

APOE, MEMORE, AND EPILEPSE

ApoE- ϵ 4 Is Associated with Reduced Memory in Long-Standing Intractable Temporal Lobe Epilepsy. Busch RM, Lineweaver TT, Naugle RI, Kim KH, Gong Y, Tilelli CQ, Prayson RA, Bingaman W, Najm IM, Diaz-Arrastia R. *Neurology* 2007;68(6):409–414. **OBJECTIVE:** To investigate the relationship between the apolipoprotein (ApoE) 4 allele and memory performance (verbal and nonverbal) in patients with medically intractable temporal lobe epilepsy (TLE) who underwent temporal lobectomy. **METHODS:** Presurgical and postsurgical memory performance was examined in 87 adult patients with TLE (4 = 22; non-4 = 65) to determine whether the expression of ApoE-4 may be associated with memory performance in this population and to examine how this relationship may be affected by duration of epilepsy. **RESULTS:** There was a significant interaction between ApoE-4 status and duration of epilepsy such that 4 carriers with a long duration of epilepsy demonstrated the poorest memory performance on both verbal and nonverbal measures. This relationship was observed both before and after temporal lobectomy, with little change in test performance over time. **CONCLUSIONS:** The ApoE-4 allele interacts with longstanding seizures to affect memory performance, both verbal and nonverbal, in patients with medically intractable temporal lobe epilepsy.

COMMENTARY

Apolipoprotein E (better known as ApoE) is of interest to virtually all neurologists and neuroscientists, as it plays a crucial role in lipid transport and homeostasis, maintenance of synaptodendritic connections, and repair of neurons after all types of injuries or stress (1). ApoE is synthesized in the liver and brain. In the brain, its main producer is the astrocyte, although neurons can also synthesize ApoE after injury. ApoE mRNA is found in the cortex and hippocampus in humans. ApoE synthesis is induced in rat hippocampal neurons after kainic acid and in human cortical neurons after infarction. The gene for ApoE (*APOE*) on chromosome 19 encodes three alleles: ApoE ϵ 2, ApoE ϵ 3, and ApoE ϵ 4. The ApoE ϵ 4 allele is the least effective of the isoforms, and when present, the result is decreased enzymatic activity of ApoE and, therefore, decreased ability to protect and repair neurons. In addition, there is some evidence that the ApoE ϵ 4 isoform is particularly susceptible to proteolysis to neurotoxic fragments (1).

The ApoE ϵ 4 allele first received neurological notoriety when it was recognized that its presence was a major risk factor for Alzheimer's disease. Fortunately, the more effective ApoE ϵ 3 allele (associated with greater ApoE enzymatic activity and better neuronal protection and repair than ϵ 4) is the most common allele, with at least half the population having the ϵ 3/ ϵ 3 genotype (2). However, at least one ApoE ϵ 4 allele is present

in 15 to 20% of people (1). These individuals have double the risk of Alzheimer's disease: 45% by age 85, compared with 20% for the overall population. The 2% of the population with ϵ 4/ ϵ 4 have a 50 to 90% chance of developing Alzheimer's by age 85 (3). Among patients with Alzheimer's disease, 40 to 80% have an ApoE ϵ 4 allele, and it is associated with earlier age of onset (1).

But ApoE ϵ 4's harm is not limited to Alzheimer's disease. It has been shown to be associated with the following negative neurological effects, among others: greater memory decline in healthy subjects; increased risk of infarct, obstructive sleep apnea, Parkinson's disease, Lewy Body disease and frontal lobe dementia; worse neurological outcome after traumatic brain injury (including boxing), intracerebral hemorrhage, and subarachnoid hemorrhage (2); more rapid progression of disability in multiple sclerosis; and increased cognitive deficits associated with sleep apnea (4) and cardiac surgery.

What about epilepsy? It was previously shown that the ApoE ϵ 4 allele is associated with increased β -amyloid deposition in the form of senile plaques in patients with intractable epilepsy: 70% of patients with plaques had at least one ApoE ϵ 4 allele compared with 27% of those without plaques (5). One study found a shorter "silent interval" between early life insult and intractable seizures in those with ApoE ϵ 4 compared with those without (6), and another study similarly found an earlier age of onset of intractable seizures (7). Patients with temporal lobe epilepsy and ApoE ϵ 4 are at greater risk of verbal learning deficits (50% of patients with ApoE ϵ 4 had these deficits compared with 19% of those without), especially those with longer duration of epilepsy (7). One investigation of patients with

cryptogenic complex partial seizures reported a greater chance of being refractory to treatment in patients with an ApoE $\epsilon 4$ allele: 40% of refractory patients were ApoE $\epsilon 4$ positive compared with 7% of those who were well controlled (8). The ApoE isoform is probably not a risk factor for epilepsy itself, except for posttraumatic epilepsy in which the presence of ApoE $\epsilon 4$ is associated with more than doubling of the risk of late seizures, as reviewed in *Epilepsy Currents* in 2004 (9,10).

In the current study, Busch et al. expand upon the correlation between ApoE $\epsilon 4$ and memory dysfunction in chronic temporal lobe epilepsy by studying adults undergoing temporal lobectomy before and after surgery. In those without ApoE $\epsilon 4$, there was no correlation at all between duration of epilepsy and memory scores. However, among patients with ApoE $\epsilon 4$, there was a clear and significant correlation. Patients with a long (>22 years) duration had lower scores on all five memory indices (verbal and nonverbal) compared to those with shorter duration. Surgery had minimal effect on memory. The authors calculated that the ApoE $\epsilon 4$ /duration-of-epilepsy interaction accounted for 18% of the variance in memory scores. They theorize that medically refractory seizures are a form of repetitive brain injury, similar to repetitive head trauma, and thus it is not surprising that repair mechanisms (for which ApoE function is vital) would be important determinants of pathology and dysfunction.

All of the above studies support the notion that ApoE status is an important determinant of the brain's response to injuries, including repetitive seizures. When ApoE function is inadequate as a result of the presence of an ApoE $\epsilon 4$ allele, the brain is less able to deal with a variety of stresses. Thus, after brain injury, seizures are more likely to develop in the presence of ApoE $\epsilon 4$ and to become refractory; amyloid deposition is more apt to occur; and there is a greater chance that temporal lobe dysfunction will develop over time. These findings raise the possibility of early identification of at-risk groups and therefore of early intervention—potentially preventing some cases of epilepsy, improving response to treatment, and ameliorating associated cognitive dysfunction. Fortunately, research into the mechanisms of ApoE is progressing rapidly. It may be possible

to convert the ApoE $\epsilon 4$ isoform into an ApoE $\epsilon 3$ -like form to block proteolysis of ApoE or to upregulate ApoE function in other ways (1). Advances in this area are likely to be widely applicable throughout neurology, including epilepsy.

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