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ASSOCIATION BETWEEN APOLIPOPROTEIN E POLYMORPHISMS AND EPILEPSY IN CHILDREN

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SUMMARY – Apolipoprotein E (APOE) plays an important role in lipid metabolism and is a proven risk factor for development of dementia and other neurodegenerative diseases. The aim of the study was to determine the possible connection between particular APOE alleles, blood lipid profile and different types of epilepsy in children. Alleles of the APOE gene, blood cholesterol (total, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol, and triglyceride levels were analyzed in blood samples of 111 children with epilepsy and 118 age- and sex-matched children without epilepsy. Distribution of APOE genotypes was the same in children of both groups. Significantly increased levels of total cholesterol and LDL cholesterol were found in control group ($Z=3.49$ and 3.52 respectively, $p<0.01$). No statistically significant difference was found between the genotypes of children with idiopathic and symptomatic epilepsy ($\chi^2=1.96$; $df=2$; $p>0.05$). There were statistically significant differences in the levels of total cholesterol ($Z=2.09$; $p<0.05$) and LDL cholesterol ($Z=2.05$; $p<0.05$) according to the type of epilepsy in favor of symptomatic epilepsy. The study confirmed that there was no connection between APOE and type of epilepsy in children and showed the children with epilepsy to have lower total cholesterol and LDL cholesterol levels. Interestingly, this also held true for children with idiopathic epilepsy compared to those with symptomatic condition.

Key words: *Apolipoprotein E; Brain plasticity; Children with epilepsy; Gene polymorphism; Lipoprotein*

Introduction

Epilepsy is a chronic disorder of the brain function with different etiologies, characterized by recurrent seizures caused by excessive electrical discharges and various clinical features and laboratory findings^{1,2}. Approximately 50 million people worldwide have epilepsy³. Epilepsy has a prevalent occurrence in childhood, since 60% of all patients suffering from epilepsy are children under the age of 16^{4,5}. During the history, classification of epilepsy has greatly changed, and universal opinion has not been formed to the present day^{6,7}. We still use the International League Against Epilepsy (ILAE) classification system from 1989, which is compatible with the International Statistical

Classification of Diseases and Related Health Problems, 10th Revision, officially in use by the Croatian Institute for Health Insurance⁸. According to etiology, epilepsy can be classified as idiopathic (possibly hereditary, no neuro-radiologically visible neuroanatomic or pathologic abnormalities, no clearly defined genetic basis), symptomatic (secondary epilepsy, acquired or with confirmed brain lesion associated with anatomic and pathologic changes), and cryptogenic (symptomatic epilepsy is suspected, but no brain lesion has been confirmed). In symptomatic epilepsy, the cause can be identified and specific treatment can be applied, while in idiopathic epilepsy no definitive cause can be found⁸. Epileptic seizures are the result of an abnormal and excessive activity and interaction of excitatory and inhibitory inputs from a number of neurons. This can lead to developmental abnormalities due to changes in distribution, transport, and movement of ions⁹. All the above-mentioned processes can be regulated by apolipoprotein E (APOE). Therefore, it is possible that

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APOE plays an important role in the occurrence and maintenance of epileptic seizures¹⁰⁻¹².

Apolipoprotein E is a glycoprotein engaged in the transport and metabolism of lipids in the entire body. It appears in three isoforms, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. APOE $\epsilon 3$ allele is most common (70%-80%), followed by APOE $\epsilon 4$ (10%-15%), and APOE $\epsilon 2$ (5%-10%)¹². The APOE gene in humans is localized at 19q 13.2. Apart from the liver, which is the main organ for plasma lipoprotein synthesis, APOE is also synthesized in astrocytes and microglia of the brain. In the brain, it takes part in cholesterol distribution during repair, growth and myelination of the nerve cell membrane during development and aging. Hence, it plays an important role not only in brain injuries, either ischemic or traumatic, but also during epileptic seizures^{13,14}.

