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THE ASSOCIATIONS OF T344C SINGLE NUCLEOTIDE POLYMORPHISM OF ALDOSTERONE SYNTHASE GENE CYP11B2 (RS1799998) WITH CLINICAL, HAEMODYNAMIC AND METABOLIC FEATURES OF PATIENTS WITH ARTERIAL HYPERTENSION AND ABDOMINAL OBESITY*

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Primary or essential form of arterial hypertension (AH) and its comorbidity with abdominal obesity (AO) remains one of the topical problems of modern cardiology and therapy [1]. Some clinical and experimental studies indicated particularly unfavorable current of essential AH with AO [1, 2].

Aldosterone (AL) activation plays significant role in the pathogenesis of AH and AO. AL causes an increase in sodium reabsorption in the kidneys, circulating blood volume, blood pressure (BP), contributes to the development of insulin resistance, hyperglycemia, dyslipidemia, stimulation of myocardial hypertrophy and fibrosis [3].

Aldosterone synthase (ALS) is an enzyme, which involved in AL formation [4]. Currently, studies conducted in both European and Asian populations show the relationship between ALS gene *CYP11B2* T344C single nucleotide polymorphism (SNP) and the development of number of diseases such as type 2 diabetes, metabolic syndrome, myocardial infarction as well as with AH [4–6]. However, in the European population only TT genotype was associated with AH from the described three genotype variants T344C SNP of ALS gene [5].

One of the early complications of AH is left ventricular hypertrophy (LVH), in the develop-

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ment of which both haemodynamic and numerous humoral and genetic factors take part [1, 7, 8]. In number of studies conducted in the European population, a connection was found between T344C SNP of ALS gene and LVH [5, 9]. However, the role of ALS gene *CYP11B2* T344C SNP in both the pathogenesis of AH and its complications remains poorly understood [10].

The aim of our work is to study the association between T344C SNP of ALS gene *CYP11B2* (rs1799998) with anthropometric, clinical, haemodynamic, structural and metabolic parameters of patients with AH and AO.

MATERIALS AND METHODS

In specialized department of hypertension and kidney diseases of the Government Institution «L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine» 112 patients (54 Men and 58 Women) with AH, stage II, 2-3 degrees and AO in accordance to ESC/ESH Recommendations, 2018 [6] at the age of 45–69 years (average age — (49 ± 6) years) were examined.

Presence of AO was diagnosed using body mass index (BMI), waist and hip circumference (WC, HC), according to IDF Recommendations, 2005. Average duration of AH was (12.5 ± 1.4) years, average duration of AO was (13.2 ± 1.8) years. 85 patients (76%) with AH and AO had burdened heredity in relation to AH (BH +), 27 patients (24%) were no burdened heredity (BH –). Among the examined patients, 90 patients (80%) had combined dyslipidemia (DLP), 74 patients (66%) — early disorders of carbohydrate metabolism, such as impaired glucose tolerance (IGT) — in 42 patients (38%), fasting glycemia (FG) — in 26 patients (23%) and combination of IGT and FG — in 6 patients (5%). Depending on the presence of LVH, AH patients with AO were divided into 2 groups: with LVH (67 patients (60%) and without LVH (45 patients (40%).

The control group was represented by 28 practically healthy residents of Kharkiv city at the appropriate age and gender without signs of EH and AO, the average age was (41 ± 4) years.

Patients underwent anthropometric measurements, general clinical and haemodynamics indices, parameters of the expanded lipid spectrum were evaluated. The levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) in serum were determined by the enzymatic method with subsequent calculation the serum level of low-density lipoprotein cholesterol (LDL-C). The state of carbohydrate metabolism by the fasting blood glucose level (BGL) and in oral glucose tolerance test (OGTT) was assessed. AL levels were determined using AL ELISA kits, DRG Instruments, GmbH. Genotyping of T344C SNP of ALS gene *CYP11B2* (rs1799998) was carried out by polymerase chain reaction (PCR) in real-time (BioRad Laboratories Pte. Ltd., Singapore).

The researches have been conducted in accordance with International Standards for the Coordinated Participation of the Surveyed, the Ethical Component of the Research and the Taking of Biomaterials. Written informed consent was obtained from all patients.

