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Differentiated Approach To Diagnostics And Treatment Of Arterial Hypertension In Patients With Autoimmune Thyroid Pathology.

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ABSTRACT

Arterial hypertension (AH) is one of the most important medical and economic problem in the world. Thyroid hormones (TH) are involved in the regulation of vascular tone. Effects of their deficiency on the course of hypertension have not been studied enough. Studying effects of TH on clinical features of AH in patients with autoimmune thyroid diseases (ATD). This study included two groups of 26 patients with hypertension. The main group (AH+SCH) included patients with ATD with subclinical hypothyroidism, the comparison group (AH+ET) - patients with AH without ATD. TSH level was 7.2±2.14 mU/l in the group AG+SCH, 2.5±1.08 mU/l in the group AG+ET ($p<0.001$), anti-thyroperoxidase level was 38.1±6.1 IU/l in the group AG+SCH, 21.8±3.7 mU/l in the group AG+ET (<0.001), thyroglobulin level 77.8±5.2 U/l in the group AG+SCH and 42.3±8.6 U/l in the group AG+ET (<0.001). Echocardiography revealed significant increases in left ventricular myocardial hypertrophy parameters in the group AH+SCH. Comparison kidneys function showed significant lower glomerular filtration rate (62.7±17.5 vs 80.7±16.7 ml/min/1.73 m2; $p <0.001$) in patients group AG+SCH. ATDs make the course of hypertension and damage of target organs more severe than in euthyroidism, therefore, patients with hypertension and ATD require correction antihypertensive therapy.

Keywords. Thyroid hormones, autoimmune thyroid diseases, subclinical hypothyroidism, arterial hypertension.

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RELEVANCE

Despite significant achievements in cardiology, circulatory system diseases (CSD) still occupy one of the leading places in the structure of total mortality. Of all the deaths from CSD in 49.9%, the cause is arterial hypertension (AH) and its complications [1].

AH is one of the most common diseases of the cardiovascular system (CVS). According to recent foreign studies, 35%-45% of the total population suffer from hypertension. In Russia, according to the results of the Epidemiology of cardiovascular diseases in Russian Federation (ECD-RF) study, the prevalence of AH is 44% [2, 3].

As is known, the regulation of vascular tone is carried out by the vasopressor and vasodepressor systems. The mechanisms of interaction of these two systems are not fully understood in our days. It is known that genetically determined factors (functioning of the renin-angiotensin-aldosterone system, vasodilating endothelial function, neurohumoral regulation of vascular tone and metabolic features) are involved in the pathogenesis of AH and lifestyle features (excessive consumption of salt, smoking, alcohol abuse , hypodynamia, long-term psychoemotional stress) [4, 5].

Currently, the goal of many researches is to find new factors that can affect the level of cardiovascular risk and the effectiveness of antihypertensive therapy [6 – 8]. A special place is occupied by studies on the comorbid course of hypertension and endocrine system diseases, especially thyroid gland (TG) disease. This is explained by the fact that the regulation of vascular tone include the participation of thyroid hormones.

The effects of thyroxine (T4) and triiodothyronine (T3) are realized through genomic and extragenomic mechanisms. When directly acting on the smooth muscle cells of the T3 vessels, Ca^{2+} exits the sarcoplasmic reticulum into the myocyte sarcoplasma, inhibits the interaction of the Ca2 + complex of calomodulin with the myosin light chain kinase, thus blocking the contraction of the smooth muscle cell and causing them to relax. The additional vasodilating effect of T3 is realized through the activation of synthesis of nitric oxide by endotheliocytes [9, 10]. In combination, the implementation of these mechanisms leads to a decrease in the total peripheral resistance (TPR). The reduction of TPR leads to an increase in renin synthesis and activation of the renin-angiotensin-aldosterone system. An increase in aldosterone concentration contributes to the delay of Na + and an increase in circulating blood volume [11].

The participation of T3 and T4 in the regulation of blood pressure makes it relevant to study the characteristics of the course of hypertension in the background of thyroid disease, accompanied by a violation of thyroid status.

The relevance of the problem of the comorbid course of hypertension and thyroid pathology is also explained by the fact that in terms of the prevalence of endocrine pathology of thyroid disease takes second place after diabetes mellitus [12]. A significant proportion of thyroid disease accounts for autoimmune pathology. According to various researchers, the prevalence of autoimmune thyroiditis (ATD) is from 5% to 46% [13 - 16]. The thyroid status in ATD may be different, but in 36% of cases ATD is accompanied by hypothyroidism of varying severity. It is also worth noting that, of all the thyroid status variants, subclinical hypothyroidism (SCH) is more common. [eleven]. SCH is characterized by an increase in the blood level of thyroid-stimulating hormone (TSH) with a normal level of free T3 and T4 [17 – 19]. A number of studies demonstrate the negative effect of the minimal deficiency of thyroid hormones on the course of cardiovascular pathology [20 – 23].

