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Original paper

APOLIPOPROTEIN E GENE POLYMORPHISM AS A RISK FACTOR FOR ISCHEMIC CEREBROVASCULAR DISEASE

Sanja Stanković[1], Zagorka Jovanović-Marković[2], Nada Majkić-Singh[1], Aleksandra Stanković[3], Sanja Glišić[3], Maja Živković[3], Vladimir Kostić[2], Dragan Alavantić[3]

[1]Institute for Medical Biochemistry, University School of Pharmacy, Clinical Center of Serbia, Belgrade, Serbia Montenegro
[2]Institute of Neurology, Clinical Center of Serbia, Belgrade, Serbia & Montenegro
[3]VINČA Institute of Nuclear Sciences, Laboratory for Radiobiology and Molecular Genetics, Belgrade, Serbia & Montenegro

Summary: The possible association of apolipoprotein E (apoE) DNA polymorphism with ischemic cerebrovascular disease was evaluated in 65 patients who had suffered completed stroke or transient ischemic attack and 330 healthy controls. ApoE genotypes were determined by restriction isotyping/MADGE analysis. Significant difference in apoE genotype frequencies between case and control group was observed ($p<0.01$). Patients affected by ischemic stroke had higher frequency of E4 allele and lower E2 allele than age-matched control subjects. Compared with persons without E4 allele, carriers of an E4 allele had 2.1 times higher risk of incident stroke. Our results indicate that the apoE gene polymorphism may be a risk factor for the development of ischemic cerebrovascular disease in Serbian population..

Key words: apolipoprotein E, ischemic cerebrovascular disease, polymorphism

Introduction

Stroke is among the most common causes of mortality and morbidity in industrial countries. It primarily affects elderly people, but about 20% of strokes occur before the age of 65. Intracerebral and subarachnoid hemorrhages account for only 15 % of all strokes whereas the other 85 % are caused by cerebral ischemia and can be distinguished according to the cause, clinical syndrome or the arterial distribution. Besides well-documented conventional risk factors hypertension, cigarette smoking and diabetes mellitus, genetic factors influence the risk of stroke. The genetic etiology of ischemic stroke is polygenic and genetic factors may act either by predisposing to conventional risk factors, by modulating the effects of such conventional risk factors on the end organs, or by direct independent effect on stroke risk. The candidate »stroke risk« genes may be conveniently divided in five groups, affecting (i) lipid metabolism, (ii) the renin-angiotensin system, (iii) haemostasis, (iv) nitric oxide production and (v) homocysteine metabolism (1).

Apolipoprotein (apo) E is a plasma protein involved in the lipid metabolism. It is one of the major protein constituents of chylomicrons, very low density lipoproteins (VLDL), their remnant particles, and high density lipoproteins (HDL). On these particles, it serves as a ligand for the uptake by lipoprotein receptors. Circulating human apoE is a single-chain protein of 34.2 kDa, encoded by a single gene. Together with the apoCI, apoCI' and apoCII genes, the apoE gene forms a gene cluster on the long arm of chromosome 19 (19q13.2). The human apoE gene is polymorphic with three common alleles (E2, E3, E4) coding for three isoforms (E2, E3, E4). The molecular basis of apoE polymorphism is cysteine-arginine interchange. ApoE3 contains a single cysteine at residue 112 and an arginine at position 158; apoE2 contains cysteine residues at both positions 112 and 158; and apoE4 contains arginine residues at both

Address for correspondence:
Sanja Stanković
Institute for Medical Biochemistry, University School of Pharmacy
Clinical Center of Serbia, Belgrade, Serbia & Montenegro
Tel/fax: +381 11 3615631
e-mail:sanjast@EUnet.yu

positions. This polymorphism leads to the presence of six different phenotypes in the human population: three homozygous (E3/3, E2/2, and E4/4) and three heterozygous (E2/3, E2/4, and E3/4)(2). Many experimental and clinical observations suggest that apoE is implicated in the atherosclerotic process (3). A meta-analysis of 14 studies has shown apoE4 allele to be associated with CHD in both men and women (4). ApoE4 allele is also a major genetic susceptibility locus for the common forms of Alzheimer's disease (2). The relationship of apoE polymorphism and cerebrovascular disorders has been examined in a number of recent studies and they have produced conflicting results as to the importance of apoE alleles in predisposition to ischemic stroke.

