroid peroxidase; antiTG Ab – autoantibodies against thyroglobulin. *Примечание.* АИТ — аутоиммунный тиреоидит; ТТГ — тиротропный гормон; АТ к ТПО — антитела к тиропероксидазе; АТ к ТГ — антитела к тироглобулину.

Moreover, the FT4 level was not beyond the reference intervals of the norm in the AIT group and control group, but was below the norm in the AIT group with psychiatric disorder, while it differed statistically significantly in the AIT group and the control group ($p = 0.048$), as well as in the AIT group and AIT group with psychiatric disorder ($p = 0.048$). Differences in this parameter between the AIT group with psychiatric disorder and the control group ($p < 0.001$) were also verifiable and statistically significant (Fig. 6).

In this study, the TSH level was not beyond the reference intervals of the norm in all three groups, while it differed statistically significantly in the AIT group and the AIT group with psychiatric disorder ($p = 0.030$); its differences were also significant between the AIT group with psychiatric disorder and the control group ($p < 0.001$). No considerable statistically difference was noted between the AIT group and the control group ($p = 0.193$) (Fig. 7).

The prolactin level in the AIT group with psychiatric disorder was higher than the normal level and differed credibly statistically significantly between the AIT group and the AIT group with psychiatric disorder ($p = 0.001$) and between the control group and the AIT group with psychiatric disorder ($p = 0.002$). No statistically significant difference was found in prolactin levels between the AIT group and the control group ($p = 0.997$) (Fig. 7).

In the analysis of aTG and aTPO indicators, the aTG level exceeded the norm in the AIT group with psychiatric disorder; however, no statistically significant difference was found among the clinical groups of patients. In addition, the aTPO level was higher than normal in the AIT group with psychiatric disorder and in the AIT group. A significant statistically significant difference in the latter parameter was observed between the AIT group and control group ($p < 0.001$). No statistically significant difference was noted between the AIT group with psychiatric disorder and

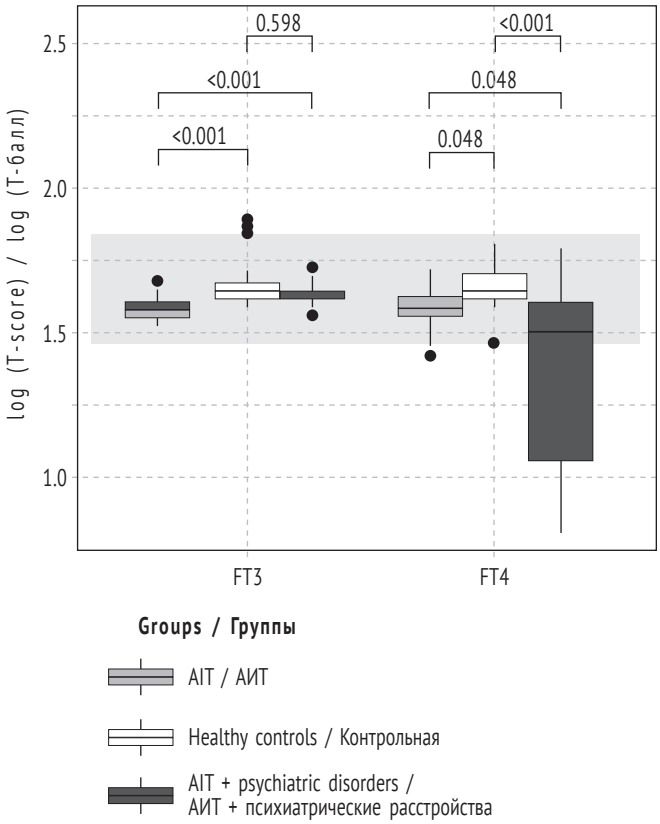

Fig. 6. Laboratory results (FT3 and FT4) using the logistic regression model. AIT – autoimmune thyroiditis

Рис. 6. Результаты лабораторных исследований (FT3 и FT4) с использованием модели логистической регрессии. АИТ — аутоиммунный тироидит