Goal: The aim of the research is to study the characteristics of the course of hypertension in patients with autoimmune thyroid pathology, accompanied by SCH.

MATERIALS AND METHODS

The study involved two groups of patients of 26 people (13 women and 3 men each). The main group (AH + SCH) included patients with essential AH and ATD with subclinical thyroid hypofunction, the comparison group (AH +ET) - patients with essential AH without thyroid disease and thyroid status disorders. The diagnosis of ATD was made on the basis of the Clinical Recommendations of the Russian Association of Endocrinologists for the diagnosis and treatment of autoimmune thyroiditis in adults (2002), SCH on the basis of clinical

recommendations for subclinical hypothyroidism of the European Thyroid Association 2013, AH, according to Recommendations for the treatment of arterial hypertension ESH / ESC 2013. The study was conducted in the cardiac departments of the Voronezh City Clinical Emergency Hospital No. 1 in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko, Ministry of Health of Russia. Before being included in the study, each patient that satisfying inclusion criteria was informed about the goals, objectives and design of the study, which is confirmed by written informed consent to participate in the study. The study did not include patients older than 65 years, with unstable angina, myocardial infarction and stroke in history, persistent atrial fibrillation, chronic heart failure IIB –III stage, chronic kidney disease stage 3 - 5, metabolic syndrome, diabetes and other endocrine history of the disease, as well as patients taking thyreostatic drugs.

The criteria for the inclusion of the patient in the main group were essential hypertension and the presence in the patient of two diagnostic criteria for ATD (increased levels of antibodies to thyroperoxidase (anti-TPO) and thyroglobulin (TgAb) and persistent hypothyroidism). The comparison group was identical to the main one, not only by sex and age, but also by body mass index (BMI).

All patients of both groups were monitored daily for blood pressure monitoring (DBPM), echocardiography (ECHO), and renal function assessment. Daily monitoring of blood pressure (DBPM) was carried out by the «Valenta» monitor (St. Petersburg, Russia) for 24 hours, the ECHO was performed on a Hitachi Aloka ProSound Alpha 7 device (Japan).

Creatinine was determined using Biolyzer 600 (Germany) biochemical analyzer and Randox (Japan) test systems, thyroid status (TSH, FT4, FT3) and the level of antithyroid antibodies were studied using an automated immuno-chemiluminescent analyzer IMMULITE 2000 XPi (Siemens , USA) using the Thyroid -IFA reagent kit (Alkor Bio, Russia).

The statistical significance of differences in quantitative parameters with a normal distribution between independent groups was evaluated using the Student t-test, with a distribution that differs from the normal one using the Mann-Whitney method. A comparison of the frequencies of qualitative traits with a normal distribution was carried out using the Pearson χ^2 test, with a distribution that is different from the normal, using the exact Fisher method. Differences in parameters were considered significant when p is less than 0.05. In the text and tables, quantitative data are presented as the average standard deviation for signs with a normal distribution and medians and the interquartile range for signs with a distribution that differs from the normal one.

Statistical data processing was performed using the STATISTICA 6.1 software package (StatSoft). The estimation of the normality of distributions was carried out using the one-sample Kolmogorov-Smirnov criterion. The statistical significance of differences in quantitative parameters with a normal distribution between independent groups was evaluated using the Student t-test, with a distribution that differs from the normal one using the Mann-Whitney method. A comparison of the frequencies of qualitative traits with a normal distribution was carried out using the Pearson χ2 test, with a distribution that is different from the normal, using the exact Fisher method. Differences in parameters were considered significant when p is less than 0.05. In the text and tables, quantitative data are presented as the average standard deviation for signs with a normal distribution and medians and the interquartile range for signs with a distribution that differs from the normal one.

THE RESULTS OF THE STUDY.

In assessing the normality of distributions, the value of the Kolmogorov-Smirnov p-test for all indicators was more than 0.05, which made it possible to consider the distribution of features normal, to apply parametric statistics methods and to present data in the form of M ±SD.

Table 1 demonstrates the comparison of thyroid status, antithyroid antibody level and thyroid volume in the main group and the comparison group.