The main purposes of the paper are a) to report the distribution of apoE genotypes and calculated frequencies of apoE alleles in patients with ischemic cerebrovascular disease, b) to determine whether a specific apoE polymorphism is a risk factor for ischemic cerebrovascular disease (ICVD; stroke or TIA). The results will be compared to the findings of other study populations, probably representing most of the published data referring to the apoE allele frequencies in various populations.

Material and Methods

Sample

Blood samples were obtained from 65 patients (women and men) younger than 65 years, who had suffered completed stroke (large-vessel stroke and lacunar stroke) or transient ischemic attack. These were proven by computed tomography or magnetic resonance of the brain. Atherosclerosis of the eye bottom and carotide and vertebral arteries was assessed by ultrasound examination. The age-matched control group consisted of 330 unrelated Serbian people. They did not show any signs of cerebrovascular disease from their health questionnaires and clinical examinations. Informed consent was obtained from each participant in the study. Personal data (age, sex, weight, height, and blood pressure) were obtained from all participants. Blood pressure measurements (mm Hg) were determined and arterial hypertension was considered to be present if an individual had a history of hypertension or was using antihypertensive agents or if systolic blood pressure exceeded 140 mmHg or the diastolic blood pressure exceeded 90 mmHg. Diabetes mellitus was considered to be present if fasting glucose levels were exceeded 7.78 mmol/L or if the individual was using antidiabetic agents. In addition, a questionnaire with approximately 30 questions was designed to obtain relevant social (marital status, profession, salary, smoking, alcohol consumption, physical activity), medical (general health, cardiovascular and cerebrovascular health, physician visits) and family history (general and cerebrovascular health of parents and siblings). Of the patients, % were found to be hypertensive and % to be diabetics. Current cigarette and alcohol consumption was found in % and %, respectively.

DNA analysis

DNA was extracted by Triton X-100 lysis, proteinase K digestion and phenol/chloroform extraction (5). When the procedure could not be carried out within 2–4 days after blood collection, the blood was frozen at –20 °C and the DNA was extracted within the following 4–8 weeks. The concentration of isolated DNA was determined by spectrophotometer (LKB-Pharmacia, Uppsala, Sweden).

A 244bp sequence of the apoE gene including the two polimorphic sites was amplified by polymerase chain reaction (PCR) in a Hybaid Omnigene thermocycler (Teddington, UK) using the oligonucleotide primer pair F4 and F6 described by Emi et al. (6). The assay conditions, RFLP analysis and products visualization were performed as published previously (7).

Statistical analysis

The frequencies of E2, E3, and E4 alleles were estimated by the gene counting method. To express variances of the allele frequencies i.e., the sample size-dependent standard error of the estimated frequencies, the upper and lower limits of the 95% confidence intervals for the three alleles were calculated. Chi-square statistics was used to test for goodness of fit to the Hardy-Weinberg equilibrium. The odds ratio (OR) and 95% confidence interval (CI) were estimated. A two-sided probability value of less than 0.05 was considered significant.

Results

Table I shows the apoE genotype and allele distribution among patients with ICVD and healthy controls. The genotype frequencies were not different from those predicted from the Hardy-Weinberg equilibrium in the ICVD and in healthy subjects. Significant difference in apoE genotype frequencies between case and control group was observed ($p<0.05$). There was a significant excess of the apoE E4 allele among ICVD patients (0.17 versus 0.09 in control subjects). Patients and control subjects had similar apoE E3 allelic frequency (0.79 in patients versus 0.78 in control subjects), but control subjects carried significantly more E2 alleles (0.05 in patients versus 0.13 in control subjects). Compared with persons without E4 allele, carriers of an E4 allele had 2.1 (95% CI 1.2–3.9) times higher risk of incident stroke. Compared with persons without E2 allele, carriers of an E2 allele had 2.9 (95% CI 1.2–6.9) times lower risk of incident stroke.

