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Features of APOE polymorphism in patients with arrhythmias depending on the severity of cognitive disorders

Abstract. *Carriers of APOE4 polymorphism are at increased risk of cognitive decline. The purpose of this work was to investigate the relationship between genetic (APOE gene polymorphism) indicators and the development of cognitive disorders in patients with arrhythmias.* ***Materials and methods.*** *A comparative analysis of the frequency of genotypes and alleles of polymorphic variants of the APOE gene was conducted. It involved 110 patients aged from 30 to 75 years (mean age 63.8 ± 4.3 years): the basic group included 86 individuals with cognitive disorders on the background of different forms of arrhythmias and the control group consisted of 24 patients with arrhythmia without cognitive impairment.* ***Results.*** *The predominance of ε3/ε3 genotype was found in 57 % of people with cognitive disorders and in 54.2 % without cognitive decline (p = 0.07). The least common was ε4/ε4 genotype, the frequency of which in cognitive impairment was 5.8 %; in patients without cognitive disorders, it was not detected at all (p < 0.001). Among heterozygous genotypes, ε3/ε4 was found in 19.8 % of patients with cognitive disorders and in 16.6 % without cognitive decline (p = 0.06); ε2/ε3 — in 11.6 and 20.8 % (p = 0.026), respectively. Individuals with mild cognitive impairment tended to accumulate genotypes ε2/ε3, ε3/ε3 and decrease genotypes ε2/ε4, ε3/ε4, which did not reach the level of statistical significance compared to those without cognitive disorders (p = 0.06). Among patients with moderate cognitive impairment, there were no carriers of ε2/ε2 and ε2/ε3 genotypes, and the frequency of carriers of ε3/ε4, ε4/ε4 genotypes (p = 0.034) increased.* ***Conclusions.*** *Carriage of the ε4 APOE allele is an additional factor that increases the risk of cognitive disorders in patients with arrhythmias, carriage of the ε2 allele can be considered a protective factor against the development of cognitive impairment.*

Keywords: *cognitive disorders; arrhythmias; APOE4; genotype*

Introduction

Disorders of higher cerebral functions are one of the most pressing medical and social problems, as they lead to a decrease in the quality of life, disorders of social and professional activities, and in the long run — to the development of dementia and complete social disadaptation [1–4]. Early diagnosis of cognitive disorders makes it possible to prescribe timely treatment and predict the onset of disability. Predementia cognitive disorders are of clinical significance since they are more amenable to therapeutic correction [5]. Detection of early, potentially reversible cognitive disorders on the background of cardiovascular pathology gives the opportunity to quickly identify groups of patients with an increased risk of cognitive dysfunction, especially among working-age population.

Most studies on cognitive disorders have investigated the role of arterial hypertension and cerebral atherosclerosis in their occurrence [6–9] but the effect of cardiac arrhythmias on the development of cognitive deficits has not been sufficiently studied.

One of the risk factors for cognitive decline is a genetic predisposition caused by a mutation in the apolipoprotein E

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(APOE, ε4) gene on chromosome 19 [10–12]. Carrying the ε4 allele of the APOE gene is associated with an increased risk of developing Alzheimer's disease, as well as an earlier age of cognitive disorders. The relationship between APOE4 and β-amyloid causes the formation of atherosclerotic plaques, and the relationship with the tau protein explains the formation of neurofibrillary tangles [12–14].

Various studies, including those in non-dementia patients, have shown the effect of APOE4 on memory, information processing, and other aspects of cognitive functions [15–17]. Identification of genetic factors associated with a high risk of cognitive dysfunction would make it possible to take preventive measures long before the onset of clinical symptoms.

An integrated approach to the study of the mechanisms of cognitive disorders in patients with arrhythmias, their early diagnosis, choosing the right treatment strategy for arrhythmias can slow the progression of cognitive deficits, which will improve not only the clinical status of patients but also their prognosis. The above positions determined the relevance of the chosen direction of research and its purpose.