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Table 1: Indicators of thyroid status, level of antithyroid antibodies and thyroid volume in the examined groups

Indicators	AH+ET, n=26	AH+SCH	p
Age, years	54,8±2,8	55,0±6,4	0,885
TSH, mU/L	**2,5±1,08**	**7,2±2,14**	**<0,001**
FT4, pg/L	14,3±3,3	13,5±2,8	0,350
FT3, pg/L	5,2±0,75	4,8±0,88	0,084
anti-TPO, IU/ml	**21,8±3,7**	**38,1±6,1**	**<0,001**
TgAb, U/L	**42,3±8,6**	**77,8±5,2**	**<0,001**
Thyroid volume, mm³	**16,4±6,7**	**20,7±3,1**	**0,046**

As follows from the data presented in Table 2, in the main group, the average daily SBP, the average daily DBP and the mean blood pressure were significantly higher, the extent of nocturnal blood pressure decrease (ENBPD) is significantly less than in the comparison group (p <0.001 for all indicators), pulse BP is not significantly different (p = 0.120).

Table 2: Some indicators of DBPM in patients of the compared groups

Indicators	AH+ET, n=26	AH+SCH	p
Average daily SBPБ, mm Hg	**132,7±6,4**	**156,5±10,1**	**<0,001**
Average daily DBP, mm Hg	**83,0±5,8**	**98,0±12,2**	**<0,001**
Pulse BP, mm Hg	55,7±3,5	57,3±3,8	0,120
Mean blood pressure, mm Hg	**103,3±2,5**	**116,7±3,4**	**<0,001**
ENBPD, %	**6,0±1,0**	**-4,0±2,0**	**<0,001**

The results of the DBPM allowed to identify differences in the proportions of patients with different degrees of hypertension and different types of circadian rhythm of blood pressure. In the AH + ET group, 14 patients (53.8%) had highly abnormal blood pressure, and 12 patients (46.2%) had grade 1 AH. Of the 26 patients with CHT, highly normal blood pressure was detected in 2 people (7.7%), grade 1 AH in 14 people (53.8%), grade 2 AH in 4 people (15.4%), and grade 3 AH in 6 people (23.1%) (Figure 1).

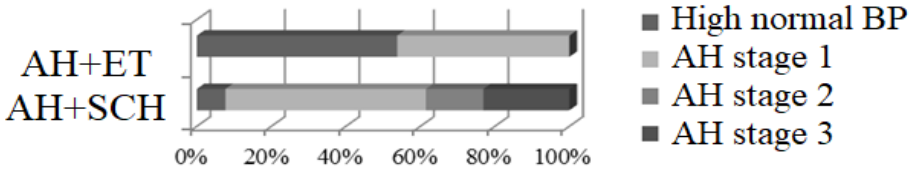

Fig.1. The structure of the stages of hypertension in the groups AH + ET and AH + SCH.

In the main group, the proportion of patients with AH II (p = 0.020) and III (p <0.001) is significantly higher and the proportion of patients with high normal blood pressure (p <0.001) is smaller.

Analysis of the occurrence of various types of circadian rhythm of blood pressure in the examined groups showed that in the main group, 5 people (18.4%) had the type “dipper”, 11 (42.3%) - “non-dipper” and 10 (39.3%) - “night-picker”. In the group of AH + ET patients with circadian rhythm type AD “dipper” 15 (57.7%) were detected, “non-dipper” - 9 (34.6%), “night-picker” - 2 (7.7%).

Figure 2 shows the ratio of types of ENBPD in the main group and the comparison group.

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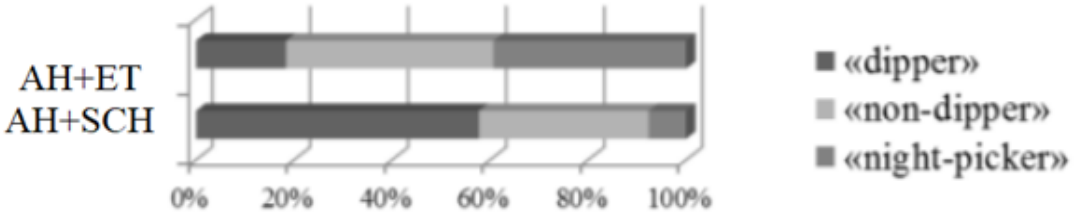

Fig. 2. The ratio of types of ENBPD in the compared groups.

In the group AH + SCH, the share of "night-picker" (p = 0.004) are significantly larger and less for "dipper" (p = 0.002). At the same time, the share of "non-dipper" is not significantly different (p = 0.285).

Thus, it is possible to conclude about a more severe course of hypertension in patients with ATD with SCH, compared with patients who do not have thyroid disease and thyroid status disorders.

In the course of the present study, the characteristics of target organ damage - heart and kidney - were also evaluated in patients with hypertension and ATD, accompanied by SCH. To assess the signs of left ventricular myocardial hypertrophy (LVH), the thickness of the interventricular septum (TMV), the left ventricular posterior wall thickness (LVPWT), end-diastolic size (EDS) and the left ventricular mass index (LVMI) were determined. Comparison of these indicators and the reliability of their differences between the groups are presented in table 3.