Table I Comparation of genotype distribution and relative allele frequencies of apoE in Serbian ICVD patients and controls

		ICVD patients		Controls	
		n	%	n	%
APOE Genotypes	2/2	0	0.00	12	0.04
	2/3	6	0.09	56	0.17
	2/4	0	0.00	7	0.02
	3/3	39	0.60	205	0.62
	3/4	18	0.28	47	0.14
	4/4	2	0.03	3	0.01
	All	65		330	
Allele	E2	0.046 (0.010–0.082)		0.132 (0.106–0.158)	
	E3	0.785 (0.714–0.856)		0.777 (0.745–0.809)	
	E4	0.169 (0.105–0.233)		0.091 (0.069–0.113)	

Discussion

This is the first study in Yugoslavia which determines the effect of apoE genotypes on risk of ICVD. Results of our study supports the finding that apoE polymorphism is associated with ICVD. The main observations are as follows: the apoE2 allele is protective for ICVD and apoE4 allele is a risk factor ICVD in patients younger than 65 years. Studies to date have produced conflicting results as to the importance of apoE alleles in predisposition to ischaemic stroke (*Table II*) (8–39).

Ferrucci et al. (17) have reported a large prospective study of persons aged >70 years and for the first time found that, independent of other traditional risk factors, carrying an E2 allele was associated with lower risk of ischemic stroke. This protective effect was limited to persons who developed a stroke within the age range 70 to 79 years, while no effect was detected in persons who developed a stroke when they were aged 80 years. These findings are consistent with a protective effect of apoE2 allele for CHD, which has been found in young and middle-aged persons but not always confirmed in older populations and with data suggesting that apoE2 allele is underrepresented in patients with vascular dementia compared with control subjects.

Our results are in conflict with the small case-control or cross-sectional studies, where E2/3 genotype has been overrepresented in patients with ischemic stroke (10, 12, 20). In a case-control study by Courdec et al (10) patients affected by ischemic stroke had an E2/3 genotype more often than non-stroke control subjects but less often than younger healthy blood donors. De Andrade et al (12) reported that after careful consideration of the contribution of established risk factors, the apoE2/3 genotype was significantly associated with carotid artery atherosclerosis as defined by B-mode ultrasonography. Among patients with cerebral infarction, Kokubo et al (28) have found that E2 alllele cariers had increased risks of cortical infarction (anatomic subtype), and atherothrombosis and cardioembolism, but not lacunar infarction (clinical subtypes). The association between E2 allele and stroke in this study was accentuated in subjects aged 70 years or older but not in those aged 40 to 69 years.

The apoE4 allele and carriers of E4 are more frequent among patients with ICVD compared with control subjects. Affected individuals with E3/4 and E4/4 genotype appear to carry this excess risk when compared with control subjects. This is similar to findings in coronary heart disease (4). The odds ratio for the E4 allele carriers confirms a modest effect of apoE in ICVD. A lot of studies found an overrepresentation of the E4 allele in ICVD patients compared with control subjects. McCarron et al (26) performed a meta analysis of existing studies that examined the apoE genotype in patients with ICVD. He demonstrated that apoE4 allele and carriers of apoE4 allele are more frequent among patients with ICVD compared with control subjects, but the E2 allele did not appear to be protective for ICVD. Selection criteria for the studies in this meta-analysis included patients older than 18 years of age who clinically and on the basis of brain imaging were diagnosed with an ischemic stroke or a TIA. Age- and gender-matched control subjects with no history of stroke or TIA were selected for each of the studies. Nine case-control studies were included in this meta-analysis. These studies had a total of 926 patients (mean age, 66.8 years) and 890 control subjects (mean age, 66.2 years). Most studies used patients with completed strokes. There was an equal sex distribution in all studies except for the report by Pedro-Botet et al (9), which assessed men only. Two of the studies were Japanese (19, 22), one was from Canada (15), and the remainders were European (8–11, 18, 23). Three reports demonstrated a positive association between the apoE4 allele and ischemic CVD (two European (9, 23), and one Japanese (19). Kessler et al (18) found that E4 allele is more common in CVD patients with large-vessel atherosclerosis than in those with other types of CVD. Eight studies were excluded for this analysis (some of which did not distinguish consistently ischemic stroke from hemorrhagic stroke) (13, 14, 40), and the study of Ferruci et al. (17) did not permit measurement of the apoE allelic frequencies. None of these population studies found an influence of E4 allele on stroke risk. In fact, Kuusisto et al (13) reported that the apoE phenotype is no longer an important risk factor of stroke or CHD in the age group of about 70 years. In a population study of apoE genotype at the age of 85, Skoog et al (40) found that E4 allele is not a risk factor strokes and TIA compared with patients without those diseases. In two prospective studies in older persons performed in Finland (13) and in Sweden (14) failed to show a significant relationship between apoE polymorphism and risk of stroke. In the Finnish study the apoE poly-