The purpose of this study was to investigate the relationship between genetic (APOE gene polymorphism) indicators and the development of cognitive disorders in patients with arrhythmias.

Materials and methods

One hundred and ten patients aged from 30 to 75 years (mean age 63.8 ± 4.3 years old) were examined, of which 86 individuals were in the basic group and 24 in the control group. The basic group included patients with cognitive disorders on the background of different forms of arrhythmias: 31 (36 %) with persistent (paroxysmal) form of atrial fibrillation, 26 (30.2 %) with permanent form of atrial fibrillation, 16 (18.6 %) with atrioventricular block degrees II–III, and 13 (15.2 %) people with sick sinus syndrome. The control group was represented by patients with arrhythmias without cognitive disorders.

Background diseases, which led to the development of arrhythmias, were ischemic and/or hypertensive heart disease — 58 (67.4 %) cases, non-coronary myocardial diseases — 14 (16.3 %), chronic rheumatic heart disease — 8 (9.3 %), thyroid pathology — 6 (7 %).

Criteria for the inclusion of patients in the study: age up to 75 years; the presence of arrhythmias verified on the basis of clinical data, electrocardiography (ECG); daily ECG monitoring; patient's ability to carry out productive contact with a doctor to evaluate cognitive status; voluntary informed patient's consent or, if necessary, the consent of the person who takes care of the patient.

Criteria for the exclusion of patients in the study: the absence of a voluntary informed patient's consent; vascular dementia (total score on the Mini-Mental State Examination (MMSE) < 24, on the Frontal Assessment Battery (FAB) < 11, on the Mattis Dementia Rating Scale (MDRS) < 115); other possible causes of cognitive disorders, including cerebrovascular diseases: Parkinson's disease and parkinsonian syndrome, Huntington's disease, Wilson-Konovalov disease, normal pressure hydrocephalus, brain tumors (primary and metastatic), neuroinfections, epilepsy, demyelinating diseases, Alzheimer's disease, frontotemporal degeneration, Lewy body dementia; brain injuries and their consequences, which are the only cause of cognitive deficits; acute cerebrovascular disorders; unstable angina, myocardial infarction during the last 3 months; any somatic diseases in the stage of decompensation, mental illness or alcoholism (including daily consumption of more than 30 ml of alcohol for the last 3 months), drug dependence. These criteria are due to the need to separate as much as possible the influence on the study results of pathology with a proven effect on cognitive functions.

Neuropsychological testing [18–20] was performed to rule out dementia. It included screening with MMSE (M. Folstein et al., 1975), FAB (B. Dubois et al., 2000), MDRS (S. Mattis, 1976), State-Trait Anxiety Inventory (C.D. Spilberger et al., 1976), Beck's Depression Inventory (A.T. Beck et al., 1975). Extensive neuropsychological testing was performed to determine the neuropsychological profile and the structure of cognitive disorders [21–25]. It included the following tests: 10 words (A.R. Luria, 1969), 5 words (E. Grober et al., 1988), verbal association test (A. Kazdin, 1982), Judgment of Line Orientation (A. Benton, 1975), unpainted objects (A.R. Luria, 1969), clock drawing (T. Sunderland et al., 1989), test of connection of numbers and letters (Trail Making Test) (R.M. Reitan, 1958), Boston Naming Test (J. Kaplan et al., 1978). Mild cognitive disorders were determined by the criteria of N.N. Yakhno et al. (2005), moderate cognitive disorders — by the criteria of R.S. Petersen (2004).

A comparative analysis of the frequency of genotypes and alleles of polymorphic variants of the APOE gene was conducted. The study consisted of two stages. In the first stage, DNA was isolated from the nuclei of peripheral leukocytes. In the second stage, a polymerase chain reaction of the APOE gene fragment was performed, followed by restriction product length analysis with 6% polyacrylamide gel electrophoresis. The results of gel electrophoresis were studied by viewing and photographing on the Praktika device (Germany) in transmitted ultraviolet light on the MacroVue transilluminator (LKB, UK).

