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Hypothyroidism syndrome as a risk factor for parasympathetic innervation disorders

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The objective: **to study the significance of the presence of hypothyroidism syndrome as a risk factor for the development of autonomic neuropathy (AN).**
Materials and methods**. The study involved 77 women, of whom 31 had hypothyroidism syndrome, and 46 had euthyroid thyroid pathology. The age of patients with hypothyroidism syndrome ranged from 24 to 57 years and averaged 42.4±9.20 years, mean age patients of the euthyroid pathology group of the thyroid gland was equal to 40.0±12.22 years (age interval 20–63 years). Patients underwent an ultrasound examination of the thyroid gland, fasting glycemia levels, A1c, TSH, T4s, T3s, blood creatinine levels, and GFR were calculated using CKD-EPI on line equations. In addition, antithyroglobulin and antithyroperoxidase levels were determined. To diagnose autonomic neuropathy, a Valsalva test and a deep breathing test were used. Statistical analysis was performed using the standard computer program Microsoft Excel.**
Results**. The state of autonomous innervation was normal in 71.0% of the examined hypothyroidism group and in 97.8% of the euthyroidism group. AN was absent both in hypothyroidism syndrome (0.0%) and in euthyroid thyroid pathology (0.0%). Moreover, the "borderline state" of autonomic innervation was observed in 29.0% of the examined groups of hypothyroidism syndrome and only 2.2% of the examined groups of thyroid euthyroid pathology (p=0.0019). The chance of finding parasympathetic disorders in the hypothyroidism group was 0.409, and in the group of euthyroid thyroid pathology was 0.022.**
Conclusions**. Thus, in the presence of hypothyroidism, the chances of finding autonomic disorders were 18.409 times higher than those for euthyroid thyroid pathology, which requires appropriate correction when planning comprehensive treatment tactics.**
Key words: *autonomic neuropathy, hypothyroidism syndrome, euthyroid pathology of the thyroid gland.*

Синдром гіпотиреозу як фактор ризику виникнення порушень парасимпатичної іннервації

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Мета дослідження: вивчення синдрому гіпотиреозу як фактора ризику розвитку автономної нейропатії (АН).
Матеріали та методи. У дослідженні взяли участь 77 жінок, з яких у 31 діагностований синдром гіпотиреозу, а у 46 – еутиреоїдна патологія щитоподібної залози (ЩЗ). Вік хворих із синдромом гіпотиреозу коливався у діапазоні від 24 до 57 років і в середньому становив 42,4±9,20 року; середній вік хворих групи еутиреоїдної патології ЩЗ дорівнював 40,0±12,22 року (віковий інтервал 20–63 року). Хворим проводили ультразвукове обстеження ЩЗ, визначали рівні глікемії натще, рівень A1c, ТТГ, Т4с, Т3с, вміст креатиніну в крові, а також обчислення СКФ за рівняннями CKD-EPI on line. Крім цього, проводили визначення рівнів антитироглобуліну і антитиропероксидази. Для діагностики АН застосовували пробу Вальсальви і тест «глибоке дихання». Статистичний аналіз проводили за допомогою стандартної комп'ютерної програми Microsoft Excel.
Результати. Стан автономної іннервації був нормальним у 71,0% обстежених групи гіпотиреозу й у 97,8% групи еутиреозу. АН була відсутня як при синдромі гіпотиреозу (0,0%), так і при еутиреоїдній патології ЩЗ (0,0%). При цьому «прикордонний стан» автономної іннервації фіксували у 29,0% обстежених групи синдрому гіпотиреозу і лише у 2,2% обстежених групи еутиреоїдної патології ЩЗ (p=0,0019). Шанс виявити парасимпатичні порушення в групі гіпотиреозу становив 0,409, а в групі еутиреоїдної патології ЩЗ – 0,022.
Заключення. Отже, за наявності гіпотиреозу шанси виявити автономні порушення в 18,409 разу перевищували такі при еутиреоїдній патології ЩЗ, що вимагає відповідної корекції під час планування тактики комплексного лікування.
Ключові слова: *автономна нейропатія, синдром гіпотиреозу, еутиреоїдна патологія щиподібної залози.*

Синдром гипотиреоза как фактор риска возникновения нарушений парасимпатической иннервации

