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The impact of the hypothalamic-pituitary-thyroid axis hormone levels on suicide risk in patients with schizophrenia

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ABSTRACT

Aim. To assess the impact of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) concentrations in the blood serum of patients with schizophrenia with suicide risk.

Materials and methods. A total of 120 patients with schizophrenia (75 women and 45 men) were examined. Suicide risk was assessed using the Beck Hopelessness Scale (BHS). Serum levels of FT3, FT4, and TSH in patients with schizophrenia were determined using enzyme immunoassay kits. Multiple linear regression analysis and one-way analysis of variance (ANOVA) were used to identify the relationships between the studied indicators.

Results. Among 120 patients with schizophrenia, 11 patients (9.2%) had elevated serum TSH values (> 4.0 mU / l), 108 (90%) had decreased FT3 levels, (< 4.0 pmol / l), 42 (35%) had decreased FT4 levels (< 10.3 pmol / l). The study revealed statistically significant differences in the level of hopelessness between the groups of patients with normal and elevated TSH ($F(1.118) = 5.160$, $p = 0.025$), as well as with normal and decreased FT3 ($F(1.118) = 4.568$, $p = 0.035$).

Conclusion. It was found that TSH and FT3 concentrations in blood serum significantly affect the level of hopelessness assessed using the Beck scale in patients with schizophrenia. The results of this study confirm the need for regular dynamic monitoring of hormone levels of the hypothalamic–pituitary–thyroid axis in patients with schizophrenia in order to maintain its normal functioning, as well as prevent adverse effects in the form of suicide attempts and suicide.

Keywords: schizophrenia, thyroid hormones, TSH, hopelessness, suicide risk

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Влияние уровней гормонов гипоталамо-гипофизарно-тиреоидной оси на суицидальный риск у пациентов с шизофренией

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РЕЗЮМЕ

Цель. Оценить влияние уровней тиреотропного гормона (ТТГ), свободного трийодтиронина (T_3св.) и свободного тироксина (T_4св.) в сыворотке крови пациентов с шизофренией с суицидальным риском.

Материалы и методы. Обследовано 120 больных (75 женщин и 45 мужчин). Суицидальный риск оценивался по шкале безнадежности Бека (Beck Hopelessness Scale, BHS). Уровни T_3св., T_4св. и ТТГ в сыворотке крови у пациентов определяли с помощью наборов для иммуноферментного анализа. Для выявления связей между исследуемыми показателями использовался множественный линейный регрессионный анализ и однофакторный дисперсионный анализ (ANOVA).

Результаты. Среди 120 пациентов с шизофренией у 11 (9,2%) были выявлены повышенные значения ТТГ в сыворотке крови (>4,0 мМЕ/л), у 108 (90%) снижены показатели T_3св. (<4,0 пкмоль/л), у 42 (35%) – снижены показатели T_4св. (<10,3 пкмоль/л). Обнаружены статистически значимые различия уровня безнадежности между группами пациентов с нормальным и повышенным показателем ТТГ ($F(1,118) = 5,160$, $p = 0,025$), а также с нормальным и сниженным показателем T_3 св. ($F(1,118) = 4,568$, $p = 0,035$).

Заключение. Установлено, что на уровень безнадежности по шкале Бека у больных шизофренией оказывают значимое влияние показатели ТТГ и T_3св. в сыворотке крови. Результаты данного исследования подтверждают необходимость регулярного динамического мониторинга показателей гормонов гипоталамо-гипофизарно-тиреоидной оси у пациентов с шизофренией с целью сохранения ее нормального функционирования, а также предотвращения неблагоприятных последствий в виде суицидальных попыток и суицидов.