Table II Association studies in ischemic stroke: apolipoprotein E

First Author	Year of Publication	Polymorphism	Methodology	Subjects (n)	Mean age (years)	Phenotype	Study result	OR (95% CI)	Allele frequencies E2	E3	E4
Mahieux et al.	1990	E2/E3/E4	Case-control Case Control	 59 28	 73 72	Ischemic stroke	Negative	3.06 (0.6–28.9)	 6 0	 84 96	 10 4
Pedro-Botet et al.	1992	E2/E3/E4	Case-control Case Control	 100 100	 64 64	Ischemic stroke	Positive E4 risk factor	2.00 (1.09–3.74)	 8 8	 73 82	 19 10
Couderc et al.	1993	E2/E3/E4	Case-control Case Control	 69 68	 72 72	Ischemic stroke or TIA	Positive E2/3 risk factor, E3/3 protective	1.34 (0.5–3.74)	 7 1	 85 93	 9 7
Coria et al.	1995	E2/E3/E4	Case-control Case Control	 104 94	 71 72	Ischemic stroke	Negative	0.83 (0.35–1.96)	 6 7	 82 78	 12 15
De Andrade et al.	1995	E2/E3/E4	Case-control Case Control	 145 224	 46–64	Carotid atherosclerosis	Positive E2/3 risk factor				
Kuusisto et al.	1995	E2/E3/E4	Cohort study	1067	69	Ischemic stroke	Negative		695	78	17
Basun et al.	1996	E2/E3/E4	Cohort study	1077	≥75	Ischemic stroke	Negative				
Hachinski et al.	1996	E2/E3/E4	Case-control Case Control	 89 89	 65 65	Ischemic stroke	Negative		 9 9	 77 84	 17 12
Terry et al.	1996	2/E3/E4	Cross sectional Case Control	 130 130	 59	IMT in patients with and without CHD	Positive		8	77	15
Ferrucci et al.	1997	E2/E3/E4	Cohort study	1664	79	Ischemic stroke	Positive E2 protective		9	77	14
Kessler et al.	1997	E2/E3/E4	Case-control ICVD Large-vessel Lacunar Cardiac embolism Other Control	 227 70 34 53 70 225		Ischemic stroke	Positive E4		 9 7 12 10 8 7	 76 74 71 78 79 81	 15 19 18 11 14 12
Nakata et al.	1997	E2/E3/E4	Case-control Case Control	 55 61	 66 67	Ischemic stroke	Negative	2.34 (0.70–8.99)	 2 6	 89 90	 9 4

Table II (continued)