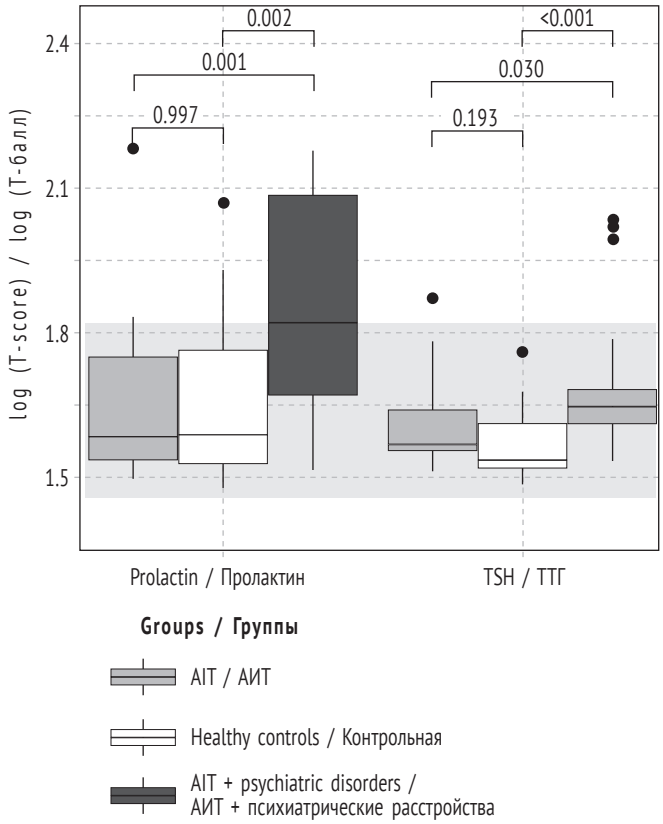

Fig. 7. Results of laboratory tests (prolactin and thyroid stimulating hormone (TSH)) using a logistic regression model

Рис. 7. Результаты лабораторных исследований (пролактин и тиротропный гормон (ТТГ)) с использованием модели логистической регрессии

the AIT group for this parameter ($p = 0.3$), as well as between the AIT group with psychiatric disorder and the control group ($p = 0.164$) (Fig. 8).

TG US data were analyzed. Using a logistic regression model, we revealed that the TG volume exceeded the norm in the AIT group and in the AIT group with psychiatric disorder. The TG volume was statistically significantly greater in the AIT group with psychiatric disorder than in the control group ($p = 0.016$). No statistically significant difference was observed between the AIT group with psychiatric disorder and the AIT group ($p = 0.371$), as well as between the AIT group and the control group ($p = 0.343$) (Fig. 9).

A statistically significant correlation was also found between psychiatric symptoms and the examined immunoendocrine parameters, as well as the symptoms of hypothyroidism and data from laboratory and instrumental studies.

Thus, the FT4 level was statistically significantly lower in patients with phobias, irritability, and attention deficit than in patients without these symptoms ($p < 0.05$) (Fig. 10). The TSH level was statistically significantly higher in patients with delirium and generalized anxiety than in patients without these symptoms ($p < 0.05$) (Fig. 10). The prolactin level was statistically significantly higher in patients experiencing panic attacks, delirium, and generalized anxiety than in patients without these symptoms ($p < 0.05$) (Fig. 10). The TG volume was statistically significantly higher in patients with delirium, generalized anxiety, and attention deficit (Figs. 9 and 10).

The FT3 level was statistically significantly lower in patients with dry elbows than in those without this symptom ($p < 0.05$). The level of antibodies to TG was statistically significantly higher in patients with reduced knee reflexes ($p < 0.05$). The aTPO level was statistically significantly higher in patients with dry elbows, reduced knee reflexes, and increased TG volume than in patients without these signs ($p < 0.05$) (Fig. 11).

Moreover, a statistically significant verifiable relationship was found between the aTPO level and the TG volume ($p < 0.05$) (Fig. 12).