The studies published so far have described the connection of APOE isoforms and their plasma concentration with the occurrence of neurodegenerative diseases, especially Alzheimer's disease. Analysis of the APOE alleles in patients suffering from Alzheimer's disease showed a significant correlation between APOE allele type 4 and development of Alzheimer's disease¹⁵⁻¹⁷. An important connection of APOE polymorphism and outcome of head injury has been reported, with patients carrying APOE $\epsilon 4$ being more likely to have unfavorable outcome 6 months after head injury as opposed to patients with other APOE isoforms^{2,18,19}. The authors studying the connection between epilepsy and APOE found a connection between APOE and early onset of temporal lobe epilepsy, as well as a higher risk of late post-traumatic seizures^{20,21}. However, to our knowledge, no study in children with different epilepsy etiology has been published so far. Epilepsy in children usually involves genetic/hereditary, unknown, metabolic, and structural changes in the brain, while acquired conditions such as head trauma, infection and cerebral stroke are rarely the cause. Considering the participation of apolipoprotein in the brain function and the plasticity of a juvenile brain, we examined the apolipoprotein genotype in childhood epilepsy patients in order to get earlier diagnosis and better therapeutic result^{18,22-24}.

Patients and Methods

The study included 254 children (131 female and 123 male) aged 2 months to 18 years, divided into the

epilepsy group consisting of 111 children diagnosed with the condition, and the age- and sex-matched control group consisting of 143 children who were observed in our department due to the signs and symptoms other than epilepsy (e.g., vertigo, headache, syncope). In the control group, there were 71 girls and 72 boys, while in the patient group there were 60 girls and 51 boys. Patient characteristics are shown in Table 1. The study was conducted in the Division of Pediatric Neurology, Department of Pediatrics, Sestre milosrdnice University Hospital Center from October 2011 to January 2017. The patients underwent complete neurological examination. Classification of epilepsy was done according to the ILAE criteria from 1989.

Table 1. Characteristics of patients with epilepsy and control subjects

	Patients with epilepsy	Control group
Subjects	111	143
Age (yrs)	9.58 (2-18)	10.86 (2-18)
Gender (male/female)	51/60	72/71

The study was approved by the Hospital Ethics Committee and performed in accordance with Helsinki Declaration. Informed consent was signed by parents or legal guardians of the children.

Peripheral blood was collected from all children. The blood samples collected were processed in the Clinical Department of Chemistry, Sestre milosrdnice University Hospital Center, where APOE genotyping and blood lipid profile was performed. Blood samples (5-7 mL) were collected in Vacutainer® tubes (BD Diagnostics, Franklin Lakes, USA) with EDTA. Until DNA isolation, they were kept at -20 °C and were analyzed within a month. Leukocyte DNA for genotyping was isolated by the standard salting-out method. The mutation detection kit contained all classic components of the polymerase chain reaction (dNTP, Mg²⁺, polymerase, primers, reaction buffer) and fluorescent probes complementary to the DNA segment located close to the polymorphism. Genotype detection is based on the melting curve analysis. The probes were perfectly complementary either to the wild-type sample or the sample with polymorphism. A computer program translates the signal to the curve with the

