Improving outcomes after ischemic stroke in patients with high free triiodothyronine levels versus hypothyroid and euthyroid patients

Abstract. Background. Thyroid dysfunction is associated with cerebrovascular diseases. However, there is a growing number of pieces of evidences that thyroid hormones may have certain neuroprotective effects. The purpose of this study was to determine the outcomes of ischemic stroke in patients with various thyroid profiles during stroke onset. Materials and methods. In this study, 121 adult patients with first-ever acute ischemic stroke were enrolled. Concentrations of free T3 (fT3), free T4 (fT4), TSH, and basic stroke risk factors were assessed during 24 h from symptoms onset. The neurologic deficit was assessed by Scandinavian Stroke Scale (SSS). The disabling deficit was defined as mRs score ≥ 3 at 6 months after stroke. Results. ANOVA showed that SSS scores were significantly higher in patients with fT3 level in the 4th quartile (≥ 5.35 pmol/L) compared to the 2nd – 3rd quartile (SSS median 48 vs. 37; p = 0.0481) and especially to the 1st quartile (≤ 3.4050 pmol/L, SSS median 48 vs. 30; p = 0.0018). According to the Kruskal-Wallis test, a patient with free T3 level above the 75th percentile has a more favorable outcome with mRs score median of 2.5 in comparison with mRs median of 4 in patients with fT3 level in the 25–75th percentiles. There was also a dose-dependent effect of fT3 level on the probability of favorable stroke outcome. Free T3 level of 6.56 pmol/L was associated with a 50% probability of the favorable outcome, and free T3 level above 8.67 pmol/L was associated with a 75% probability of the favorable stroke outcome. Conclusions. The study showed that patients with high serum free triiodothyronine level during stroke onset experienced more favorable stroke outcome, even in comparison with patients with normal serum free T3 levels. Higher levels of serum free triiodothyronine are also associated with less severe neurologic deficit in the acute phase. There is a dose-dependent effect of free triiodothyronine level on the probability of favorable stroke outcome. These findings suggest that thyroid metabolism is not only a factor impacting the course of ischemic stroke but also a potential target for therapeutic correction.

Keywords: ischemic stroke; outcome; thyroid hormones; triiodothyronine

Introduction

Stroke and its consequences is a global medical, social and economic challenge. According to published epidemiological studies, one in four people in the world has or will have a stroke [1]. Indicator of prematurely lost years of a full life (Disability-Adjusted Life Years) according to 2012 data globally amounted to 113 million years [2]. In 32 European countries in 2017 direct economic losses associated with stroke amounted to 60 billion euros [3]. Despite some stabilization of the incidence of stroke in high-income
countries, the absolute incidence in the world continues to increase.

The results of several controlled randomized trials of treatment in the hyperacute stroke phase were published in recent years. All studies have confirmed the obvious advantage of an integrated approach in the treatment of AIS caused by thrombotic occlusion of the intracranial arteries of the carotid system. This approach consists in using a combination of systemic thrombolysis and endovascular thrombectomy in the first few hours after the onset of the first symptoms of acute stroke [2, 3]. However, reperfusion therapy is possible only within a relatively narrow therapeutic window [4]. In cases where thrombolysis or thrombectomy is not indicated or there are no opportunities for its implementation, approaches to patient management during the acute period of stroke include both secondary prevention of cerebrovascular disease and an attempt to reduce the severity of neurologic deficit by protecting ischemic (but potentially viable) brain tissue in penumbra zone [5]. Nevertheless, despite the diversity of neuroprotective drugs, different in their mechanism of action and effective in preclinical studies, none of them has enough clinical efficacy. In this regard, the search for new approaches to neuroprotection remains one of the most important tasks of modern neuropharmacology [5].

The survival of the brain tissue under ischemia depends on the intensity of metabolism, oxygen demand, as well as the ability to maintain the redox potential and support the synthesis of high-energy compounds (ATP, etc.). The mechanism of action of most neuroprotectors is based on the effects on these processes [6, 7].

Over the past decades, special attention had been paid to the neuroprotective properties of endogenous molecules such as VEGF, erythropoietin, brain neurotrophic factor, etc. It is known that triiodothyronine, an active form of the thyroid hormone thyroxin, separates tissue respiration and oxidative phosphorylation. This process leads to disruption of the Krebs cycle, reduced ATP production, hyperthermia, and has a potentially negative effect in acute cerebral ischemia [8]. On the other hand, triiodothyronine is known to have several neuroprotective effects: it contributes to the uptake of neurotoxic glutamate by astrocytes, stimulation of the Na+/K+ membrane channels in neurons, the restoration of intracellular pH [9]. Thus, selective therapeutic effect on thyroid metabolism (stimulation or inhibition of the function of thyroid hormones) may be a promising potential target for new approaches to the treatment of stroke.