Ключевые слова: шизофрения, тиреоидные гормоны, ТТГ, безнадежность, суицидальный риск

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Schizophrenia is a severe mental disorder that often begins with a catastrophe experienced by the patient. It usually has a chronic course, is accompanied by anhedonia, leads to disability and a significant decrease in the duration and quality of patient life [1, 2]. The comorbid somatic-symptom disorder (cardiovascular diseases, obesity, diabetes mellitus, etc.) and suicide are the main causes of early mortality and reduce the life expectancy of patients with schizophrenia by an average of 10 years [3, 4]. Despite the fact that the pathophysiological mechanisms of schizophrenia are still poorly understood, studies have shown that neuroendocrine disorders can play an important role in its development, determine its course, clinical manifestations, as well as in the occurrence of concomitant pathology, complications, and adverse effects of antipsychotics [5–7].

The functional state of the hypothalamic–pituitary–thyroid axis is of great importance for the development and normal functioning of the brain [6]. Previous studies have shown a connection between fluctuations in thyroid hormone levels and various manifestations of mental disorders and response to therapy [5–9]. Our recent studies revealed a significant decrease in serum levels of thyroid hormones and thyroid-stimulating hormone (TSH) in patients with schizophrenia compared to healthy individuals [7, 10].

The role of various thyroid conditions in the formation of psychopathological symptoms as part of schizophrenia has already been reflected in the literature [6, 7, 10, 11]. This fact once again emphasizes the multifactorial nature of not only the disorder itself, but also the leading symptoms in the clinical pattern. Thus, the predictive role of thyroid hormones and TSH in relation to the schizophrenia prognosis is now obvious. For example, there is a strong negative correlation between negative symptoms that have an unfavorable course and the TSH level [12]. In addition, changes in the thyroid hormone level are associated with antipsychotic treatment, in which subclinical hypothyroidism often develops [13]. However, the role of the hypothalamic–pituitary–thyroid axis in the development of suicidal behavior in patients with schizophrenia remains poorly understood, and the available data are ambiguous.

For example, it was found that individuals with and without a history of suicide attempts differed only in the level of free triiodothyronine (FT3) [14]. Moreover, patients with a history of suicide attempts were more likely to have low levels of free T3 [14]. Another study showed that suicidal thoughts were more common in patients with schizophrenia only with higher levels of free thyroxine (free T4) [11]. It is also assumed that low TSH levels may be associated with a predisposition to depression and suicidal behavior [15, 16]. This led us to the hypothesis of a "pessimistic" relationship between TSH, thyroid hormones, schizophrenia, and suicide risk.

The aim of the study was to evaluate the TSH, free T3, and free T4 concentrations in the blood serum of patients with schizophrenia at a risk of suicide.

MATERIALS AND METHODS

The study was conducted according to the protocol approved by the local Bioethics Committee at the Mental Health Research Institute of Tomsk National Research Medical Center (Protocol No. 147 of 22.11.2021). During the study, we examined 120 patients with schizophrenia (75 (62.5%) women and 45 (37.5%) men, F20.0 according to ICD-10) aged 43 [36; 52] years and with a disease duration of 15 [9; 23] years, who were treated at the clinic of the Mental Health Research Institute. The inclusion criteria for this study were as follows: age 18–55 years, confirmed diagnosis of schizophrenia according to ICD-10 criteria, signed voluntary consent to participate in the study. The exclusion criteria were the following: clinically evident dependence on psychoactive substances except for tobacco, mental retardation or dementia, no known neurological disorders (brain injury, stroke), thyroid disease, hormone replacement therapy.

At the beginning of the study, all patients received basic therapy, 95 (79.2%) of them were receiving first-generation antipsychotics: haloperidol, zuclopenthixol, chlorpromazine, chlorprothixene, 25 (20.8%) – second-generation antipsychotics: quetiapine, clozapine, olanzapine, risperidone in therapeutic doses approved by the Russian Ministry of Healthcare, which were recalculated to chlorpromazine equivalent (CPZeq). This recalculation made it possible to calculate the median of the total antipsychotic load, which ultimately amounted to 482.5 [271; 758.5] mg/day, while the duration of therapy was 11 [5; 19] years.