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Цель исследования: изучение синдрома гипотиреоза как фактора риска развития автономной нейропатии (АН).
Материалы и методы. В исследовании приняли участие 77 женщин, из которых у 31 диагностирован синдром гипотиреоза, а у 46 – эутиреоидная патология щитовидной железы (ЩЖ). Возраст больных с синдромом гипотиреоза находился в диапазоне от 24 до 57 лет и в среднем был равен 42,4±9,20 года; средний возраст больных группы эутиреоидной патологии ЩЖ был равен 40,0±12,22 года (возрастной интервал 20–63 года). Больным проводили ультразвуковое обследование ЩЖ, определяли уровни гликемии натощак, уровень A1c, ТТГ, Т4с, Т3с, содержание креатинина в крови, а также вычисление СКФ по уравнениям CKD-EPI on line. Помимо этого проводили определение уровней антитироглобулина и антитиропероксидазы. Для диагностики АН применяли пробу Вальсальвы и тест «глубокое дыхание». Статистический анализ проводили с помощью стандартной компьютерной программы Microsoft Excel.
Результаты. Состояние автономной иннервации было нормальным у 71,0% обследованных группы гипотиреоза и у 97,8% группы эутиреоза. АН отсутствовала как при синдроме гипотиреоза (0,0%), так и при эутиреоидной патологии ЩЖ (0,0%). При этом «пограничное состояние» автономной иннервации фиксировали у 29,0% обследованных группы синдрома гипотиреоза и лишь у 2,2% обследованных группы эутиреоидной патологии ЩЖ (p=0,0019). Шанс выявить парасимпатические нарушения в группе гипотиреоза составил 0,409, а в группе эутиреоидной патологии ЩЖ равнялся 0,022.
Заключение. Таким образом, при наличии гипотиреоза шансы выявить автономные нарушения в 18,409 раза превышали таковые при эутиреоидной патологии ЩЖ, что требует соответствующей коррекции при планировании тактики комплексного лечения.
Ключевые слова: *автономная нейропатия, синдром гипотиреоза, эутиреоидная патология щитовидной железы.*

Autonomic neuropathy (AN), characterized by damage to the innervation of internal organs, can develop with many diseases, including autoimmune and genetic pathology [1], but diabetes is the main reason for its development [2]. AN is described in diseases characterized by functional pathology of the thyroid gland (thyroid gland) [1], however, while hundreds and even thousands of studies have been devoted to autonomic diabetic neuropathy to the whole world, only a few dozen works have been devoted to the study of autonomic innervation disorders in thyroid pathology.

The objective: to study the significance of the presence of hypothyroidism syndrome as a risk factor for the development of autonomic neuropathy.

MATERIALS AND METHODS

The study involved 77 women, of whom 31 had hypothyroidism syndrome and 46 had thyroid euthyroid pathology.

The age of patients with hypothyroidism syndrome ranged from 24 to 57 years and averaged 42.4±9.20 years. The minimum age of patients with a euthyroid thyroid pathology group was 20 years, and the maximum was 63 years. Moreover, the average age of patients in this group corresponded to 40.0±12.22 years and did not statistically significantly differ ($p>0.05$) from the age of patients in the hypothyroidism group.

The criteria for inclusion in the study were:

- the presence of a female;
- age 18–65 years;
- the presence of manifest or subclinical hypothyroidism syndrome (untreated or inadequately treated) or the presence of thyroid diseases in a state of euthyroidism.

Exclusion criteria from the study were:

- age over 65 years;
- the presence of diabetes mellitus or prediabetes (A1c ≥ 5.7%, fasting glycemia of 100 mg/dl and higher) [6,7];
- the presence of a serious pathology on the part of the cardiovascular or respiratory system, limiting the possibility of conducting tests on the functional state of the autonomic nervous system;
- reception of b-blockers;
- GFR level less than 60 ml / sec / 1.73 m^2;
- lack of data to identify compliance with the inclusion criteria in the study and the exclusion criteria from it: glycohemoglobin (A1c); fasting glycemia; thyroid stimulating hormone (TSH); free thyroxine (T4c); free triiodothyronine (T3c); antithyroglobulin (anti-TG) and antithyroperoxidase (anti-TPO); ultrasound examination of the thyroid gland;

An ultrasound examination of the thyroid gland was performed on a SonoScape apparatus manufactured by SonoScape Ltd (China) and Sonomed (Italy). Fasting glycemia levels were determined using a Precision PCx Medi Sense laboratory glycemic test apparatus (Abbot, USA) and corresponding test strips. A1c level was determined on an express analyzer («SDA1c Care» (SD biosensor, Korea) using the appropriate «test kit». Blood creatinine values were determined on a Reflotron Plus express analyzer (Roche Diagnostics Corporation, Switzerland) using the corresponding «test strip.» GFR was also calculated using the CKD-EPI on line equations [13] The levels of TSH, T4c, and T3c were determined on a SelexOn express analyzer manufactured by Infopia Co. Ltd, Korea.