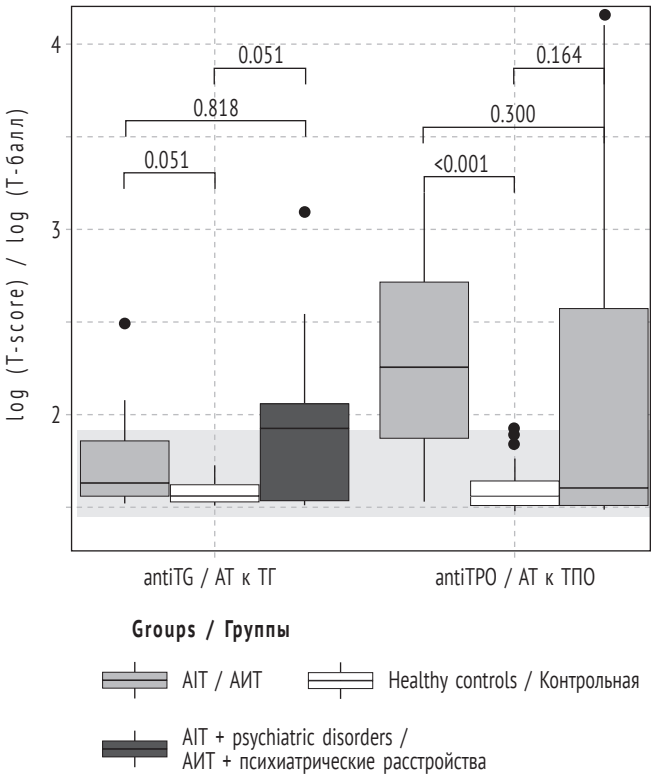

Fig. 8. Results of laboratory tests using the logistic regression model. AIT – autoimmune thyroiditis; antiTG – autoantibodies to thyroglobulin; antiTPO – autoantibodies to thyroid peroxidase

Рис. 8. Результаты лабораторных исследований с использованием модели логистической регрессии. АИТ — аутоиммунный тиреоидит; АТ к ТГ — антитела к тиреоглобулину; АТ к ТПО — антитела к тиропероксидазе

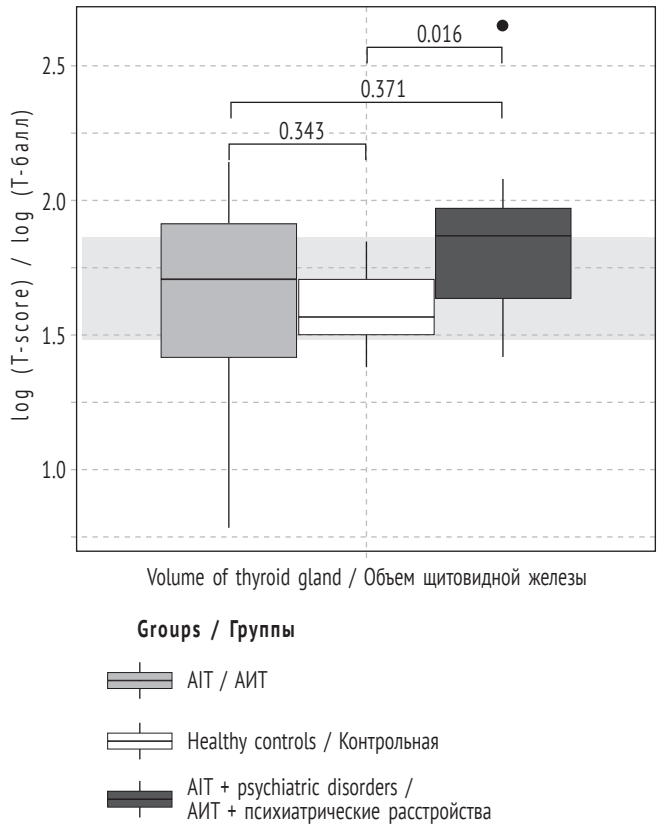

Fig. 9. Comparative analysis of thyroid volume according to the results of ultrasound using a model of logistic regression

Рис. 9. Сравнительный анализ объема щитовидной железы по результатам ультразвукового исследования с использованием модели логистической регрессии