Based on the results, the presence of the ε2, ε3 or ε4 allele and the possible genotype of the patient (ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, ε4/ε4) were determined. The choice of patient groups was determined by the widely available literature on the influence of the APOE genotype not only on the state of cognitive functions but also on vascular risk factors.

The results of statistical processing of quantitative variables are represented by the means and standard deviations (M ± SD). In the study, application package Statistica for Windows v. 8.0 (StatSoft Inc, USA, 2012) was used in accordance with the recommendations for processing the results of biomedical research.

Results and discussion

With an objective evaluation of the cognitive sphere in the basic group using neuropsychological tests, the mild cognitive disorders were detected in 50 (58.1 %) patients, and moderate cognitive disorders — in 36 (41.9 %). Neuropsychological pattern in patients with arrhythmias is represent-

ed by neurodynamic and regulatory disorders manifested in the deterioration of executive functions, auditory verbal memory, spatial gnosis, perception, concentration, decreased speed of psychomotor processes. Mild cognitive disorders were more common in patients with persistent (paroxysmal) atrial fibrillation (odds ratio (OR) 1.47, confidence interval (CI) 1.13–1.88, p = 0.036), moderate cognitive disorders — in those with permanent form of atrial fibrillation (OR 2.15, CI 1.45–3.32, p < 0.001) and with atrioventricular block degrees II–III (OR 2.62, CI 1.51–4.13, p < 0.001).

Analysis of the frequency of genotypes depending on the presence of cognitive disorders revealed a natural predominance of ε3/ε3 genotype, which occurred with a frequency of 57 % (in individuals with cognitive disorders) and 54.2 % (in patients without cognitive disorders) (p = 0.07). The least common was ε4/ε4 genotype, it was detected in 5.8 % of patients with cognitive disorders and was not found in people without cognitive impairment (p < 0.001). Among heterozygous genotypes, patients with cognitive disorders most often had ε3/ε4 genotype (19.8 %); its frequency in individuals without cognitive disorders was 16.6 % (p = 0.06). In patients with cognitive decline, ε2/ε3 genotype was detected in 11.6 % of cases, and those without cognitive disorders — in 20.8 % (p = 0.026) (Fig. 1).

Among individuals with cognitive disorders, 27 (31.4 %) carriers of at least one ε4 allele were identified. Other patients had ε2/ε2, ε2/ε3, ε3/ε3 genotypes, which according to the most literature data are not risk factors for neurodegenerative pathology.

People with mild cognitive disorders tended to accumulate genotypes ε2/ε3, ε3/ε3 and decrease genotypes ε2/ε4, ε3/ε4, which did not reach the level of statistical significance compared to the patients without cognitive impairment (p = 0.06) (Table 1). Among individuals with moderate cognitive disorders, there were no carriers of ε2/ε2 and ε2/ε3 genotypes, and the frequency of ε3/ε4, ε4/ε4 genotypes increased (p = 0.034).

Carrying the ε4 allele of the APOE gene at the trend level is associated with an increase in very-low-density lipoprotein cholesterol. Associations with the concentration of triglycerides and high-density lipoprotein cholesterol were not found. In patients with two ε4 alleles, plasma levels of total cholesterol and very-low-density lipoprotein cholesterol were significantly higher than in carriers of one allele and in the absence of the APOE4 genotype (p = 0.024 and p = 0.018, respectively). These results confirm the hypothesis of some researchers about the effect of APOE4 on the synthesis of very-low-density lipoprotein cholesterol [26].

Patients who were ε4 carriers by ε2/ε3/ε4 APOE polymorphism had higher C-reactive protein, interleukin-6 compared with non-carriers but no significant difference was found (p > 0.05 for both comparisons). The content of tumor necrosis factor α tended to increase in non-carriers of the ε4 allele compared to individuals with APOE4(+) (p = 0.06).