In recent years, more publications appeared in the literature about the possible effect of thyroid hormones on the risk of development, severity, and outcome of acute ischemic stroke. Nevertheless, the results of the published works are rather contradictory [10]. Finally, the nature of the influence of hyper- or hypothyroidism on the course and outcome of a stroke is still unclear.

The purpose of this study was to determine the outcomes of ischemic stroke in patients with various thyroid profiles during stroke onset.

Materials and methods

This study was conducted at the single clinical and research center — V.K. Gusak Institute of Urgent and Reparative Surgery. This study enrolled 121 patients (women — 69, men — 52) aged 42 to 78 years with first-ever acute ischemic heterogeneous stroke. Patients with verified autoimmune thyroiditis or malignancy were excluded from the study. Within 24 hours from stroke onset, basic stroke risk factors were analyzed. Serum free triiodothyronine (fT3), free thyroxine (fT4), and the thyroid-stimulating hormone (TSH) were determined using the ELISA method (ChemWell EIA analyzer with DRG International assay kits). Blood sampling was performed within 24 hours from stroke onset. The neurologic deficit was assessed using Scandinavian Stroke Scale (SSS). Poor stroke outcome was assumed as 3 or more points on the modified Rankin Scale (mRs) after 6 months from stroke onset. Thyroid hormones and TSH levels below the 25th and above the 75th percentiles were assumed as “low” and “high”, respectively.

Statistical analysis was performed using MedCalc v14 software. Continuous data with non-normal distribution is presented as median and 95% CI. For analyzing the variation of neurologic deficit, the ANOVA method was used and patients were divided into subgroups by T3 levels: “hypothyroid” (T3 below the 25th percentile), “euthyroid” (T3 in the 25–75th percentile), “hyperthyroid” (T3 above the 75th percentile). For determining the impact of thyroid hormones on stroke outcome using logistic regression, the patients were dichotomized into subgroups with good outcomes (mRs 0–2) and poor outcomes (mRs 3–6).

Results

Strokes in the carotid territory were the most frequent (71 % of all patients), with the atherothrombotic subtype being the most common (66 %). The leading basic risk factors were arterial hypertension (66 %), coronary heart disease (24 %), atrial fibrillation (29 %).

According to the laboratory reference indicators, 63 patients had thyroid hormone levels in the reference range, 34 patients had laboratory hypothyroidism, and 24 patients had laboratory hyperthyroidism. The distribution of thyroid hormone levels is presented in Table 1.

According to previous clinical studies, including our studies, low serum free triiodothyroine was considered a factor for poor stroke outcome [13, 14]. So, we divided enrolled patients into subgroups according to free T3 levels in stroke onset to determine possible differences in the demographic characteristics in these subgroups. The demographic characteristics of the examined patients, according to free T3 levels at stroke onset, are presented in Table 2.

According to the statistical analysis, male patients with stroke prevailed in the euthyroid and high T3 group, but there were no other statistically significant differences in demographic data.

The correlation analysis using the Spearman rank correlation method revealed a positive statistically significant relationship between the level of free triiodothyronine and the severity of neurologic deficit on the SSS scale. A statistically significant relationship was also found between the level of free thyroxine and the presence of atrial fibrillation. Among other factors, an inverse correlation was observed between the level of C-reactive protein and the severity of neurologic
deficit on the SSS scale (R = −0.397, p = 0.0004). No other significant relationships were found between thyroid hormones, the neurologic deficit severity, and the presence of basic risk factors for stroke.

The ANOVA test showed that patients with fT3 level in the IV quartile (≥ 5.35 pmol/L; 95% CI 5.01–5.61) had a less severe stroke (greater SSS scores) compared to patients with fT3 level in II–III quartiles (SSS median is 48 points in Q4 vs 37 points in Q2–3; p = 0.0481), and significantly less severe stroke compared to patients with a T3 level in the first quartile (≤ 3.4050 pmol/L, SSS median 48 points in Q4 vs 30 points in Q1; p = 0.0018). The results of the ANOVA test are presented in Figure 1.