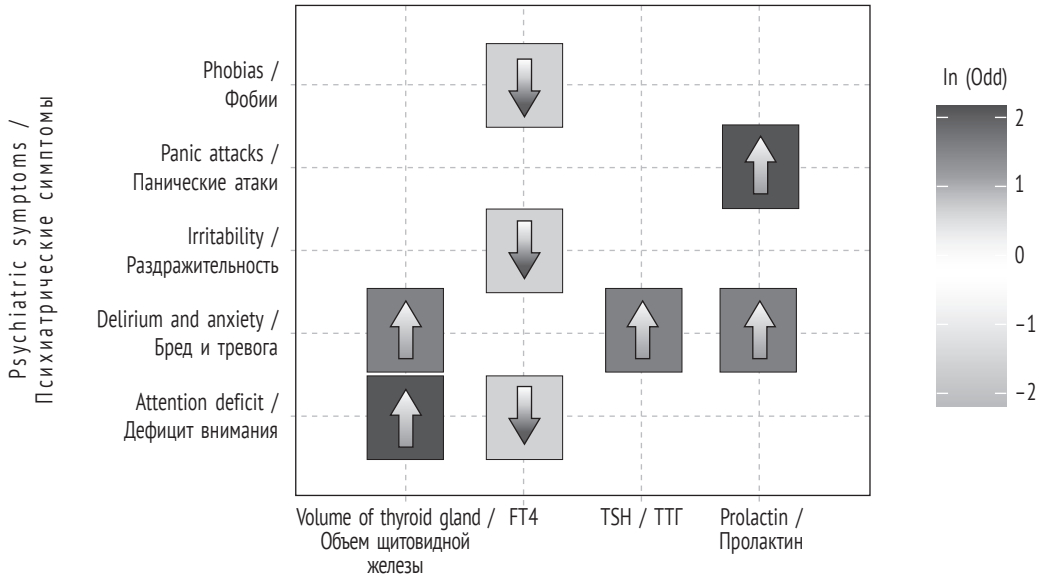

Fig. 10. Statistically significant associations between psychiatric symptoms and laboratory instrumental data. TSH – thyroid stimulating hormone

Рис. 10. Статистически значимые связи между психиатрическими симптомами и данными лабораторно-инструментальных исследований. ТТГ — тиротропный гормон

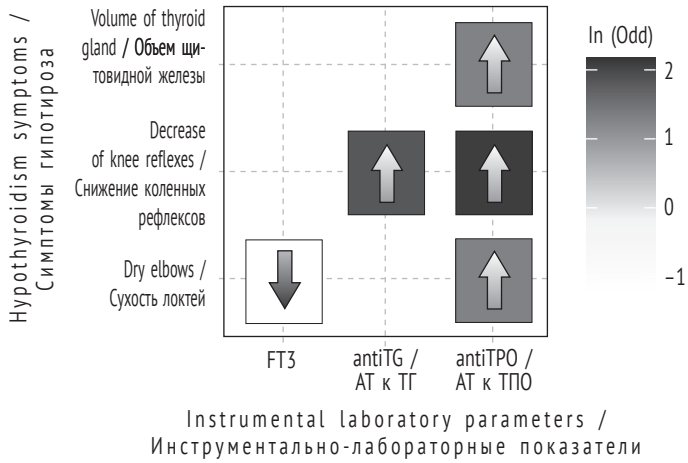

Fig. 11. Statistically significant relationships between symptoms of hypothyroidism and laboratory instrumental findings. antiTG – autoantibodies to thyroglobulin; antiTPO – autoantibodies to thyroid peroxidase

Рис. 11. Статистически значимые связи между симптомами гипотироза и данными лабораторно-инструментальных исследований. АТ к ТГ — антитела к тироглобулину; АТ к ТПО — антитела к тиропероксидазе

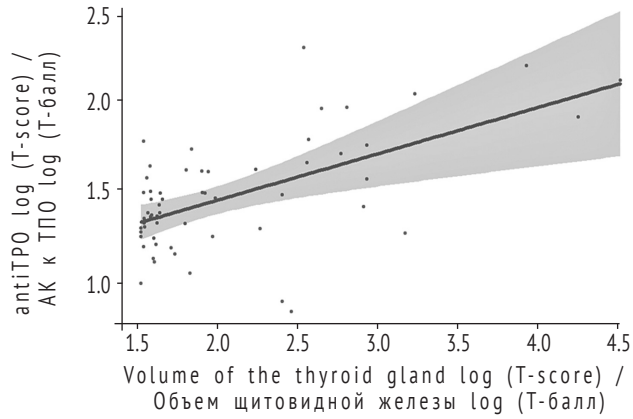

Fig. 12. The correlation between antiTPO level and thyroid gland volume

Рис. 12. Связь между уровнем антител к тиропероксидазе (АТ к ТПО) и объемом щитовидной железы

DISCUSSION

AIT can occur with various neuropsychiatric disorders; however, in our study, in patients with AIT and comorbid mental disorders, a schizophrenic-like clinical manifestation prevailed. At the same time, HE initially manifests as neuropsychiatric disorders. Thus, the following question arises: should patients with increased levels of antithyroid antibodies and other AIT criteria, and different verified psychiatric disorders, be considered patients with AIT and comorbid psychiatric disorder or as patients with HE? As regards to the diagnostic difficulties, HE does not have specific clinical signs or generally recognized laboratory markers [23]. AIT with hypothyroidism does not have clinical manifestations that would be incompatible with the diagnosis of HE. The obtained data so far do not enable drawing an unambiguous conclusion of any of the interpretations, but it is necessary to establish the mechanistic role of the same factors in the pathogenesis of both AIT and HE.