Patients with APOE4(+) compared to those with APOE4(–) had significantly higher indicators that characterized the condition of the lateral ventricles (p = 0.031). The width of the subarachnoid space at the level of the frontal pole differed significantly between the studied groups: 5.9 ± 0.5 mm vs. 4.2 ± 0.7 mm, respectively (p = 0.049). In the group of APOE4(+), the size of the third ventricle was 6.1 ± 0.5 mm, of APOE4(–), it was 5.7 ± 0.8 mm (p = 0.67). Patients with APOE4(+) were diagnosed with internal cerebral atrophy more than 1.6 times often (in 44.0 % of cases): mild — in 27.3 %, moderate — in 45.4 %, severe — in 27.3 %; in the APOE4(–) group, this indicator was 27.9 % (mild — in 58.8 %, moderate — in 41.2 %). When analyzing the morphometric characteristics, it can be stated that in patients of basic main group with the studied APOE genotype, cognitive disorders developed against the background of atrophic brain process.

APOE4 carriage had a greater negative impact on the mnestic sphere of cognitive activity (Table 2).

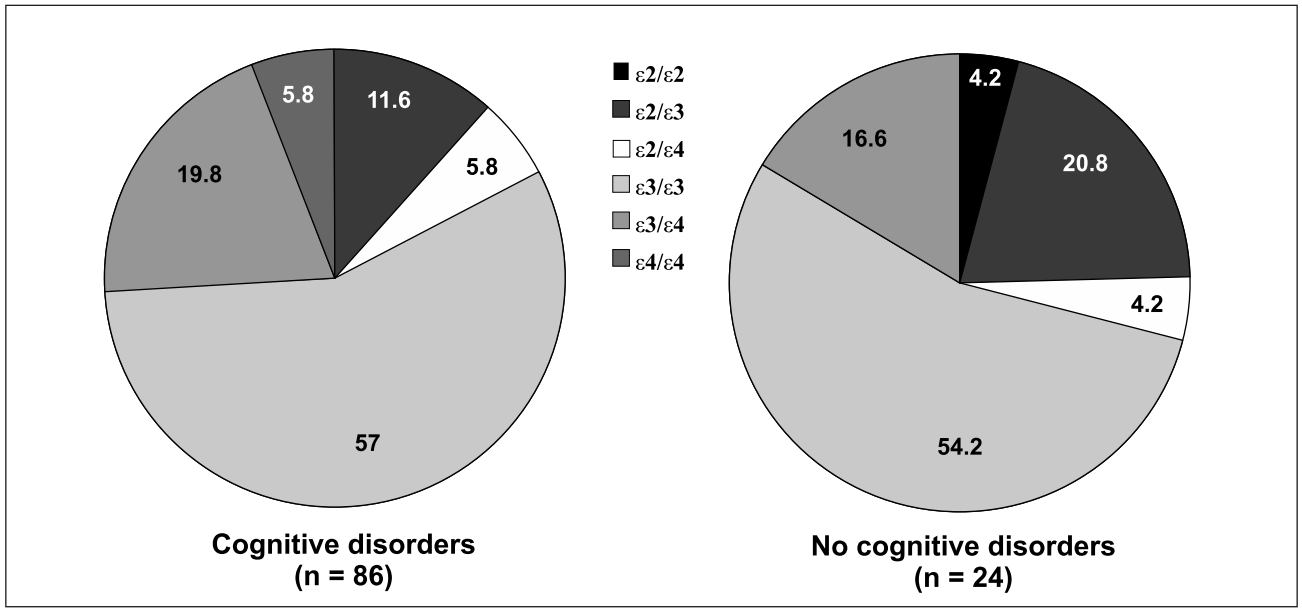

Figure 1. The frequency of ε genotypes of the APOE gene in the studied groups, %

Table 1. Frequency of ε genotypes of the APOE gene among patients with arrhythmias depending on the severity of cognitive disorders, n (%)