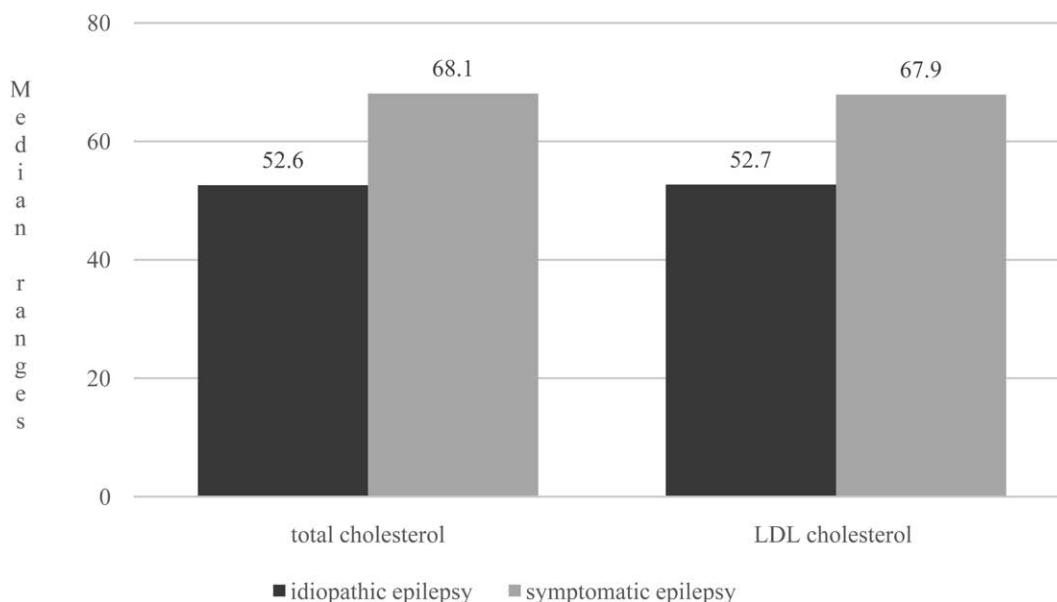


Fig. 1. Cholesterol levels according to type of epilepsy.

maximum at the melting temperature based on which the genotype is identified.

Plasma concentrations of cholesterol (total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol), and triglycerides were determined from peripheral blood samples collected from all subjects using standard clinical practice after 18-hour fasting. Serum was obtained from whole blood without addition of anticoagulants (manufacturers of vacuum tubes, Greiner Bio-One, Austria) following centrifugation for 15 min at 3500 rpm. The instrument, or automatic analyzer was AU2700 (Beckman, USA) or Architect c8000 (Abbott, USA), depending whether the results were recorded before or after 2014. Until July 2014, we used Beckman, and since then Abbott instrument.

Standard reference range for plasma lipid concentrations was used to determine whether a patient had a low (below or within the reference interval) or high (above the reference interval) concentration of every biochemical parameter tested. Reference values were as follows: total cholesterol ≤ 5 mmol/L; HDL ≥ 1 mmol/L for females and ≥ 1.2 mmol/L for males; LDL ≤ 3 mmol/L; and triglycerides ≤ 2 mmol/L.

Data processing applied descriptive statistics. All statistical analyses were performed using SPSS version 13.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

There was no statistically significant difference in the observed and expected APOE genotype frequencies between the patients with epilepsy and control group ($p=0.834$), and it can be argued that the APOE gene polymorphisms were equally distributed in children suffering from epilepsy and in the general population. The highest proportion of alleles belonged to $\epsilon 3/\epsilon 3$ (50.0% to 62.9%) as wild-type, whereas the $\epsilon 2/\epsilon 2$ and $\epsilon 4/\epsilon 4$ alleles were 20–25 times smaller in size. However, there was a statistically significant between-group difference in the levels of total plasma cholesterol ($Z=3.49$; $p<0.01$) and LDL cholesterol ($Z=3.52$; $p<0.01$), i.e. control group subjects had higher total cholesterol and LDL cholesterol levels.

Distribution of particular APOE gene polymorphisms depending on the type of epilepsy did not differ significantly among the focal, generalized, and unclassified types of epilepsy ($p=0.529$). The distribution of individual APOE gene polymorphisms depending on the epilepsy subtype (focal idiopathic or symptomatic, generalized idiopathic or symptomatic, epileptic syndrome, unclassified) did not show significant differences ($p=0.554$) as neither did the distribution of individual APOE polymorphisms depending on symptomatic or idiopathic subtype of epilepsy.