The result of the ANOVA test suggests that low triiodothyronine levels are associated with a more severe neurologic deficit, while high levels may have potential neuroprotective effects. There were no statistically significant variations of the SSS score in subgroups of patients by the fT4 or TSH levels.

Table 1. Distribution of thyroid hormones levels (95% CI)

| Parameter                    | Free T3, pmol/L       | Free T4, pmol/L       | TSH, IU/l         |
|------------------------------|-----------------------|-----------------------|------------------|
| Median                       | 4.63 (4.35–4.79)      | 16.4 (15.62–16.60)    | 1.32 (1.02–1.43)  |
| 25th percentile              | 3.57 (3.01–4.22)      | 14.69 (13.84–15.38)   | 0.83 (0.64–1.01)  |
| 75th percentile              | 5.36 (5.01–5.61)      | 18.1 (17.0–17.98)     | 2.3 (1.59–3.24)   |

Table 2. Demographic characteristics of the examined patients, n (%)
after adjustment for other stroke risk factors (age, hypertension, carotid stenosis, glucose level, C-reactive protein, SSS score).

To confirm the independent effect of the fT3 level on the stroke severity and exclude the influence of co-factors, a multivariate regression analysis was performed. The regression model included basic risk stroke factors (age, arterial hypertension, blood pressure on admission, atrial fibrillation, IHD, diabetes mellitus, smoking), C-reactive protein, free thyroxine, TSH, free T3/free T4 ratio. The variables were introduced in the regression model using the forward method.

To assess the impact of the fT3 level on stroke outcome, the multiple logistic regression method was used. Basic stroke risk factors (age, hypertension, blood pressure at admission, atrial fibrillation, coronary artery disease, diabetes mellitus, smoking) and C-reactive protein, free thyroxine, TSH levels, fT3/fT4 ratio were included in the regression model. Lower fT3 levels were independently associated with poor stroke outcome (odds ratio = 0.3408, 95% CI 0.15–0.77).

To compare stroke outcomes in patients with different thyroid profiles, we used the ANOVA method with the Kruskal-Wallis criterion. The patients were also divided into three groups according to the free T3 level: below the 25th percentile, the 25–75th percentiles, above the 75th percentile. The test reported overall differences in mRs score in groups with T = 7.64; p = 0.0175. The Jonckheere-Terpstra trend test was positive with a p-value = 0.00950. There were statistically significant differences in mRs scores between the high T3 group and euthyroid group and between euthyroid and low T3 groups. The median of mRs score was 4 in low T3 and euthyroid groups and 2.5 in a high T3 group. The graphical results of the Kruskal-Wallis test are presented in Figure 2.

To describe dose-dependent effect of the free T3 level on the probability of a favorable stroke outcome, a probit regression analysis was performed. Dose-dependent effect of the free T3 level on stroke outcome with mRs < 3 score was observed with p = 0.0114. The graphical results of a probit regression analysis are presented in Figure 3.

The findings of a probit regression analysis demonstrated that the free T3 level of 6.56 pmol/L was associated with a 50% probability of a favorable outcome, and the free T3 level above 8.67 pmol/L was associated with a 75% probability of a favorable stroke outcome.

**Table 3. Thyroid hormones, CRP levels, and age of patients with different stroke outcomes**

| Parameter                  | mRs 0–2 (n = 48) | mRs 3–6 (n = 120) | P-value |
|----------------------------|------------------|-------------------|---------|
| Age, years                 | 68 (55–70.4)     | 76 (72–77)        | 0.0006  |
| Free T3, pmol/l            | 4.815 (4.57–5.5798) | 4.43 (4.036–4.65) | 0.0173  |
| Free T4, pmol/l            | 16.1 (14.61–17.22) | 16.5 (15.466–16.834) | NS      |
| TSH, IU/l                  | 1.305 (0.779–1.86) | 1.16 (0.99–1.43)  | NS      |
| C-reactive protein, mg/L   | 6.29 (5.26–8.04)  | 16.1 (8.565–24.696) | 0.0140  |
| Free T3/free T4 ratio      | 0.366 (0.287–0.343) | 0.27 (0.2355–0.304) | 0.0374  |

Notes: free T3 — free triiodothyronine; free T4 — free thyroxine; TSH — thyroid-stimulating hormone.
In turn, an excess of calcium ions disrupts the operation of ion pumps and simultaneously activates many catabolic enzymes, resulting in depolarization and disintegration of the intracellular membranes. The destruction of mitochondrial membranes involves apoptosis due to the release of proapoptotic proteins.