According to the well-known principle of Hans Selye, diseases are interesting for the clinician, that is, in the way they differ from each other, but for the pathologist, they are interesting in a way that they are similar to each other [4].

This study is pathophysiologically significant due to the demonstration of immunoendocrine aspects that correlate with psychiatric disorders in AIT. The study demonstrated that a number of hormonal parameters (such as prolactin, TSH, and FT4 levels) correlate with the presence of psychiatric disorders in AIT. The literature presents data on hyperprolactinemia in untreated schizophrenia in both sexes [17, 27]. Polish scientists have established a link between TSH levels and psy-

chotic disorders [31]. Findings of the influence of FT4 on bioelectric processes, neurogenesis, and neuronal plasticity of the brain have been published [12].

All this is consistent with our data and raises the question of the intrinsic effects of the dysfunction of these endocrine parameters in psychotic disorders. Moreover, we did not establish a correlation between mental disorders and titers of autoantibodies to thyroid antigens, although this was previously reported by Japanese scientists [30, 32]. The results indicate that further research is required to explore the immunoendocrine basis of cerebral dysfunctions in AIT.

CONCLUSIONS

1. A significant relationship ($p < 0.05$) was found between a number of immunoendocrine parameters and some psychiatric symptoms, namely, between a decreased FT4 level and presence of psychiatric symptoms such as phobias, irritability, attention deficit; between elevated TSH levels and symptoms such as delirium and generalized anxiety; and between increased prolactin levels and psychiatric symptoms such as panic attacks, delirium, and generalized anxiety.

2. A significant relationship ($p < 0.05$) was established between psychiatric symptoms (such as delirium, generalized anxiety, and attention deficit) and an enlarged TG.

3. A significant relationship ($p < 0.05$) was noted between the symptoms of hypothyroidism and laboratory parameters, that is, between a decreased FT3 level and dry elbows, between an increased aTG level and a decrease in knee reflexes, and between an increased aTPO level and symptoms of hypothyroidism such as decreased knee reflexes and dry elbows.

4. A significant relationship ($p < 0.05$) was established between an enlarged TG and an increased aTPO level.

The study was performed in accordance with the Decree of the Government of the Russian Federation No. 220 and agreement 14.W03.31.0009 on the allocation of a grant from the Government of the Russian Federation for state support of scientific research conducted under the guidance of leading scientists. This study also presents results of scientific research of the Laboratory of the Mosaic of Autoimmunity of St. Petersburg State University, obtained using the resource center for the development of molecular and cellular technologies in the St. Petersburg State University Science Park.

REFERENCES

1. Аметов А.С. Избранные лекции по эндокринологии. – М.: МИА, 2011. – 541 с. [Ametov AS. Izbrannye lektsii po ehndokrinologii. Moscow: MIA; 2011. 541 p. (In Russ.)]
2. Антонова К.В. Психические расстройства в клинике эндокринных заболеваний // Русский медицинский журнал. – 2006. – Т. 14. – № 26. – С. 1889. [Antonova KV. Mental disorders in the clinic of endocrine diseases. *Russian medical journal*. 2006;14(26):1889. (In Russ.)]
3. Белкин А.И. Психические нарушения при заболеваниях щитовидной железы (клиника, патогенез, лечение): Автореф. дис. ... докт. мед. наук. – М., 1968. – 43 с. [Belkin AI. Mental disorders in diseases of the thyroid gland (clinic, pathogenesis, treatment). [dissertation abstract] Moscow; 1968. 43 p. (In Russ.)]
4. Гусова А.Б., Кашинский А.А. Энцефалопатия Хашимото — аутоиммунное заболевание головного мозга. – Харьков: ФЛП Кудлай В.В.; 2013. – 232 с. [Gusova AB, Kashinskiy AA. Ehntsefalopatiya Khashimoto – autoimmunnoe zabolevanie golovnogo mozga. Khar'kov: FLP Kudlay VV; 2013. 232 p. (In Russ.)]
5. Добржанская А.К. Психические и нейрофизиологические нарушения при эндокринных заболеваниях. – М.: Медицина, 1973. – 191 с. [Dobrzhanskaya AK. Psikhicheskie i neirofiziologicheskie narusheniya pri ehndokrinnykh zabolevaniyakh. Moscow: Meditsina; 1973. 191 p. (In Russ.)]
6. Дорофейкова М.В., Калашникова А.В., Строев Ю.И., Чурилов Л.П. Энцефалопатия Хасимото — клинические данные, механизмы развития // Труды Мариинской больницы. – 2012. – № 9. – С. 97–101. [Dorofeykova MV, Kalashnikova AV, Stroev YuI, Churilov LP. Ehntsefalopatiya Khasimoto – klinicheskie dannye, mekhanizmy razvitiya. *Trudy Mariinskoy bol'nitsy*. 2012;(9):97–101. (In Russ.)]
7. Селье Г. От мечты к открытию: как стать ученым / Пер. с англ. Н.И. Войскунской под ред. М.Н. Кондрашовой, И.С. Хорола. – М.: Прогресс, 1987. – 366 с. [Selye H. From dream to discovery: how to become a scientist. Translated from English N.I. Voiskunsaya ed. by M.N. Kondrashova, I.S. Khorol. Moscow: Progress; 1987. 366 p. (In Russ.)]
8. Строев Ю.И., Фесенко Ю.А., Чурилов Л.П., Даниленко О.В. Гормонально-метаболические детерминанты человеческого поведения: стресс и психоневрологические нарушения // Уральский журнал психиатрии, наркологии и психотерапии. – 2014. – № 3. – С. 30–42. [Stroev YuI, Fesenko YuA, Churilov LP, Danilenko OV. Gormonal'no-metabolicheskie determinanty chelovecheskogo povedeniya: stress i psikhonevrologicheskie narusheniya. *Ural'skiy zhurnal psikhiatrii, narkologii i psikhoterapii*. 2014;(3):30–42. (In Russ.)]