Schmidt et al.	1997	E2/E3/E4	Cross-sectional MARCD + MARCD –	 61 219	 50–70	Silent white matter disease	Positive E2/3 risk factor		 12 5	 79 86	 9 9
Aalto-Setala et al.	1998	E2/E3/E4	Cross sectional ICVD Cerebrovascular atherosclerosis + Cerebrovascular atherosclerosis – Control	231 83 148 203	 < 60	Carotid atherosclerosis in patients with ischemic stroke	Negative		4 4 2 6	76 75 79 70	20 21 19 24
Ji et al.	1998	E2/E3/E4	Case-control Case Control	 123 117		Ischemic stroke	Positive	2.19 (1.18–4.21)			15 8
Margaglione et al.	1998	E2/E3/E4	Case-control Stroke + Stroke – Control	 100 108 398	 66 61 <40	Ischemic stroke	Positive E4 allele risk factor, E3/3 protected	3.13 (1.52–6.44)	6 8 6	76 85 85	18 7 9
McCarron et al.	1998	E2/E3/E4	Cohort study	640	71	Ischemic stroke survival	Positive E4 allele risk factor		8	76	16
Peng et al.	1999	E2/E3/E4	Case-control Case Control	 90 90	 63 63	Ischemic stroke	Positive E3/E4 risk factor		 8 11	 79 83	 13 6
McCarron et al.	1999	E2/E3/E4	Case-control Case Control	 767 735	 67 66	Ischemic stroke	Positive	1.73 (1.34–2.23)	 6 6	 80 85	 14 9
Catto et al.	2000	E2/E3/E4	Case-control Case LACI TACI PACI POCS Control	 592 169 120 174 52 289	 73 72.5	Celebral infarction	Negative		 5 7 7 7	 80 78 80 80	 15 15 13 13
Kokubo et al.	2000	E2/E3/E4	Case-control Stroke Cerebral infarction Lakunarni infarction Control	 322 201 74 1126		Ischemic stroke	Positive E2 E3/E4		9 10 4 5	79 81 88 85	12 9 8 11

Table II (continued)

McCarron et al.	2000	E2/E3/E4	Case-control Case TACI PACI POCS LACI	 189 37 57 21 75	 69.4		Negative	 1.73 (1.34–2.23)	 7 4 7 3 11	 77	 16 15 21 5 17
Chowdhury et al.	2001	E2/E3/E4	Case-control Case Control	 147 190		Ischemic stroke	Positive	3.1 (1.1–9)			
Frikke-Schmidt et al.	2001	E2/E3/E4	Case-control ICVD + >50% stenosis ICVD ICVD Control	 452 75 211 8938	 63 43 70 67	Ischemic stroke / carotid stenosis	Negative		 7 6 9 8	 75 74 74 75	 18 20 17 17
MacLeod et al.	2001	E2/E3/E4	Case-control Case >70 years <70 years Control	 266 225 400	 65.7 77 53		Negative	E4 0.75 (0.5–1.07)	0.07 0.08 0.07 0.06 0.08	0.8 0.81 0.80 0.78 0.77	0.13 0.15 0.13 0.17 0.15
Serteser et al.	2001	E2/E3/E4	Case-control Case Control	 79 126	 62.9 58.6	 Ischemic stroke	Positive E4		 5 21	 137 210	 16 21
Slooter et al.	2001	E2/E3/E4	Cross sectional Case	 5401	 69	Carotid atherosclerosis	Negative		 9	 76	 15
Topić et al.	2001	E2/E3/E4	Case-control CVI stenosis Control	 56 36 124	 65 65	Ischemic stroke / Carotid atherosclerosis			 8 12 5	 84 76 91	 9 12 4
Yang et al.	2002	E2/E3/E4	Case-control Case Control	 36 100	 42 /	Ischemic stroke	Positive E4		 17 11	 51 79	 32 10
Luthra et al.	2002	E2/E3/E4	Case-control Case Control	 63 57	 56.4 39.4	Ischemic stroke	Positive E4	4.2 (1.8–10.1)	 5 9	 39 42	 19 6
Szolnoki et al.	2002	E2/E3/E4	Case-control Case Small vessel Large-vessel Mixed type Control	 689 211 292 186 652	 61 59 61 60	Ischemic stroke	Positive E4	 3.2 (1.3–7.8) 2.6 (1.4–4.7) 0.9 (0.4–2.1) 2.4 (1.4–4)	0.07 0.11 0.07 0.05 0.09	0.68 0.62 0.67 0.75 0.78	0.25 0.27 0.26 0.20 0.13
Souza et al.	2003	E2/E3/E4	Case-control Case Control	 107 100	 69 69	Ischemic stroke (atherothrombotic)	Positive E3	2.16 (1.12–4.18)	 2 5	 93 86	 5 9
Jin et al.	2004	E2/E3/E4	Case-control Case Control	 226 201	 48.5 47.1	Cerebral infarction	Positive E4		 21 23	 370 351	 61 28
Pezzini et al.	2004	E2/E3/E4	Case-control Case Control	 124 147	 34.7 34.8	Ischemic stroke	Positive E4	2.00 (1.08–3.70)	 13 14	 204 259	 31 21