Statistical processing of the results was performed using variation statistics computer licensed software programs «SPSS», comparing the differences between groups by using Student's t-test and Student's t-test for multiple comparisons with the Bonferroni amendment, the Chi-Square Test for Hardy-Weinberg Expectations ($\chi 2$). Odds Ratio (OR) was calculated according to Bland J. M., 2000. The methods of correlation analysis (r Spirman) were also used. The value of the confidence interval (CI) which was accepted as statistically significant was 95% *(95% CI)* (significance level $p = 0.05$).

RESULTS AND THEIR DISCUSSION

The distribution of the examined AH patients with AO and control group for the polymorphic variants of T344C SNP ALS gene CYP11B2 is given in Table. There were no significant differences in the distribution of T344C SNP of ALS gene *CYP11B2* between the control group and AH patients with AO in the genotypes ($p > 0.05$). The frequence of T allele

Table

The frequency of T344C single nucleotide polymorphisms of aldosterone synthase gene CYP11B2 in patients with essential hypertension and abdominal obesity and healthy residents of Kharkiv city (abs, %)

Patients	Control (n = 28)		Patients with EH and AO (n = 112)		X^2	p	OR (95% CI)
Genotypes	abs.	%	abs.	%			
TC Genotypes	8	29.9	52	46.4	1.05	0.305	2.10 (0.44–4.31)
TT Genotypes	10	35.5	23	20.5	1.07	0.300	0.458 (0.23–2.24)
CC Genotypes	10	35.5	37	33.1	8.01	0.897	0.917 (0.32–2.91)

Student t test;
p — significance of difference between EH patients with AO and control group.

was 0.500 in the control, 0.433 in patients with AH and AO, C allele — 0.500 in the control and 0.567 in patients with AH and AO ($p > 0.05$). The sum parts of «hypertensive» TT and TC genotypes [5] was (18/28 = 64.5%) in control against (75/112 = 66.9 %) in AH patients with AO ($p > 0.05$).

In the analysis, there were no significant differences in T344C SNP of ALS gene *CYP11B2* depending on anthropometric particular patients (the body weight (BW), BMI, WC and HC) and integral haemodynamic parameters (the levels of systolic and diastolic BP (SBP, DBP), heart rate (HR). The distribution of T344C SNP ALS gene CYP11B2 by genotypes also did not differ significantly among patients with AH and AO depending on the presence or absence of burdened heredity in relation to AH (BH). The sum of parts of «hypertensive» TT + TC genotypes were (61/85 = 71.8%) in patients with AH and AO and BH presence and (14/27 = 51.8%) in patients with BH absence ($p > 0.05$).

When analyzing the relationship between T344C SNP of ALS gene *CYP11B2* (rs1799998) with metabolic parameters of patients with AH and AO the following data were obtained. There were no significant differences in T344C SNP of ALS gene *CYP11B2* depending on the serum levels of TC, TG, LDL-C and fasting BGL and after OGTT in examined patients.

At the same time in our study, the significant differences in HDL-C levels depending on T344C SNP of ALS gene *CYP11B2* between genotypes was obtained. The serum level of HDL-C in patients with TT genotype (1.40 ± 0.32 mmol/L) was significantly higher than in patients with TC genotype (1.12 ± 0.23 mmol/L) ($p = 0.01$). Perhaps, that high level of HDL-C in AH patient and AO with TT genotype was due to the stimulation effects of this lipid fraction on AL synthesis through increased expression of ALS, which is described in literature [11]. At the same time there are no significant differences in AL levels depending on the polymorphic variants of ALS gene *CYP11B2:* AL levels for TT genotypes — (172.62 ± 18.15) pg/mL vs (146.73 ± 14.41) pg/mL for TC genotypes ($p = 0.34$) and vs (191.67 ± 19.08) for CC genotypes ($p = 0.58$).

Certain differences in the distribution of T344C SNP of ALS gene *CYP11B2* by genotypes, depending on LVH presence or absence in patients with AH and AO were obtained. The sum of parts of «hypertensive» TT + TC genotypes were (18/28 = 64.5%) in the control and (55/67 = 82.1%) ($p > 0.05$) in AH patients with AO and LVH presence, and only (20/45 = 44.4%) in patients with LVH absence ($p < 0.05$). In patients with LVH presence, a significant prevalence of «hypertensive» TT + TC genotypes expressiveness of ALS gene *CYP11B2* was observed ($p < 0.05$).

