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APOE ε4 is Associated with Postictal Confusion in Patients with Medically Refractory Temporal Lobe Epilepsy

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Summary

This study examined the relationship between the APOE ε4 allele and postictal confusion in patients with medically intractable temporal lobe epilepsy (TLE). Patients with at least one ε4 allele (n = 22) were three times more likely to exhibit postictal confusion (68%) than the 63 patients without ε4 (43%). These preliminary results demonstrate that APOE ε4 is associated with an increased risk of postictal confusion in patients with medically intractable TLE, suggesting possible dysfunction in neuronal recovery mechanisms.

Introduction

Postictal confusion is characterized by impaired awareness and often occurs after complex partial or generalized seizures. It has been defined as "temporary incoherence, inability to respond to contact or unfamiliarity with environment" (Epilepsy Foundation, 2007). Postictal confusion typically lasts less than 15 min (Bromfield et al., 2006), but occasionally persists for longer durations. Although postictal confusion occurs in many patients with temporal lobe epilepsy (TLE), and particularly those with amygdala atrophy (Guerreiro et al., 1999), its causes are poorly understood.

A primary genetic candidate related to postictal confusion is apolipoprotein E (APOE). Initially known for its role in cholesterol transport, research has established that APOE plays an important role in neuronal repair after injury (see Mahley, 1988 and Mahley et al., 2006 for reviews). Compared to the ε2 and ε3 alleles, ε4 has been associated with suboptimal clinical outcomes and/or poor prognoses after acute neuronal injury in both murine models (Horsburgh et al., 2000, Sabo et al., 2000 and Sheng et al., 1998) and humans (Alberts et al., 1995, Sorbi et al., 1995, Tardiff et al., 1997 and Teasdale et al., 1997).

Given the association between ε4 and neurological dysfunction, Ely et al. (2007) hypothesized that ε4 may increase the duration of delirium during critical illness. They found that ε4 was associated with increased duration of delirium in 53 mechanically ventilated patients with various disorders (e.g., sepsis, pneumonia) in an intensive care unit setting. Specifically, those with at least one ε4 allele had a median duration of delirium of 4 days, while those without an ε4 allele had a median duration of delirium of 2 days. These authors hypothesized that impaired neuronal recovery mechanisms associated with ε4, such as increased inflammatory response, may contribute to the persistence of delirium in patients with this allele.

Based on evidence that ε4 is related to impaired neuronal recovery mechanisms and that epileptic seizures cause neuronal injury (Houser, 1992 and Vezzani and Granata, 2005), ε4 may be associated with impaired neuronal recovery after seizures, leading to increased risk of postictal confusion. Thus, the purpose of this study was to determine if the APOE ε4 allele is related to greater incidence of postictal confusion in patients with medically intractable TLE.

Methods

The data for this retrospective study were obtained from a patient registry approved by the Cleveland Clinic Institutional Review Board. Two individuals were excluded due to unavailable postictal confusion data, resulting in a sample of 85 individuals who underwent anterior temporal lobectomy for the treatment of medically intractable TLE (right = 42; left = 43). A detailed description of participant characteristics and inclusion criteria are reported elsewhere (Busch et al., 2007). Briefly, patients were included in the study if they had a Full Scale IQ of 70 or higher and had frozen or paraffin-embedded tissue that underwent DNA analysis. See Table 1 for a description of demographic and seizure variables across groups.

Postictal confusion was coded by two independent raters (M.D. and J.C.) based on review of the initial intake evaluation report and the video-EEG monitoring report. Raters were blinded to ε4 status, and interrater reliability for a subsample was acceptable ($\alpha = 0.86$). Postictal confusion was defined by epileptologist notation in the medical record that (1) the participant or family reported postictal confusion on direct questioning during the initial clinical evaluation, or (2) the word "confusion," regardless of duration, was used to describe the postictal period after at least one of the seizures during video-EEG monitoring. Duration of confusion was noted in 27 of the 42 patients for whom postictal confusion was reported in the medical records and ranged from 1 to 300 min (median = 10, interquartile range = 24). Notation of postictal dysphasia was not considered to reflect postictal confusion. APOE status was determined by DNA extracted from 20 mg of frozen or paraffin-embedded brain tissue obtained at time of surgery. For additional details regarding the methods used for DNA genotyping, please see Busch et al. (2007).