Several experimental studies demonstrated that after the in vivo addition of T3 in astrocyte culture, the number of glutamate transporter proteins GLT-1 and GLAST increased. The activation of glutamate uptake by astrocytes significantly reduced the “glitoxic” effect of this neurotransmitter on the neurons [23]. Another experiment revealed that triiodothyronine reduced the activity of NMDA receptors in hippocampal neurons, which, according to the authors, prevented glutamate–induced cell death [24].

The key role of iodothyronines in the expression of synthesis and stimulation of ion-exchange pumps has been proved. So, T3 activates the expression of the sodium/hydrogen exchanger gene, which in turn is responsible for removing excess protons and normalizing intracellular pH. Under the action of T3, the number of Na⁺/K⁺-ATPases integrated into the membranes increases, the functioning of Ca²⁺-ATPases increases, which ultimately contributes to the normalization of the ion balance of neurons [25].

Normal functioning of ion pumps is not possible in ATP pool depletion in cells under ischemic conditions. When studying the effect of T3 on astrocyte cultures, an increase in the expression of palmitate beta-oxidation enzymes in mitochondria: beta-hydroxyacyl-CoA dehydrogenase, beta-thiolase, and enoyl-CoA hydratase was recorded [26]. As a result, the amount of ATP increased in astrocytes. Since the protective role of these cells in stroke is considered to be proven, the authors of the study concluded that it was the normalization of energy exchange under the action of triiodothyronine in astrocytes that significantly reduced the lesion area in experimental models of transient cerebral ischemia and stroke.

A comparison of two experimental models of ischemic stroke — transient and with constant occlusion revealed another important feature of the neuroprotective effect of T3 — inhibition of protein synthesis of aquaporin-4 with transient occlusion [27]. As a result of the treatment of experimental animals with triiodothyronine preparations, a marked decrease in swelling and the area of brain damage was observed, the probability of a favorable outcome increased but only in the model of transient ischemia.

It is known that iodothyronines regulate metabolic processes by binding not only to nuclear receptors (a classical genomic mechanism) but also to membrane receptors localized on the αβ3 integrin protein (non-genomic mechanism) [28, 29]. After the hormone binds to a receptor on the integrin surface, the signal is transmitted to an enzyme from the family of mitogen-activated protein kinases — MAP-kinase extracellular signal-regulated kinase 2. Next, some proteins are activated, including the secretion of the basic fibroblast growth factor, bFGF [33]. The study of bFGF function in modeling transient global cerebral ischemia revealed a significant neuroprotective effect [34]. Injections of the basic fibroblast growth factor suppressed the processes of autophagy of neurons and reduced the rate of apoptosis by inhibiting the translocation of the p53 protein into the mi-
Conclusions

The study showed that patients with high serum free triiodothyronine level during stroke onset have a more favorable stroke outcome, even in comparison with patients with normal serum free T3 levels. Higher levels of serum free triiodothyronine are also associated with a less severe neurologic deficit in the acute phase. There is a dose-dependent effect of free triiodothyronine level on the probability of a favorable stroke outcome. These findings suggest that thyroid metabolism is not only a factor impacting the course of ischemic stroke but also a potential target for therapeutic correction. It is reasonable to monitor thyroid hormone levels during a stroke, while the analysis of serum free triiodothyronine can be used to predict a high risk of an unfavorable stroke outcome. There is a need to conduct further clinical trials to determine the safety and efficacy of additional supplements of synthetic triiodothyronine analogs in reducing stroke severity and risk of stroke unfavorable outcomes.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Відомо, що дисфункція щитоподібної залози може мати певні нейропротекторні ефекти. Дані останніх років свідчать про те, що гормони щитоподібної залози асоційовані з підвищеним ризиком розвитку цереброваскулярних захворювань. Однак експериментальних даних останніх років щодо впливу щитоподібної залози асоційованої з підвищеним ризиком розвитку цереброваскулярних захворювань є недостатньо.

**Мета дослідження:** визначити взаємозв'язок між рівнем вільного трийодтироніну (вT3) і неврологічним дефіцитом у пацієнтів з ішемічним інсультом.

**Матеріал і методи.** У дослідженні браво 121 пацієнт із ішемічним інсультом. Пацієнти оцінювалися за модифікованою шкалою Ренкіна. Результати відносяться до трьох періодів: до інтервалів 1-го і 2-3-го квартилей.