9. Строев Ю.И., Чурилов Л.П. Эндокринология подростков. – СПб.: ЭЛБИ, 2004. – 384 с. [Stroev YuI, Churilov LP. Ehndokrinologiya podrostkov. Saint Petersburg: ELBI; 2004. 384 c. (In Russ.)]
10. Строев Ю.И., Чурилов Л.П. Аутоиммунный тиреоидит Хасимото, его последствия и коморбидность // Руководство по аутоиммунным заболеваниям для врачей общей практики / Под ред. И. Шенфельда, П.Л. Мерони, Л.П. Чурилова. – СПб.: ЭЛБИ-Медкнига, 2017. – С. 298–325. [Stroev YuI, Churilov LP. Autoimmunnyi tireoidit Hashimoto, ego posledstviya i komorbidnost'. In: Rukovodstvo po autoimmunnym zabolevaniyam dlya vrachei obshchei praktiki. Ed. by I. Shenfel'd, P.L. Meroni, L.P. Churilov. Saint Petersburg: ELBI–Medkniga; 2017. P. 298-325. (In Russ.)]
11. Строев Ю.И., Чурилов Л.П. Гипокальциемия и фобии в клинической картине аутоиммунного тиреоидита // Сибирский медицинский журнал (г. Томск). – 2011. – Т. 26. – № S1. – С. 239–240. [Stroev YuI, Churilov LP. Gipokal'tsiemiya i fobii v klinicheskoi kartine autoimmunnogo tireoidita. *The Siberian medical journal (Tomsk)*. 2011;26(S1):239-240. (In Russ.)]
12. Строев Ю.И., Чурилов Л.П. Самый тяжелый элемент жизни (к 200-летию открытия йода) // Биосфера. – 2012. – Т. 4. – № 3. – С. 313–342. [Stroev YuI, Churilov LP. The heaviest bioelement (on the 200th anniversary of the discovery of iodine). *Biosphere*. 2012;4(3):313-342. (In Russ.)]
13. Строев Ю.И., Чурилов Л.П. Случай бесплодного брака, связанный с аутоиммунным тиреоидитом и клинически бессимптомной макроаденомой гипофиза (пролактиномой) // Клиническая патофизиология. – 2016. – Т. 22. – № 1. – С. 72–79. [Stroev YuI, Churilov LP. A case of infertile marrige related to autoimmune thyroiditis and clinically latent pituitary macroadenoma (prolactinoma). *Clinical pathophysiology*. 2016;22(1):72–79. (In Russ.)]
14. Строев Ю.И., Чурилов Л.П., Калашникова А.В. Психиатрические маски гипотироза // Сибирский медицинский журнал (Томск). — 2011. — Т. 26. — № S1. — С. 240. [Stroev YuI, Churilov LP, Kalashnikova AV. Psychiatric masks of hypothyroidism. *Sibirskiy meditsinskiy zhurnal (Tomsk)*. 2011; 26(Suppl. 1):240. (In Russ.)]
15. Целибеев Б.А. Психические нарушения при эндокринных заболеваниях. – М.: Медицина, 1966. – 206 p. [Tselibeev BA. Psikhicheskie narusheniya pri ehndokrinnykh zabolevaniyakh. Moscow: Meditsina; 1966. 206 p. (In Russ.)]
16. Юнилайнен О.А., Доровских И.В. Гиперпролактинемия, ассоциированная с приемом нейролептиков // Социальная и клиническая психиатрия. – 2013. – Т. 23. – № 1. – С. 100–106. [Yunilainen OA, Dorovskikh IV. Hyperprolactinemia caused by the use of neuroleptics. *Social and clinical psychiatry*. 2013;23(1):100-106. (In Russ.)]
17. Albayrak Y, Beyazyüz M, Beyazyüz E, Kuloğlu M. Increased serum prolactin levels in drug-naive first-episode male patients with schizophrenia. *Nord J Psychiatry*. 2014;68(5):341-346. https://doi.org/10.3109/08039488.2013.839739.
18. Asher R. Myxoedematous madness. *Br Med J*. 1949;2(4627):555-562. https://doi.org/10.1136/bmj.2.4627.555.
19. Brain L, Jellinek E, Ball K. Hashimoto's disease and encephalopathy. *Lancet*. 1966;2(7462):512-514. https://doi.org/10.1016/s0140-6736(66)92876-5.
20. Canton A, de Fabregas O, Tintore M. Encephalopathy associated to autoimmune thyroid disease: a more appropriate term for an underestimated condition? *J Neurol Sci*. 2000;176(1):65-69. https://doi.org/10.1016/s0022-510x(00)00302-6.
21. Castillo P, Woodruff B, Caselli R, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol*. 2006;63(2):197-202. doi: 10.1001/archneur.63.2.197.
22. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? *Arch Neurol*. 2003;60(2):164-171. https://doi.org/10.1001/archneur.60.2.164.
23. Churilov LP, Sobolevskaia PA, Stroev YI. Thyroid gland and brain: enigma of hashimoto's encephalopathy. *Best Pract Res Clin Endocrinol Metab*. 2019;33(6):101364. https://doi.org/10.1016/j.beem.2019.101364.
24. Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. *J Neurol Sci*. 2004;217(2):165-168. https://doi.org/10.1016/j.jns.2003.09.007.
25. Marshall GA, Doyle JJ. Long-term treatment of Hashimoto's encephalopathy. *J Neuropsychiatry Clin Neurosci*. 2006;18(1):14-20. https://doi.org/10.1176/jnp.18.1.14.
26. Matsunaga A, Yoneda M. [Anti-NAE autoantibodies and clinical spectrum in Hashimoto's ence-