To compare prevalence of postictal confusion in those with and without at least one ε4 allele, patients were grouped by presence or absence of an ε4 allele and presence or absence of postictal confusion. Those homozygous and heterozygous for the ε4 allele were combined into a single group due to the small number of individuals with ε4/4 ($n = 4$). Groups did not significantly differ on demographic or seizure variables, including side of epilepsy. Thus, side of epilepsy was not further considered in the following analyses.

Results

At least one APOE ε4 allele was present in 26% of the patients ($n = 22$; ε2/4 = 1, ε3/4 = 17, and ε4/4 = 4) and was not present in the remaining study patients ($n = 63$; ε2/3 = 13, ε3/3 = 50). The distribution of APOE genotypes was consistent with what is typically observed in the general

population and did not deviate from Hardy–Weinberg equilibrium. Postictal confusion was present in 42 patients (49%).

A chi-square analysis revealed that patients with an ε4 allele were more likely to experience postictal confusion than those without ε4 ($\chi^2[1] = 4.18$, $p = .036$). Specifically, of the 22 individuals with APOE ε4, 15 demonstrated postictal confusion (68%), while only 27 of the 63 without APOE ε4 exhibited postictal confusion (43%; see Table 2). Further, the odds ratio for predicting confusion based on the presence of ε4 was 2.86 (CI = 1.02–7.97, $p = .045$), suggesting that ε4 carriers were almost three times more likely to demonstrate postictal confusion than patients without ε4.

Discussion

The results of this study suggest that the presence of the APOE ε4 allele increases the risk of postictal confusion in patients with medically intractable TLE. Patients who possessed at least one ε4 allele were at significantly greater risk for postictal confusion than those without an ε4 allele.

One potential reason for the association between ε4 and postictal confusion is that ε4 may impair neuronal recovery from injury. APOE ε4 has been related to poor neuronal recovery in murine models of stroke and closed head injury (Horsburgh et al., 2000, Sabo et al., 2000 and Sheng et al., 1998). Further, human studies have demonstrated that ε4 is related to impaired recovery from, or poor prognosis after, acute events such as closed head injury, cerebral hemorrhage, ischemia, and cardiopulmonary bypass surgery (Alberts et al., 1995, Sorbi et al., 1995, Tardiff et al., 1997 and Teasdale et al., 1997). Recently, Ely et al. (2007) demonstrated that ε4 was associated with increased duration of delirium in mechanically ventilated patients in an intensive care unit.

The mechanisms by which APOE affects neuronal recovery are not fully understood. One potential hypothesis is that APOE down-regulates the inflammatory response in an isoform-specific manner (Grocott et al., 2001 and Lynch et al., 2003). For example, human studies have found that APOE ε4 was associated with an increase in the systemic inflammatory response in patients following cardiopulmonary bypass (Grocott et al., 2001) and was associated with more severe symptoms and/or increased prevalence of neuroinflammatory disorders such as multiple sclerosis (Evangelou et al., 1999, Kinnecom et al., 2007 and Schmidt et al., 2002). Specifically, ε4 has been shown to be less effective than ε2 and ε3 at suppressing glial activation in the context of brain inflammation (Barger and Harmon, 1997, Egensperger et al., 1998 and Laskowitz et al., 2001). The relationship between APOE ε4 and inflammation, in combination with evidence that seizures are associated with neuronal inflammatory processes (Vezzani and Granata, 2005), suggests that inflammation may be a mediating factor in the relationship between ε4 and postictal confusion.

Additional potential mechanisms for the effect of the APOE allele on postictal confusion come from the Alzheimer disease literature. APOE ε4 has been found to result in increased Aβ peptide binding (Strittmatter et al., 1993), decreased cytoskeletal stability including microtubule breakdown and impaired neurite outgrowth (Mahley et al., 1995, Nathan et al., 1995 and Strittmatter et al., 1994), and decreased synaptogenesis and synaptic plasticity after neuronal injury (Levi et al., 2003). Over time, these factors may result in decreased functional reserve capacity and poorer recovery from seizures in patients with epilepsy.