**Результати.** Суттєвий різниці було виявлено у групі пацієнтів з рівнем вT3 у 4-му квартилі (≥ 5,35 пмоль/л) мали значно тяжчий неврологічний дефіцит порівняно з пацієнтами з рівнем вT3 у 2–3-му квартилі (менш ніж 5,35 пмоль/л) (p = 0,0048) і особливо порівняно з пацієнтами з рівнем вT3 у 1-му квартилі (≤ 3,4050 пмоль/л, mediana SSS 48 проти 37 балів, p = 0,0481) і особливо порівняно з пацієнами з рівнем вT3 в 1-му квартилі.

**Оригінальні дослідження /Original Researches/**

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Поліпшення наслідків ішемічного інсульту у пацієнтів із високим рівнем вільного трийодтироніну порівняно з пацієнтами з гіпо- та еутиреозом

Резюме. Актуальність. Відомо, що дисфункція щитоподібної залози асоційована з підвищеним ризиком розвитку цереброваскулярних захворювань. Однак експериментальні дані останніх років свідчать про те, що гормони щитоподібної залози можуть мати певні нейропротекторні ефекти.

**Матеріал та методи.** У дослідження був включений 121 пацієнт із ішемічним інсультом. Пацієнти оцінювалися за модифікованою шкалою Ренкіна. Результати відносяться до трьох періодів: до інтервалів 1-го і 2-3-го квартилей. Дослідження був включений 121 пацієнт із ішемічним інсультом. Пацієнти оцінювалися за модифікованою шкалою Ренкіна. Результати відносяться до трьох періодів: до інтервалів 1-го і 2-3-го квартилей.

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Улучшение исходов ишемического инсульта у пациентов с высоким уровнем свободного трийодтиронина по сравнению с пациентами с гипо- и euthyreозом

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Резюме. Актуальность. Известно, что дисфункция щитовидной железы ассоциирована с повышенным риском развития cerebrovascularных заболеваний. Однако накопленные в течение последних лет экспериментальные данные свидетельствуют о том, что гормоны щитовидной железы могут иметь определенные нейропротекторные эффекты.

Цель исследования: определить взаимосвязь между уровнем свободного трийодтиронина и гормональным исходом инсульта через 6 месяцев.

Материалы и методы. В исследование был включен 121 пациент с впервые развившимся острым ишемическим инсультом. Концентрации свободного трийодтиронина (свТ3), свободного тироксина (свТ4), тиреотропного гормона и наличие базисных факторов риска инсульта оценивались в течение 24 часов с момента появления симптомов. Неврологический дефицит оценивался по Скандинавской шкале инсульта (SSS). Неблагоприятный функциональный исход определялся как показатель mRs ≥ 3 баллов через 6 месяцев после перенесенного инсульта.

Результаты. Тест ANOVA показал, что пациенты с уровнем свТ3 в 4-м квартиле (≥ 5,35 пмоль/л) имели значительно более тяжелый неврологический дефицит по сравнению с пациентами с уровнем свТ3 в 2–3-м квартилях (медиана SSS 48 баллов против 37 баллов, p = 0,0481) и особенно по сравнению с пациентами с уровнем свТ3 в 1-м квартиле (≤ 3,4050 пмоль/л, медиана SSS 48 против 30, p = 0,0018). Соответственно Краскела — Уоллиса, пациенты с уровнем свободного Т3 выше 75-го процентиля имели более благоприятный функциональный исход со средним значением по модифицированной шкале Рэнкина 2,5 балла по сравнению с пациентами с уровнем свТ3 в 25–75-м процентилях (со средним значением по модифицированной шкале Рэнкина 4 балла). Результаты анализа пробит-регрессии свидетельствуют о дозозависимом влиянии уровня свТ3 на вероятность благоприятного исхода инсульта.

Выводы. Исследование показало, что пациенты с высоким уровнем свободного трийодтиронина при дебюте ишемического инсульта имеют более благоприятный функциональный исход, даже по сравнению с пациентами с нормальным уровнем свободного Т3. Более высокие уровни свободного трийодтиронина также ассоциируются с менее тяжелым неврологическим дефицитом в острой фазе. Выявлено дозозависимое влияние уровня свободного трийодтиронина на вероятность благоприятного исхода инсульта. Полученные данные свидетельствуют о том, что тиреоидный профиль является не только фактором, влияющим на течение ишемического инсульта, но и потенциальной мишенью для терапевтической коррекции.

Ключевые слова: ишемический инсульт; исход; гормоны щитовидной железы; трийодтиронин