phalopathy. (In Japanes)]. *Rinsho Byori*. 2009;57(3):271-278.
27. Petrikis P, Tigas S, Tzallas AT, et al. Prolactin levels in drug-naive patients with schizophrenia and other psychotic disorders. *Int J Psychiatry Clin Pract*. 2016;20(3):165-169. https://doi.org/10.1080/13651501.2016.1197274.
28. Snyder PJ, Jacobs LS, Utiger RD, Daughaday WH. Thyroid hormone inhibition of the prolactin response to thyrotropin-releasing hormone. *J Clin Invest*. 1973;52(9):2324-2329. https://doi.org/10.1172/JCI107421.
29. Tan ZS, Vasan RS. Thyroid function and Alzheimer's disease. *J Alzheimer's Dis*. 2009;16(3):503-507. https://doi.org/10.3233/JAD-2009-0991.
30. Uchida Y, Kato D, Adachi K, et al. Passively acquired thyroid autoantibodies from intravenous immunoglobulin in autoimmune encephalitis: Two case reports. *J Neurol Sci*. 2017;383:116-117. https://doi.org/10.1016/j.jns.2017.11.002.
31. Wysokiński A, Kłoszewska I. Level of thyroid-stimulating hormone (TSH) in patients with acute schizophrenia, unipolar depression or bipolar disorder. *Neurochem Res*. 2014;39(7):1245-1253. https://doi.org/10.1007/s11064-014-1305-3.
32. Yoneda M, Fujii A, Ito A, et al. High prevalence of serum autoantibodies against the amino terminal of alpha-enolase in Hashimoto's encephalopathy. *J Neuroimmunol*. 2007;185(1-2):195-200. https://doi.org/10.1016/j.jneuroim.2007.01.018.