This fact demonstrates a significant association of «hypertensive» genotypes of ALS gene *CYP11B2* with LVH formations, which is consistent with the results of studies in the European population [5,9,10].

When analyzing the correlations between T344C SNP of ALS gene *CYP11B2* (rs1799998) with studied anthropometric, clinical, haemodynamic, structural and metabolic parameters

of patients with AH and AO the following data were obtained. The significant direct correlations between «hypertensive» T allele frequency and AH duration (r = – 0, 35, p < 0, 05) and left ventricular mass index (r = + 0, 46, p < 0.05) and left atrium diameter (r = + 0, 37, p < 0.05) were found.

CONCLUSIONS

1. The distribution of T344C single nucleotide polymorphism genotypes of aldosterone synthase gene *CYP11B2* among healthy individuals and patients with arterial hypertension and abdominal obesity does not significantly differ and is similar to that in the European population.
2. The serum level of HDL-C in patients with TT genotype was significantly higher than in patients with TC genotype (p = 0.01).
3. The association between TT + TC genotypes of ALS gene *CYP11B2* and left ventricular hypertrophy (p < 0.05) in the examined patients was shown.
4. The significant direct correlations between «hypertensive» T allele of aldosterone synthase gene frequency and the duration of arterial hypertension and the severity of pathological remodeling of the heart were found.

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THE ASSOCIATIONS OF T344C SINGLE NUCLEOTIDE POLYMORPHISM OF ALDOSTERONE SYNTHASE GENE CYP11B2 (RS1799998) WITH CLINICAL, HAEMODYNAMIC AND METABOLIC FEATURES OF PATIENTS WITH ARTERIAL HYPERTENSION AND ABDOMINAL OBESITY

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The aim: To study the association between T344C single nucleotide polymorphism (SNP) of aldosterone synthase (ALS) gene *CYP11B2* (rs1799998) with anthropometric, clinical, haemodynamic, structural and metabolic parameters of patients with arterial hypertension (AH) and abdominal obesity (AO).

Materials and methods: 112 patients with AH II stage, 2–3 degrees with AO aged 45–69 years were surveyed. Control group is composed of 28 healthy city residents of the appropriate age and gender. Haemodynamic parameters, blood glucose levels, glucose tolerance test, the expanded lipid spectrum, aldosterone levels were evaluated. Genotyping of T344C SNP of ALS gene *CYP11B2* was performed by polymerase chain reaction in real-time. Statistical data processing was carried out using SPSS packages.

Results: The distribution of T344C SNP genotypes of ALS gene *CYP11B2* among healthy individuals and patients with AH and AO does not significantly differ and is similar to that in the European population. The serum level of HDL-C in patients with TT genotype was significantly higher than in patients with TC genotype ($p = 0.01$). The association between TT + TC genotypes of ALS gene *CYP11B2* and left ventricular hypertrophy (LVH) ($p < 0.05$) in the examined patients was shown. The significant direct correlations between «hypertensive» T allele of aldosterone synthase gene frequency and the duration of AH and the severity of LVH were found.

Conclusions: The associations between TT + TC genotypes T344C SNP of ALS gene, and the presence of LVH as well as between TT genotypes and elevated serum level HDL-C in AH patients with AO were established.

Key words: arterial hypertension, abdominal obesity, single nucleotide polymorphism, aldosterone synthase gene.

АСОЦІАЦІЇ ОДНОНУКЛЕОТИДНОГО ПОЛІМОРФІЗМУ T344C ГЕНУ АЛЬДОСТЕРОН-СИНТАЗИ CYP11B2 (RS1799998) З КЛІНІЧНИМИ ГЕМОДИНАМІЧНИМИ ТА МЕТАБОЛІЧНИМИ ОСОБЛИВОСТЯМИ ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ І АБДОМІНАЛЬНИМ ОЖИРІННЯ

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Мета: Вивчити асоціації між однонуклеотидним поліморфізмом (ОНП) T344C гену альдостерон-синтази (АС) *CYP11B2* (rs1799998) і антропометричними, гемодинамічними, структурними та метаболічними параметрами у пацієнтів на артеріальну гіпертензію (АГ) з абдомінальним ожирінням (АО).