Although not investigated in the current study, seizure-aggravating variables may mediate the relationship between ε4 and postictal confusion. Studies examining the relationships between APOE ε4 and epilepsy prevalence/severity have yielded mixed results (Blümcke et al.,

1997, Diaz-Arrastia et al., 2003, Gambardella et al., 1999, Ponomareva et al., 2007 and Yeni et al., 2005). Sporiš et al. (2005) found that patients with epilepsy and an ε4 allele were less likely to respond to antiepileptic medications than those without ε4. They surmised that this finding may reflect destabilization of lipid binding associated with the ε4 allele, leading to greater instability of the neuronal membrane and more frequent uncontrolled electrical discharges in patients. Further, postictal confusion has been related to more diffuse spiking abnormalities and brain atrophy (Gambardella et al., 1995). Thus, the increased neuronal membrane instability associated with ε4 may lead to increased prevalence of postictal confusion.

Interestingly, the ε4 allele was also associated with decreased memory abilities in a subsample of patients from the current study who had longstanding epilepsy, further highlighting the effect of ε4 on these individuals (Busch et al., 2007). It is possible that ε4 is associated with more global cognitive dysfunction compared to those without ε4, resulting in decreased ability to compensate during the postictal period. This remains to be investigated.

The results of the current study offer a first glance at the relationship between APOE ε4 and postictal confusion, although they are limited by several factors. First, the behavioral manifestations of postictal confusion and postictal language disturbance may overlap, making it difficult to distinguish between the two. Due to the greater prevalence of postictal dysphasia in patients with dominant TLE, the occurrence of postictal confusion may be overestimated in this population. Although more patients with left TLE exhibited postictal confusion than those with right TLE in the current study, this difference was not significant, and the side of epilepsy did not moderate the relationship between APOE allele and postictal confusion. This suggests that confusion was distinguishable from dysphasia, and postictal language abnormalities did not significantly affect the current findings. A second limitation of this study is that coding of

confusion was based on patient/family report and observation during video-EEG monitoring. As this was a retrospective study, no standard and explicit behavioral criteria were used to define confusion in the medical record. Lack of objective behavioral criteria may have reduced reliability of this variable. The sample size in each cell was small after being stratified for both ε4 status and postictal confusion (n = 7–36 per cell). However, despite the reduction in statistical power that could result from decreased reliability and the small sample size, this study found that APOE ε4 resulted in an increased risk of postictal confusion. Finally, the relationship between APOE and postictal confusion requires replication in additional, broader samples, including populations with less severe epilepsy, to determine the generalizability and pervasiveness of this relationship. Future research with larger and broader epilepsy samples and more specific behavioral criteria for postictal confusion will be needed to further elucidate the role of APOE ε4 in postictal confusion and factors that may moderate or mediate this relationship.

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Table 1. Demographic and seizure variables across patient groups

Variable	**No postictal confusion**		**Postictal confusion**	
	−ε4 (*n* = 36)	**+ε4 (*n* = 7)**	**−ε4 (*n* = 27)**	**+ε4 (*n* = 15)**
Age	34.4 (11.7)	37.3 (13.4)	39.0 (11.2)	34.5 (9.4)
Education	12.7 (1.8)	13.1 (1.7)	13.6 (2.3)	13.9 (3.0)
Full Scale IQ	94.4 (13.3)	99.6 (19.6)	93.9 (10.3)	97.2 (13.8)
Age at seizure onset	12.3 (9.9)	10.4 (8.8)	16.5 (10.4)	15.4 (9.4)
Duration of seizures	21.4 (11.7)	27.0 (17.4)	22.4 (14.8)	19.1 (8.6)
Sex				
Male	15 (42%)	3 (43%)	11 (41%)	7 (47%)
Female	21 (58%)	4 (57%)	16 (59%)	8 (53%)
Race				
White	34 (94%)	7 (100%)	26 (96%)	15 (100%)
Black	2 (6%)	0	0	0
Hispanic	0	0	1 (3%)	0
Side of epilepsy				
Left	17 (47%)	2 (29%)	17 (63%)	7 (47%)
Right	19 (53%)	5 (71%)	10 (36%)	8 (53%)

Data represent mean (S.D.) or *n* (%). All continuous variables with the exception of IQ are represented in years. −ε4 = participants without an ε4 allele; +ε4 = participants with at least 1 ε4 allele.

Table 2. Frequency of patients with and without an APOE ε4 allele who did and did not exhibit postictal confusion, $\chi^2[1] = 4.18$, $p = .04$

	Postictal confusion		**Total**
	No	**Yes**	
APOE			
−ε4	36	27 (43% of −ε4)	63
+ε4	7	15 (68% of +ε4)	22
Total	43	42	85

−ε4 = participants without an ε4 allele; +ε4 = participants with at least 1 ε4 allele.