◆ Information about the authors

Polina A. Sobolevskaia — Researcher, Laboratory of the Mosaic of Autoimmunity, Saint Petersburg State University, Saint Petersburg, Russia. E-mail: dr.polinasobolevskaia@bk.ru.

Boris V. Andreev — MD, PhD, Dr Med Sci, Professor, P.P. Kaschenko 1st City Mental Hospital, Nikolskoe, Leningrad Region, Russia. E-mail: bandreev1947@list.ru.

Anton N. Gvozdetckii — Graduate Student, Saint Petersburg State University, Saint Petersburg, Russia. E-mail: comisora@yandex.ru.

Anastasia A. Dolina — Student, Research Assistant, Laboratory of the Mosaic of Autoimmunity, Saint Petersburg State University, Saint Petersburg, Russia. E-mail: dolinanast.357@mail.ru.

Anna M. Stepochkina — Student, Research Assistant, Laboratory of the Mosaic of Autoimmunity, Saint Petersburg State University, Saint Petersburg, Russia; Senior research assistant, Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences, Saint Petersburg, Russia. E-mail: annastepochkina23.11@mail.ru.

Yurii I. Stroev — MD, PhD, Professor, Saint Petersburg State University, Saint Petersburg, Russia. E-mail: svetlanastroeva@mail.ru.

Vladimir J. Utekhin — MD, PhD, Associate Professor, Saint Petersburg State University, Saint Petersburg, Russia; Associate Professor, St. Petersburg State Pediatric Medical University of the Ministry of Health of the Russian Federation, Saint Petersburg, Russia. E-mail: utekhin44@mail.ru.

◆ Информация об авторах

Полина Анатольевна Соболевская — научный сотрудник, лаборатория мозаики аутоиммунитета. ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург. E-mail: dr.polinasobolevskaia@bk.ru.

Борис Владимирович Андреев — д-р мед. наук, профессор, СПбГБУ «Психиатрическая больница № 1 им. П.П. Кащенко», Ленинградская область, с. Никольское. E-mail: bandreev1947@list.ru.

Антон Николаевич Гвоздецкий — аспирант, ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург. E-mail: comisora@yandex.ru.

Анастасия Александровна Долина — студентка, лаборант-исследователь, лаборатория мозаики аутоиммунитета, ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург. E-mail: dolinanast.357@mail.ru.

Анна Михайловна Степочкина — студентка, лаборант-исследователь, лаборатория мозаики аутоиммунитета, ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург; старший лаборант-исследователь, ИЭФБ РАН «Институт эволюционной физиологии и биохимии им. И.М. Сеченова» Российской академии наук, Санкт-Петербург. E-mail: annastepochkina23.11@mail.ru.

Юрий Иванович Строев — канд. мед. наук, профессор. ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург. E-mail: svetlanastroeva@mail.ru.

Владимир Иосифович Утехин — канд. мед. наук, доцент, ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург; доцент, ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: utekhin44@mail.ru.

◆ Информация об авторах

Tamara V. Fedotkina — PhD, Leading Researcher, Saint Petersburg State University, Saint Petersburg, Russia; PhD, Associate Professor, Department of Histology and Embryology, St. Petersburg State Pediatric Medical University Ministry of Health of the Russian Federation, Saint Petersburg, Russia. E-mail: t.v.fedotkina@gmail.com.

Leonid P. Churilov — MD, PhD, Associate Professor, Head of the Department of Pathology, Deputy Head of Laboratory of the Mosaic of Autoimmunity, Saint Petersburg State University, Saint Petersburg, Russia; Leading Researcher, St. Petersburg State Research Institute of Phthisiopulmonology of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: elpach@mail.ru.

◆ Information about the authors

Тамара Викторовна Федоткина — канд. биол. наук, ведущий научный сотрудник, ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург; доцент, кафедра гистологии и эмбриологии, ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: t.v.fedotkina@gmail.com.

Леонид Павлович Чурилов — канд. мед. наук, доцент, заведующий кафедрой патологии, зам. руководителя лаборатории мозаики аутоиммунитета, ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург; ведущий научный сотрудник, ФГБУ «Санкт-Петербургский научно-исследовательский институт фтизиопульмонологии» Минздрава России, Санкт-Петербург. E-mail: elpach@mail.ru.