The genotypes showed a correlation to plasma LDL levels ($p=0.02$). Depending on the type of epilepsy, there was a statistically significant difference in the levels of total cholesterol ($Z=2.09$; $p<0.05$) and LDL cholesterol ($Z=2.05$; $p<0.05$) in favor of symptomatic epilepsy. No statistically significant difference was found between the genotypes of children with idiopathic and symptomatic epilepsy ($\chi^2=1.96$; $df=2$; $p>0.05$). These results are shown in Figure 1.

The χ^2 -test used for genotype and Mann Whitney U test for cholesterol showed that there were no statistically significant relations between the genotype, HDL, type of the disease, and triglyceride levels in either group.

Discussion

Currently, there are only a few studies related to APOE in children. Our study showed that there was no difference in the genotypes of children with epilepsy compared to control group, similarly to previous studies performed in adult patients²⁵⁻²⁷. Those studies in adult patients also showed the APOE $\epsilon 3/\epsilon 3$ genotype to be most common in both groups, while $\epsilon 2/\epsilon 2$ was rarely present, which is consistent with our study. Interestingly, our control group had higher total and LDL cholesterol levels, in contrast to some earlier studies which showed total and LDL cholesterol levels to be significantly higher in subjects with epilepsy^{26,28}. A possible explanation for this are different eating habits (e.g., in Croatia, both inland and Mediterranean cuisines are consumed). It is also interesting to note that genotypes showed a correlation to LDL levels and marginal correlation to total plasma cholesterol levels, although there were no differences in genotype frequencies between the patient and control groups. This may indicate that genotype is just one of the factors involved in the cholesterol turnover in epilepsy.

The possible limitations of this study were the inability to measure APOE concentration (higher APOE concentration is connected with higher levels of total and LDL cholesterol), and the fact that only a few subjects with some genotypes were examined.

Since both the etiology of epilepsy and the immature nature of the brain in children have a significant impact on the outcome of the disease, it is clear that APOE polymorphisms could have considerable effect on the type of epilepsy in children²⁹. The results of our

study did not show correlation between the APOE polymorphism and the type of epilepsy in children, which partly confirms some of the studies conducted on adults^{30,31}. In previous studies, many authors tried to connect APOE with temporal lobe epilepsy and mesial hippocampal sclerosis. Some authors could not find any connection, which they attributed to the limited size of the sample, and concluded that only patients with the APOE $\epsilon 4$ allele might have an increased risk of developing epilepsy with mesial hippocampal sclerosis³¹. However, other authors report that patients having temporal lobe epilepsy have a larger concentration of APOE in plasma compared to controls. It was finally concluded that there was a connection between APOE and temporal lobe epilepsy^{26,27,31,32}. In our study, we did not try to prove the correlation between APOE and temporal lobe epilepsy since the lesion itself is very rare in children³³. Some studies showed a strong correlation between the APOE $\epsilon 4$ allele and epilepsy, most notably a study conducted on a population of the Han Chinese, but other studies disputed these results^{18,27,34}. The APOE $\epsilon 4$ allele is a risk factor for intracellular accumulation of beta-amyloid which plays the key role in the increase of nerve cell sensitivity to damage. The presence of APOE $\epsilon 4$ reduces the ability of the brain to repair the damage and create new synapses. Therefore, it can be concluded that APOE is a gene potentially involved in synaptogenesis and that its polymorphisms can result in development of temporal lobe epilepsy³⁵. The results of our study showed no correlation between particular alleles and type of epilepsy. The reason may be an insufficient number of subjects or interplay of other factors involved. Considering previous studies which failed to prove the connection between APOE and febrile convulsions and thus could not establish the fact that APOE affects the prognosis of febrile convulsions and further development of epilepsy, our results could be interpreted as an additional confirmation that there is no such connection in children^{36,37}. Other studies on the role of epilepsy as a comorbidity in children with cerebral palsy and the connection with APOE report the same findings³⁸.