morphism also had no effect on CHD. In the Swedish study the rates of stroke showed a rising, but not significant, trend across the E2/3, E3/3, and E4/3 genotypes, and the fraction of cognitive impairment attributable to stroke was lowest (2%) in the E2/3 group compared with the E3/3 and the E3/4 groups (9%). Both negative studies were performed in North European populations, which show distinct differences from other populations in dietary intake and distribution of apoE genotypes. Patients selected for study for reasons in addition to ischemic stroke were also not included in the meta-analysis (two such studies selected noninsulin-dependent diabetic patients (41, 42), and another assessed end-stage renal disease patients (43). One study did not use age-matched control subjects (21). In Chinese uremic patients Lim et al (43) found that the incidence and cumulative occurrence of stroke increased significantly in those with the apoE4 allele and this preliminary observation suggests that E4 allele could be a predisposing genetic marker for ICVD in these uremic patients. Aalto-Setala et al (21) did not notice significantly different apoE allele frequencies in cohort of stroke patients from those observed in a normal Finish population.

Until today we can not for sure answer the question: Is the apoE4 allele really a risk factor for ischemic CVD? A few studies published after 1999 found a positive association between apoE4 allele frequencies (28, 29, 35), but the others did not find this association. Atherosclerosis in large arteries has been related chiefly to lipid levels and hypertension, whereas the atherosclerotic process in smaller arteries has been related to hypertension. The results in study of Kokubo et al (28), demonstrate the association of apoE2 allele with atherothrombosis and cortical infarction (large arteries) and the association of apoE4 allele with atherothrombosis but no association of apoE2 or E4 allele with penetrating artery region or lacunar infarction (smaller arteries). Therefore, it is thought that apoE may affect only larger arteries, although this remains to be studies further.

How can we explain the inconsistencies and almost conflicting results between studies which goal were determination of apoE alleles in predisposition to ischemic stroke. Such inconsistencies may be due to inaccurate stroke classification, small sample sizes, different age ranges, or the removal of fatal cases in the acute phase. These studies almost failed to subdivide stroke patients according to their pathogenesis. An accurate classification of stroke subtypes (differentiation between thromboembolic and hemorrhagic stroke) is crucial because strokes are heterogeneous in origin, different pathogenic mechanisms involved in cerebral ischemia. We believe our study has several advantages over previous studies. First, we diagnosed and classified stroke subjects in stroke subtypes by use of serial CT or MRI findings. We did not use hospital-discharge or death records to prevent misclassification Cases were recruited in their very acute phases, as early as possible within a 24-hour period after stroke onset, thus allowing us to recruit fatal cases into our study.

Many of these individual studies did not rich significance, probably due to their small size. Because the case-control studies were not designed as prospective association studies, there may have been a tendency to which mostly survivors, who may have possessed an elevated E4 frequency. The study by Margaglione et al (23), which explicitly examined survivors of ischemic CVD, had more than twice the apoE4 allelic frequency as control subject. Our study enrolls patients prospectively. Different ethnic groups can also affect the result of these studies. The apoE4 allelic frequency is lower in Japanese populations compared with white populations. However, even among Europeans there are geographic differences, with an E4 frequency as high as 0.24 in Finland and as low as 0.07 in Italy. Also, we must notice that the frequencies obtained for healthy Serbian population (622 subjects), unexpectedly high compared with other populations, may contribute to the significant difference in apoE2 allele between patients and controls (7).

Apparent discrepancies in different case-control studies may arise from differences in the ages of the subjects under study. Age-matches control subjects are also important in this type of study because age can influence apoE allelic frequencies in a population: there is a decrease in E4 and increase in the E2 allele frequency with old age. Mean age of our stroke individuals was lower than that of a French (72.3 years), Spanish (years) and two Scandinavian series (68.9 and >80 years, respectively), and close to that (64.4) of a series in which a relation between apoE4 and ischemic stroke was suggested. Age distribution may be an important confounding factor: risk factor profiles of ischemic stroke vary in various age classes. Differences in the control subject selection among studies may account, at least in part, for some of these discrepancies, particularly in view of the low frequency of the E4 allele. In addition, E4 allele frequencies comparable to ours (<0.10) have been reported in three Italian studies.