The levels of antithyroglobulin and antithyroperoxidase were determined on a BioScreen MS-500 apparatus using reagents of the Human company (Germany).

Due to the fact that the «VM Center of Endocrinology, Diabetes and Metabolism» was a private medical institution, the main limiting factor was the patient's financial ability to fully undergo an appropriate examination.

To diagnose autonomic neuropathy, a Valsalva test and a deep breathing test were used. The results of the Valsalva test were evaluated by the Valsalva index, the results of the deep breath test were evaluated by two indicators: the Expiratio / Inspiratio index (E/I) and the Inspiratio - Expiratio index (I-E) [2, 5–7] To interpret the values of each of the three indicated indices, the corresponding criteria proposed by Ewing D.J [5] and Mirzazade V.A. were used [6]. When evaluating the values of indices, it was possible to have 3 types of answers: «norm»; «Border state»; «ADN».

Below is the data on the scoring of the results that formed the basis of the study:

1) «Norm» – 0 points;
2) «Borderline condition» – 1 diagnostic point;
3) «AN» – 2 diagnostic points.

Due to the fact that according to the results of the Valsalva test, each patient could receive only 2 ratings, and according to the results of the «deep breathing» test, each patient could receive 4 ratings, to equalize the «weight» of each test, the number of points scored according to the results of the Valsalva test was multiplied by 2. Assume that the patient in total scored 2 points according to the results of Valsalva's test and 4 points according to the results of the «deep breathing» test. The total assessment of the results of this patient will be: 2 2 + 4 = 8 (diagnostic points).

Statistical analysis was performed using the standard computer program Microsoft Excel [8]. Group data are presented as mean (M) ± standard deviation (SD). The statistical significance of differences between the fractions was determined using the ^{2} on line method [8]. A methodology for determining odds and odds ratio has been applied [9, 10]. The odds calculation with a 95% confidence interval was calculated on line [12].

RESULTS AND ITS DISCUSSION

Of 31 patients with hypothyroidism syndrome, 5 patients (16.1%) had postoperative hypothyroidism, 24 (77.4%) had hypothyroidism that developed as a result of autoimmune thyroiditis, 2 patients (6.5%) had iatrogenic hypothyroidism due to excessive therapy for toxic goiter .

In the euthyroid thyroid pathology group (n=46), 1 patient (2.2%) had diffuse toxic goiter in the state of euthyroidism, 7 (15.2%) patients had adequately controlled hypothyroidism, 38 patients (82.6%) had autoimmune thyroiditis in state of euthyroidism.

The state of autonomous innervation was normal in 71.0% of the examined hypothyroidism group and in 97.8% of the euthyroidism group. AN was absent both in hypothyroidism syndrome (0.0%) and in euthyroid thyroid pathology (0.0%). Moreover, the «borderline state» of autonomic innervation was observed in 29.0% of the examined groups of hypothyroidism syndrome and only 2.2% of the examined groups of thyroid euthyroid pathology ($p=0.0019$).

As can be seen from table 1, the chance to find parasympathetic disorders in the hypothyroidism group was 0.409. The

Data on the chance of finding parasympathetic disorders in the group of hypothyroidism and in the group of euthyroid thyroid pathology

Indicator	Value
The chance to find parasympathetic disorders in the hypothyroidism group	0.409
The chance to find parasympathetic disorders in the euthyroid thyroid pathology group	0.022
The odds ratio (OR)	18.409
The odds ratio standard error (S)	1.086
The lower bound is 95% confidence interval (CI)	2.192
The upper limit of the 95% confidence interval (CI)	154.602

chance of finding parasympathetic disorders in the euthyroid thyroid pathology group was 0.022.

Thus, in the presence of hypothyroidism, the chances of finding autonomous disorders were 18.409 times higher than those for euthyroid thyroid pathology. The data obtained were statistically significant ($p<0.05$).

CONCLUSIONS

1. Autonomic innervation disorders were detected in 29.0% of cases in the hypothyroidism group and only 2.2% of cases in the thyroid euthyroid pathology group.

2. Both in the hypothyroidism group and in the euthyroidism group, no gross violations of autonomic innervation were detected.

3. In the presence of hypothyroidism, the chances of finding autonomous disorders were 18.409 times higher than those for euthyroid thyroid pathology. The data obtained were statistically significant ($p<0.05$).

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