Our study showed that subjects with symptomatic epilepsy had higher levels of total and LDL cholesterol compared to subjects suffering from epilepsy of an unknown cause. It is well known that cholesterol plays a significant role in synaptogenesis and is also

important for myelination and growth of membranes both during development and adulthood. Good regulation and impermeability of the blood-brain barrier is very important for this process. Cholesterol is mostly accumulated in the brain during perinatal development and adolescence, at the same time with myelination. When the myelination process ends, the concentration of cholesterol in the brain decreases and the level of cholesterol depends on external source. APOE in the brain parenchyma assists in the regulation of plasma lipids and metabolism of cholesterol. In case of damage to the cells of the central nervous system, APOE also plays an important role as a recovery factor in regeneration in some of the cells during re-myelination through redistribution of lipids. When the cholesterol reaches the maximum required level, 24-hydroxylase catalyzes cholesterol into 24S-hydroxycholesterol (24-OHC), which can be removed in the presence of HDL, and in this way protects the neurons from the toxic effect³⁹⁻⁴¹. High cholesterol and its damaged metabolism leads to imbalance which increases the risk of development of various conditions and diseases affecting the brain (Alzheimer's disease, other neurodegenerative diseases, cerebrovascular diseases) and which may be a cause of symptomatic epilepsy. *In vitro* studies showed that cholesterol overload in plasma membrane resulted in the increase of amyloid- β in the primary neuronal culture. That is a pathologic marker for the occurrence of not only Alzheimer's disease but also of other brain affecting diseases including epilepsy^{42,43}. Therefore, it is important to understand that inadequate cholesterol regulation can lead to changes in its distribution and transport, which is a basis for development of epileptic seizures and finally, epilepsy itself.

Finally, our research showed that APOE polymorphisms could not be strongly correlated to the occurrence of epilepsy or type of epilepsy in children and, therefore, they cannot be a predictive factor for the outcome of the disease.

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Sažetak

POVEZANOST POLIMORFIZMA APOLIPOPROTEINA E I EPILEPSIJE U DJECE

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Apolipoprotein E (APOE) ima veliku ulogu u metabolizmu lipida i dokazan je čimbenik rizika za razvoj demencije i drugih neurodegenerativnih bolesti. Cilj istraživanja bio je utvrditi moguću povezanost pojedinih alela APOE, profila lipida u krvi i različitih tipova epilepsije u djece. Aleli APOE, kolesterol u krvi (ukupni kolesterol, lipoproteini visoke gustoće i lipoproteini niske gustoće (LDL)) te vrijednosti triglicerida analizirani su u uzorcima krvi kod 111 djece s epilepsijom i 118 djece podudarne dobi i spola bez epilepsije. Distribucija APOE genotipova bila je ista u djece obje skupine. Značajno povišene razine ukupnog kolesterola i LDL kolesterola utvrđene su u kontrolnoj skupini ($Z=3,49$ odnosno $3,52$, $p<0,01$). Nije pronađena statistički značajna razlika između genotipova djece s idiopatskom i simptomatskom epilepsijom ($\chi^2=1,96$; $df=2$; $p>0,05$). Postojale su statistički značajne razlike u razinama ukupnog kolesterola ($Z=2,09$; $p<0,05$) i LDL kolesterola ($Z=2,05$; $p<0,05$) ovisno o vrsti epilepsije u korist simptomatske epilepsije. Studija je potvrdila da ne postoji povezanost između APOE i tipa epilepsije u djece te je pokazala da djeca s epilepsijom imaju niži ukupni kolesterol i LDL kolesterol, ali je nađeno da djeca koja imaju simptomatsku epilepsiju imaju veću koncentraciju ukupnog i LDL kolesterola u odnosu na one s idiopatskom epilepsijom.

Ključne riječi: *Apolipoprotein E; Plastičnost mozga; Djeca s epilepsijom; Polimorfizam gena; Lipoprotein*