E4 and E2 allelic frequencies tend to decline and to increase with age, respectively, but a reduction of E4 is already present in octogenarians, while the increment in E2 allelic frequency has been detected only in centenarians. Several hypotheses may be proposed to explain the interaction between age and apoE genotype. If a specific risk factor is potentiated in the presence of a specific genotype, and if this risk factor is related to selective mortality at younger ages, the genotype may appear to have less of an impact at older ages. Indeed, a mechanism of selective mortality has been also suggested to explain why some risk factors for stroke, such as hypertension, become less important in old age. Furthermore, since the incidence rate of stroke increases with age, other (possi-

bly not already identified) risk factors may play a critical role in the causation of strokes in older individuals. An alternative hypothesis is based on the fact that E2 has been associated with both antiatherogenic and atherogenic changes, and the balance between these two effects may be different in different periods of life. However, differences in some other biological, socioeconomic, or lifestyle factors (diet in particular) may influence such an association; for example, the fat intake of the elderly is lower than that of younger people. Carriers of the E2 allele may have a greater chance of endothelial weakening in intracerebral arteries because of lower cholesterol levels, whereas the diminished impact of the E4 allele on LDL levels in elderly groups may also explain our findings of a decreased association between E4 and stroke in elderly subjects. Such age-dependent changes in the association of the E2 or E4 alleles with stroke have also been suggested in previous studies. Positive associations between the E4 allele and stroke have been detected only in subjects aged <70 years on average. Conversely, a positive association between the E2 allele and stroke has been found in subjects aged >70 years on average. In cohort studies, Ferrucci et al (17) reported that the protective effect of E2 decreased progressively with age and after 80 years was no longer statistically significant, whereas Kuusisto et al (13) and Basun et al (14) found no association between apoE and cerebral infarction in elderly subjects.

Although our findings do not currently affect clinical practice, additional knowledge of the role of genes in ischemic stroke may improve our understanding of the cause of stroke; provide new insights in prevention and factors that influence the outcome of stroke, as new therapeutic targets when preventive strategies have failed.

POLIMORFIZAM GENA ZA APOLIPOPROTEIN E KAO FAKTOR RIZIKA ZA ISHEMIJSKU BOLEST MOZGA

Sanja Stanković[1], Zagorka Jovanović-Marković[2], Nada Majkić-Singh[1], Aleksandra Stanković[3], Sanja Glišić[3], Maja Živković[3], Vladimir Kostić[2], Dragan Alavantić[3]

[1]Institut za medicinsku biohemiju, Farmaceutski fakultet, Klinički centar Srbije, Beograd, Srbija i Crna Gora
[2]Institut za neurologiju, Klinički centar Srbije, Beograd, Srbija i Crna Gora
[2]VINČA, Institut za nuklearne nauke, Laboratorija za radiobiologiju i molekularnu genetiku, Beograd, Srbija i Crna Gora

Kratak sadržaj: Kod 65 pacijenata koji su imali moždani udar ili prolazni ishemijski napad i 330 zdravih kontrola, ispitivano je da li postoji povezanost polimorfizma gena za apoE sa ishemijskom bolešću mozga. Genotipovi apoE određeni su restrikcionom tipizacijom/MADGE analizom. Utvrđena je statistički značajna razlika u frekvencijama genotipova apoE kod pacijenata i kontrola ($p<0,01$). Kod pacijenta sa ishemijskom bolešću mozga utvrđena je veća frekvencija alela E4 i manja frekvencija alela E2 u odnosu na odgovarajuće kontrole. Poređenjem sa osobama koje nisu nosioci alela E4, osobe sa alelom E4 imaju 2.1 put veći rizik od dobijanja ishemijske bolesti mozga. Naši rezultati pokazuju da je polimorfizam gena za apoE faktor rizika za dobijanje ishemijske bolesti mozga u srpskoj populaciji.

Ključne reči: apolipoprotein E, ishemijska bolest mozga, polimorfizam

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