Genotype	No cognitive disorders (n = 24)	Mild cognitive disorders (n = 50)	Moderate cognitive disorders (n = 36)
ε2/ε2	1 (4.2)	0*	0*
ε2/ε3	5 (20.8)	10 (20)	0*♦
ε2/ε4	1 (4.2)	2 (4)	3 (8.3)
ε3/ε3	13 (54.2)	28 (56)	21 (58.3)
ε3/ε4	4 (16.7)	8 (16)	9 (25)*
ε4/ε4	0	2 (4)*	3 (8.3)*♦

Notes: * — statistically significant differences compared to the individuals without cognitive decline (p < 0.05); ♦ — statistically significant differences compared to the group of patients with mild cognitive disorders (p < 0.05).

Table 2. The results of neuropsychological examination of patients in the basic group with different APOE4 genotype

Neuropsychological tests	APOE4(+)	APOE4(–)	p
MMSE	24.0 ± 0.8	25.8 ± 0.4	0.045
FAB	13.2 ± 0.6	14.8 ± 0.4	0.028
MDRS	121.2 ± 2.1	128.4 ± 2.9	0.046
10 words			
Direct reproduction: — first; — second; — third. Delayed reproduction	 3.3 ± 0.2 3.8 ± 0.3 4.4 ± 0.4 4.2 ± 0.4	 4.5 ± 0.5 5.3 ± 0.6 6.1 ± 0.7 6.8 ± 0.8	 0.027 0.026 0.036 0.004
5 words			
Direct reproduction: — first; — second. Delayed reproduction	 2.2 ± 0.2 2.5 ± 0.3 2.7 ± 0.3	 3.0 ± 0.3 3.5 ± 0.4 3.9 ± 0.5	 0.028 0.047 0.041
Literal associations	7.8 ± 0.5	10.1 ± 0.8	0.016
Categorical associations	9.7 ± 0.8	12.8 ± 1.2	0.033
Judgment of Line Orientation	20.9 ± 1.1	22.7 ± 1.4	0.31
Unpainted objects	7.6 ± 0.2	8.4 ± 0.3	0.028
Clock-drawing test	7.8 ± 0.2	8.7 ± 0.4	0.045
Trail Making Test, block A	69.4 ± 3.8	58.8 ± 3.3	0.036
Trail Making Test, block B	142.1 ± 7.8	113.1 ± 6.2	0.004
Boston Naming Test, literal clues	6.8 ± 0.8	4.0 ± 0.5	0.003
Boston Naming Test, categorical clues	4.8 ± 1.0	2.2 ± 0.5	0.021
Reactive anxiety	44.3 ± 3.1	36.6 ± 2.3	0.047
Personal anxiety	42.6 ± 2.7	37.4 ± 2.5	0.16
Depression	17.5 ± 1.7	13.3 ± 1.2	0.045

Table 3. Relationship between the risk of cognitive disorders and APOE genotypes in patients with arrhythmias

Indicator	OR	95% CI	p
Cognitive disorders and ε2/ε3	0.65	0.14–1.27	0.006
Cognitive disorders and ε2/ε4	1.44	1.11–1.87	0.012
Cognitive disorders and ε3/ε3	0.81	0.32–1.47	0.026
Cognitive disorders and ε3/ε4	2.63	1.31–4.12	< 0.001
Cognitive disorders and ε4/ε4	4.25	2.57–6.18	< 0.001

Differences in cognitive disorders depending on the presence of the APOE4 genotype had various modalities and were associated with visual-spatial disorders (clock-drawing test) ($r = -0.57$, $p < 0.001$), memory disorders according to MMSE ($r = -0.51$, $p < 0.001$), 10 words ($r = -0.54$, $p < 0.001$) and 5 words tests ($r = -0.47$, $p = 0.001$), MDRS ($r = 0.44$, $p = 0.003$). Patients with APOE4 had more pronounced violations of regulatory functions, which was confirmed by a lower score on verbal associations ($r = -0.51$, $p < 0.001$), Trail Making Test, block B ($r = -0.48$, $p = 0.001$), Boston Naming Test ($r = 0.46$, $p = 0.001$).