Individual registration cards were filled out for all patients included in the study. The card included

general information, a set of sociodemographic, clinical, and therapeutic characteristics, as well as psychometric examination data. An objective assessment of the severity of psychopathological manifestations was performed using the Positive and Negative Syndrome Scale (PANSS) [17] in the adapted Russian version – SCI-PANSS [18]. The total PANSS score for the entire sample was 107 [96; 116], the severity of positive symptoms was 25 [22; 28] points vs. 24 [22; 29] negative with general psychopathological symptoms – 56 [51; 61]. Suicide risk was assessed using the Beck Hopelessness Scale (BHS) [19], which measures the severity of negative attitude towards one's own perceived future and makes it possible to indirectly determine suicide risk [20]. Studies using this scale have shown that it can be used to assess suicide risk [21], including in patients with schizophrenia [22].

Blood was collected from fasting patients in the morning from the cubital vein into Vacuette vacuteiner tubes, and the blood serum was obtained by centrifugation at 2,000 rpm for 30 minutes. Concentrations of TSH, FT3, and FT4 in the blood serum were determined by solid-phase enzyme immunoassay using Vector-Best reagent kits (Novosibirsk, Russia). In accordance with the manual of the kits, the reference intervals for FT3, FT4, and TSH in the blood serum were 4.0–8.6 pmol / l, 10.3–24.5 pmol / l, and 0.4–4.0 mU / l, respectively.

The statistical analysis was performed using the Statistica 12.0 software package (Dell). The Shapiro–Wilk test was used to check for the normality of the data sample. It showed that all the data we obtained did not fit the normal distribution. Therefore, the quantitative data are presented as the median (*Me*) of the lower and upper quartiles [Q_1; Q_3]. Qualitative data are presented as frequency indicators in absolute (*n*) and relative units (%). Multiple linear regression analysis and one-way analysis of variance (ANOVA) were used to identify the relationships between the studied indicators. The results were considered statistically significant at $p = 0.05$.

RESULTS

Using multiple linear regression, we verified the effect of each hormone on the level of hopelessness in patients (Table). It turned out that the model obtained during the calculations was statistically insignificant (F (3.116) = 1.166, $p = 0.325$). R^2 was 0.029, which indicates that TSH and thyroid hormone levels explain 2.9% of the variability in the level of hopelessness according to the Beck scale. All studied predictors of hopelessness (TSH ($t = –1.676$, $p = 0.096$), FT3 ($t = –0.607$, $p = 0.544$), and FT4 ($t = –0.224$, $p = 0.822$)) were statistically insignificant.

Table

Values of the coefficients in the multiple linear regression model for the dependence of hopelessness on TSH and thyroid hormone levels

Indicator	Coefficient (B)	Standard error	*t*-test	*p*
Constant	9.012	2.711	3.323	0.001
TSH	–0.426	0.254	–1.676	0.096
FT3	–0.397	0.654	–0.607	0.544
FT4	–0.045	0.203	–0.224	0.822

Then, TSH and thyroid hormone levels were transformed into categorical variables (0 – normal, 1 – abnormal) based on the reference values. Thus, among 120 patients with schizophrenia, 11 patients (9.2%) had elevated serum TSH levels (> 4.0 mU / l), 108 (90%) had decreased FT3 levels (< 4.0 pmol / l), and 42 (35%) had decreased FT4 level (<10.3 pmol / l). Accordingly, based on the categories obtained, the effect of the hypothalamic–pituitary–thyroid axis hormone levels on the level of hopelessness was assessed using one-way ANOVA (Fig.).

The results of one-way ANOVA test revealed statistically significant differences in the level of hopelessness between the groups of patients with normal and elevated TSH (F (1.118) = 5.160, $p = 0.025$), as well as with normal and reduced FT3 (F (1.118) = 4.568, $p = 0.035$). The presented groups of patients were comparable in terms of sociodemographic, clinical, and therapeutic indicators ($p > 0.05$). Thus, the level of hopelessness according to the Beck scale in patients with schizophrenia was significantly affected by TSH and FT3 concentrations in the blood serum.

DISCUSSION

The study assessed the effect of the hypothalamic–pituitary–thyroid axis hormone levels on the risk of suicide in patients with schizophrenia. During the analysis of variance, we found a significant effect of serum TSH and FT3 in these patients on the level of hopelessness, which confirms the role of thyroid function in the suicidal behavior of patients with schizophrenia.

