THE APOLIPOPROTEIN E EPSILON (ε) 4 ALLELE IS IMPORTANT FOR TRAUMA-RELATED EPILEPSY

Increased Risk of Late Posttraumatic Seizures Associated with Inheritance of APOE Epsilon4 Allele

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BACKGROUND: Late posttraumatic seizures are a common complication of moderate and severe traumatic brain injury. Inheritance of the apolipoprotein E *(APOE)* ε4 allele is associated with increased risk of Alzheimer disease, progression to disability in multiple sclerosis, and poor outcome after traumatic brain injury.

OBJECTIVE: To determine whether inheritance of *APOE* ε4 is associated with increased risk of developing late posttraumatic seizures.

METHODS: In this prospective study in the neurosurgical service at an urban level I trauma center, patients admitted with a diagnosis of moderate and severe traumatic brain injury were enrolled. Six months after injury, patients were contacted to determine functional outcome [according to the Glasgow Outcome Scale–Expanded (GOS-E)] and the presence of late posttraumatic seizures. Genotype at the *APOE* locus was determined by restriction fragment length polymorphism analysis.

RESULTS: DNA and outcome information was obtained from 106 subjects. Six months after injury, 31 (29%) had a poor outcome (GOS-E score, 1–4), 47 (44%) had an intermediate outcome (GOS-E score, 5–6), and 28 (26%) had a favorable outcome (GOS-E score, 7–8). Twenty-one (20%) patients had at least one late posttraumatic seizure. The relative risk of late posttraumatic seizures for patients with the ε4 allele was 2.41 (95% confidence interval, 1.15–5.07; $P = .03$). In this cohort, inheritance of APOE ε4 was not associated with an unfavorable GOS-E score 6 ($P = .47$).

CONCLUSIONS: Inheritance of the *APOE* ε4 allele is associated with increased risk of late posttraumatic seizures. In this cohort, this risk appears to be independent of an effect of ε4 on functional outcome. A better understanding of the molecular role of *APOE* in neurodegenerative diseases may be helpful in developing antiepileptogenic therapies.

COMMENTARY

In the search for genetically determined influences on neurologic disease, the apolipoprotein E epsilon 4 polymorphism (*APOE* ε4) allele has emerged as an important risk factor. Inheritance of this allele was first associated with an increased risk of Alzheimer disease (1), and subsequently, exploration of its influence on other neurologic illnesses was undertaken (2,3). Diaz-Arrastia et al. have now discovered that *APOE* ε4 is also a risk factor for late posttraumatic seizures.

The role of apolipoprotein E in the brain is intriguing in terms of its implications for epileptogenesis. It is vital for lipid transport in nervous system structures and is a critical component of the mechanism for maintenance and repair of injured cell membranes as well as for the growth of neurites, dendritic remodeling, and synaptogenesis (4). Indeed, expression of *APOE* genes is increased in the hippocampi of rats after induction of status epilepticus by intraamygdalar injection of kainate, indicating an increased need for lipid transport during the period of recovery and repair in the hippocampus that follows severe seizures (5). The genetically imparted APOE isoforms influence the effectiveness of this repair process, and APOE ε4 is less adequate than the two other isoforms, APOE ε2 and APOE ε3, for repair of neuronal injury. The differential effect of the APOE isoforms also is relevant for seizure-related injury. For example, in models of convulsive brain injury, *APOE* ε3 expression, but not *APOE* ε4 expression, is associated with protection against kainate-induced neuronal damage (6).

The significance of the *APOE* ε4 allele for epilepsy has been evaluated in several populations. As the authors pointed out, in 1997, Gouras et al. (7) evaluated the presence of the *APOE* ε4 allele in subjects undergoing temporal lobectomy. Of patients who showed β-amyloid deposition in the form of senile plaques in the resected temporal lobe, 70% were *APOE* ε4 allele carriers, compared with a 27% carrier frequency in age-matched patients without senile plaques. These findings are consistent with the

conclusion that the *APOE* $\varepsilon 4$ allele is integral to the pathology of illnesses in which there is an overproduction of β-amyloid deposition, such as Alzheimer disease and Down syndrome—a spectrum that also may include epilepsy.

Three conflicting reports regard the inheritance of the *APOE* $\varepsilon 4$ allele as a risk factor for temporal lobe epilepsy (TLE). Blumcke et al. (8), in 1997, evaluated 125 subjects with TLE and found that 15.5% had the *APOE* $\varepsilon 4$ allele, a figure similar to the frequency in the general European population. They found no association between the genotype and age at onset, history of febrile seizures, family history of epilepsy, surgical outcome, or neuropathologic findings. However, Briellmann et al. (9) later reported the on the association of the *APOE* $\varepsilon 4$ allele and magnetic resonance imaging (MRI) findings in 43 patients with intractable TLE from their Australian population. They found a significant difference in mean age at onset of epilepsy between the 10 *APOE* $\varepsilon 4$ carrier subjects (5 ± 5 years) and the noncarrier subjects (15 ± 10 years) ($P = .005$ by the Mann–Whitney U test, although there was no difference in quantitative MRI findings or the presence of hippocampal sclerosis. Further evidence for a lack of association of TLE and *APOE* $\varepsilon 4$ allele was recently reported in an Italian population (10). The authors found no increased frequency of the genotype in 63 nonlesional TLE patients, compared with a control group of 220 normal subjects.

The existing literature supports no clear association between the risk of the occurrence of nonlesional TLE and the *APOE* $\varepsilon 4$ allele. However, Diaz-Arrastia et al. make a strong case for an increased risk of epilepsy in carriers after traumatic brain injury. The *APOE* $\varepsilon 4$ allele carriers were well matched with the noncarriers on several parameters, including severity of head injury, initial Glasgow Coma Scale score, the need for an intracranial surgical procedure, length of stay, demographic characteristics, and the occurrence of early posttraumatic seizures. Notably, subjects with very mild head injury were excluded from the study. The occurrence of early posttraumatic seizures (defined as within 7 days of head injury) was three (10.3%) of 29 in the carriers and four (5.2%) of 77 in the noncarriers, which was not statistically different. However, by 6 months after the injury, 10 (34.5%) of 29 carriers had a late posttraumatic seizure (defined as >7 days after head injury), compared with 11 (14.3%) of 77 noncarriers. This difference was significant ($P = .03$) and indicated a relative risk imparted by the *APOE* $\varepsilon 4$ allele of 2.41 (95% confidence interval, 1.15–5.07). It is not stated in this report how many of the subjects had developed epilepsy or recurrent late posttraumatic seizures.

The association of the *APOE* $\varepsilon 4$ allele with the development of late seizures in the setting of head trauma implies that the presence of this allele is more conducive to epileptogenesis compared with the other *APOE* alleles and underscores the intuitive notion that pristine neuronal repair can be important in preventing epileptogenesis. Speculatively, the reason that an association between the *APOE* $\varepsilon 4$ allele and the prevalence of TLE cannot be demonstrated may be because TLE is usually not primarily traumatic in etiology. Further exploration of the meaning of this genotype in epilepsy is merited.

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