Table 3: Linear parameters and the left ventricular mass in patients of the compared groups

Indicators	AH+ET, n=26	AH+SCH	p
EDS, cm	**5,1±0,5**	**5,5±0,4**	**0,003**
TMV, cm	1,0±0,15	1,1±0,2	0,05
LVPWT, cm	1,0±0,15	1,1±0,3	0,135
LVM, cm	**188,3±10,4**	**250,6±12,2**	**<0,001**
LVMI, g/m^3	**93,1±3,5**	**138,4±6,2**	**<0,001**

Based on the data presented in Table 3, it was found that of the linear dimensions of the left ventricle, only the EDS differs statistically significant: in patients of the AH + SCH group, this indicator is bigger (p = 0.003). LVPWT and TMV in patients of the main group and the comparison group do not differ significantly (p = 0.135 and p = 0.05, respectively). LVMI is significantly higher in patients with AH and ATD with SCH (p <0.001).

Comparison of the functional status of the kidneys showed statistically significant higher levels of creatinine (130.0 ± 6.9 vs 101.8 ± 14.2; p <0.001) in patients with hypertension and autoimmune thyroid disease (130.0 ± 6.9 vs 101.8 ± 14.2; p <0.001) and significantly lower glomerular filtration rate (62.7 ± 17.5 vs 80.7 ± 16.7 ml / min / 1.73 m2; p <0.001).

All patients who participated in the study received antihypertensive drugs in the form of mono-, two- and three-component therapy. In the AH + ET group, monocomponent antihypertensive therapy was prescribed in 3 patients (11.5%), two-component - 16 (61.5%), three-component - 7 (27%), in the AH + SCH group 1 patient (3.9%) received one antihypertensive drug, 9 patients (34.6%) - two drugs and 16 patients (61.5%) - three drugs.

As the data show, the proportion of patients who were prescribed a permanent two-component (p = 0.031) and three-component (p = 0.009) antihypertensive therapy in the main group was significantly higher. At the same time, the proportion of patients who received constant monocomponent antihypertensive therapy did not differ significantly between the main group and the comparison group (p = 0.134).

In the background of ongoing antihypertensive therapy, most patients in both groups felt the need to take emergency medications.

The shares of patients of the groups AH + ET and AH + SCH, additionally receiving antihypertensive drugs for emergency care, are presented in Figure 3.

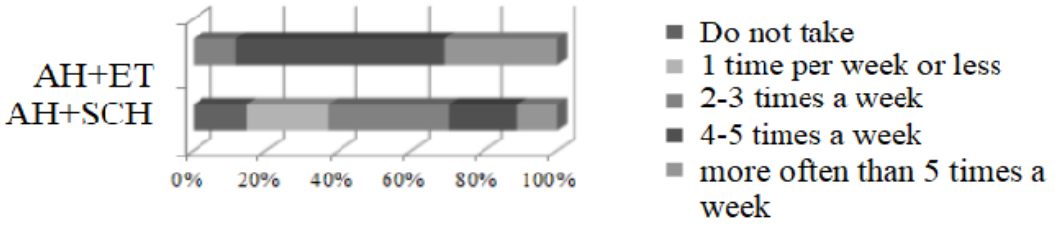

Fig. 3. Ratio of frequencies of additional antihypertensive medication in the groups AH + ET and AH + SCH.

Analysis of the frequency of additional antihypertensive medication showed that in the AH + SCH group compared with the AH + ET group, the proportion of patients taking additional antihypertensive drugs 4-5 times a week (57.7% vs 18.4%; p = 0.004) and more often than 5 times a week (30.8% vs 11.5%; p = 0.047), and the proportion of patients who do not need an additional dose of antihypertensive drugs that need 1 time a week or less, and 2-3 times week is significant less (0% vs 15.4%, p = 0.021, 0% vs 23.1%, p = 0.006 and 11.5% vs 34.6%, p = 0.030, respectively).

CONCLUSIONS

1. In patients with hypertension and autoimmune pathology of the thyroid gland accompanied by SCH, there is a more unfavorable course of hypertension than in patients with normal thyroid status: they have a higher degree of hypertension and more often the prognostically unfavorable type of circadian rhythm “night-picker”.

2. In the background of autoimmune thyroid pathology in patients with hypertension, a more pronounced target organ damage is observed: a greater severity of LVH and a lower glomerular filtration rate than those examined who do not have thyroid disease and thyroid status disorders.

3. Concomitant autoimmune pathology of the thyroid gland contributes to reducing the effectiveness of antihypertensive therapy: to achieve a target level of blood pressure, it is necessary to prescribe a larger number of drugs, while patients with SCH in the background of ATD more often need to take additional antihypertensive drugs.

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