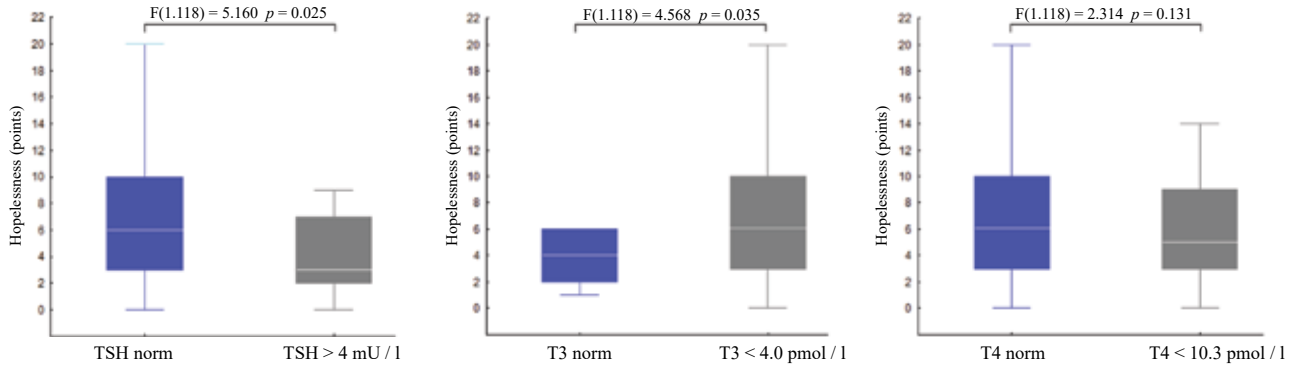

Figure. Boxplots of the level of hopelessness depending on the indicators of the hypothalamic–pituitary–thyroid axis hormones

Many authors associate TSH with psychotic symptoms, anxiety and depression [15, 16]. TSH can increase the risk of suicide by exacerbating anxiety, depression, and psychotic symptoms [23]. However, our study showed that patients with elevated TSH values (subclinical hypothyroidism) had a lower level of hopelessness and, as a result, a lower risk of suicide. On the other hand, in patients with reduced FT3, we observed a significantly more pronounced level of hopelessness. Our findings regarding the effect of triiodothyronine on suicide risk in patients with schizophrenia comply with the results of previous studies presented in the systematic review and meta-analysis of F.J.K. Toloza et al. [24].

As is known, TSH and thyroid hormones interact with each other using a negative feedback mechanism [25]. A decrease in thyroid hormones (hypofunction) entails an increase in the synthesis of TSH by the pituitary gland. Thus, we assume that patients with schizophrenia and hypothyroidism have increased synthesis of TSH, which has a compensatory effect on thyroid function and on the concentrations of FT3 and FT4, in particular, and can also contribute to reducing the suicide risk.

CONCLUSION

This study has shown the need for continuous dynamic monitoring of the hypothalamic–pituitary–thyroid axis hormone level in individuals with schizophrenia in order to preserve and maintain normal neuroendocrine balance, as well as to prevent suicide attempts and suicide.

It should be emphasized that our study does not directly assess the cause-and-effect relationships between suicide risk and hypothyroidism, which dispels the initial pessimistic assumptions, however, in accordance with the results obtained, monitoring of these indicators is extremely important for patients with schizophrenia, especially in regions with iodine deficiency.

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Authors' contribution

Kornetova E.G. – conception and design, review of publications on the topic of the article, drafting of and editing the manuscript. Galkin S.A. – review of publications on the topic of the article, drafting of and translating the manuscript, statistical analysis. Lobacheva O.A. – review of publications on the topic of the article, sample survey. Mednova I.A. – sample survey, database formation. Kornetov A.N. – conception and design, review of publications on the topic of the article, drafting of and editing the manuscript, translating the manuscript. Bokhan N.A. – final approval of the manuscript topic.

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