Carriers of the APOE4(+) genotype had higher levels of depression and anxiety compared to those with the APOE4(–) genotype (OR 3.74, CI 1.72–7.38, $p = 0.008$). The presence of the ε4 allele contributes to the development of anxiety disorders and depression.

Carriage of the ε4 APOE allele is an additional factor that increases the risk of cognitive disorders in patients with arrhythmias, carriage of the ε2 allele can be considered a protective factor against cognitive disorders (Table 3).

Thus, a direct comparison of the results of neuropsychological research in patients with the APOE4(+) genotype revealed more pronounced cognitive decline. The APOE4(+) genotype is an unfavorable factor in the development of cognitive and affective disorders.

Conclusions

1. Carriage of the APOE4(+) genotype is associated with a greater rate of cognitive decline (OR 3.44, CI 1.94–5.15, $p < 0.001$), and carriage of the APOE4(–) genotype contributes to the preservation of cognitive functions (OR 0.73, CI 0.23–1.37, $p < 0.001$) in patients with cardiac arrhythmias.

2. Individuals with arrhythmias and risk factors for cognitive dysfunction should be genotyped with APOE, which will help identify groups at maximum risk of developing cognitive disorders and prevent them. If one or two ε4 alleles are detected, a control neuropsychological examination should be performed at least once every 3 months.

3. Further comprehensive study of the effect of APOE4 isoforms on the cognitive function of patients at risk of developing Alzheimer's disease, in particular those with amnesic mild cognitive impairment against the background of arrhythmias, seems to be important for the search for new methods to predict the course of cognitive disorders and develop individualized approaches to their therapy.

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Особливості поліморфізму гена APOE в пацієнтів з аритміями залежно від вираженості когнітивних розладів

Резюме. ***Актуальність.*** Носії поліморфізму APOE4 мають підвищений ризик зниження когнітивних функцій. ***Мета дослідження:*** вивчити взаємозв'язок між генетичними (поліморфізм гена APOE) показниками та розвитком когнітивних розладів у пацієнтів з аритміями. ***Матеріали та методи.*** Провели порівняльний аналіз частоти генотипів та алелей поліморфних варіантів гена APOE в 110 пацієнтів віком від 30 до 75 років (у середньому 63,8 ± 4,3 року): 86 осіб із когнітивними порушеннями на фоні різних форм аритмій становили основну групу, контрольна група включала 24 хворі з аритміями без когнітивних розладів. ***Результати.*** Переважання ε3/ε3 генотипу встановили в 57 % пацієнтів із когнітивними розладами та в 54,2 % без когнітивних порушень (p = 0,07). Найменш поширеним був ε4/ε4 генотип, частота якого при когнітивних розладах становила 5,8 %, у пацієнтів без когнітивних розладів його не знаходили (p < 0,001). Серед гетерозиготних генотипів ε3/ε4 виявили в 19,8 % пацієнтів із когнітивними розладами та в 16,6 % — без зниження когнітивних функцій (p = 0,06); ε2/ε3 — в 11,6 і 20,8 % (p = 0,026) відповідно. У пацієнтів із легкими когнітивними розладами існувала тенденція до накопичення генотипів ε2/ε3, ε3/ε3 і зниження генотипів ε2/ε4, ε3/ε4, що не досягало рівня статистичної вірогідності порівняно з особами без когнітивних порушень (p = 0,06). Серед пацієнтів із помірним зниженням когнітивних функцій немає носіїв генотипів ε2/ε2 і ε2/ε3, а також збільшена частота носійства генотипів ε3/ε4, ε4/ε4 (p = 0,034). ***Висновки.*** Носійство алеля ε4 APOE є додатковим чинником, що збільшує ризик розвитку когнітивних порушень у пацієнтів з аритміями, носійство алеля ε2 можна вважати протективним чинником щодо розвитку когнітивних розладів.

Ключові слова: когнітивні розлади; аритмії; APOE4; генотип