Матеріали та методи. Обстежено 112 пацієнтів на АГ II стадії, 2–3 ступеня з АО у віці 45–69 років. Контрольну групу склали 28 здорових мешканців міста відповідного віку і статі. Оцінювали гемодинамічні параметри, рівні глюкози в крові натще, після глюкозо-толерантного тесту, розгорнутий ліпідний спектр, рівні альдостерону (АЛ). Генотипування ОНП T344C гена АС *CYP11B2* проводили за допомогою полімеразної ланцюгової реакції в режимі реального часу. Статистична обробка даних проводилася з використанням пакетів SPSS.

Результати. Розподіл генотипів ОНП T344C гена АС серед здорових осіб і пацієнтів на АГ з АО достовірно не відрізнявся, що співпадає з даними, які отримані в європейських популяціях. Рівень холестерину ліпопротеїнів високої щільності (ХС ЛПВЩ) в сироватці крові у пацієнтів з ТТ генотипом був достовірно вищий, ніж у пацієнтів з ТС генотипом ($p = 0,01$). Була виявлена асоціація між ТТ + ТС генотипом гена АС і наявністю гіпертрофії лівого шлуночка (ГЛШ). Встановлені достовірні прямі кореляції між частотою Т еллелю гена АС і тривалістю АГ та вираженістю ГЛШ у даних пацієнтів.

Висновки. Встановлені асоціації між ТТ + ТС генотипами ОНП T344C гена АС і наявністю ГЛШ, а також між ТТ генотипом і підвищенним рівнем ХСЛПВЩ в сироватці крові у хворих на АГ з АО.

Ключові слова: артеріальна гіпертензія, абдомінальне ожиріння, однонуклеотидний поліморфізм, ген альдостерон-синтази.

АССОЦИАЦИИ ОДНОНУКЛЕОТИДНОГО ПОЛИМОРФИЗМА T344C ГЕНА АЛЬДОСТЕРОНСИНТАЗЫ CYP11B2 (RS1799998) С КЛИНИЧЕСКИМИ, ГЕМОДИНАМИЧЕСКИМИ И МЕТАБОЛИЧЕСКИМИ ОСОБЕННОСТЯМИ БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ И АБДОМИНАЛЬНЫМ ОЖИРЕНИЕМ

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Цель: Изучение ассоциации между однонуклеотидным полиморфизмом (ОНП) T344C гена альдостерон-синтазы (АС) *CYP11B2* (rs1799998) и антропометрическими, гемодинамическими, структурными и метаболическими параметрами у пациентов с артериальной гипертензией (АГ) и абдоминальным ожирением (АО).

Материалы и методы. Обследовано 112 пациентов с АГ II стадии, 2–3 степени с АО в возрасте 45–69 лет. Контрольную группу составили 28 здоровых жителей соответствующего возраста и пола. Оценивали гемодинамические параметры, уровни глюкозы в крови натощак, после глюкозо-толерантного теста, развернутый липидный спектр, уровни альдостерона. Генотипирование ОНП T344C гена АС *CYP11B2* проводили с помощью полимеразной цепной реакции в режиме реального времени. Статистическая обработка данных проводилась с использованием пакетов SPSS.

Результаты. Распределение генотипов ОНП T344C гена АС среди здоровых лиц и пациентов з АГ и АО достоверно не отличались, что совпадает с данными полученными в европейских популяциях. Уровень холестерина липопротеинов высокой плотности (ХС ЛПВП) в сиворотке крови у пациентов с ТТ генотипом был достоверно более высоким, чем у пациентов с ТС генотипом ($p = 0,01$). Была выявлена ассоциация между ТТ + ТС генотипом гена АС и наличием гипертрофии левого желудочка (ГЛЖ). Обнаружены достоверные прямые корреляции между частотой Т аллеля гена АС, длительностью АГ и выраженостью ГЛЖ у данных пациентов.

Выводы. Установлены ассоциации между ТТ + ТС генотипом ОНП T344C гена АС и наличием ГЛЖ, а также между ТТ генотипом и повышенным уровнем ХС ЛПВП у сыворотке крови больных АГ и АО.

Ключевые слова: артериальная гипертензия, абдоминальное ожирение, однонуклеотидный полиморфизм, ген альдостерон-синтазы.