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ApoE ε4 genotype and the age at onset of temporal lobe epilepsy: A case—control study and meta-analysis

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Summary In order to investigate the role of ApoE ε4 as a modifier of the age at onset of temporal lobe epilepsy (TLE), we performed a molecular epidemiology study in 78 patients with mesial temporal lobe epilepsy and hippocampal sclerosis. Genotyping was done by a PCR-RFLP assay. In order to better estimate the role of this variant as a modifier of the age at onset, we also performed a systematic review of the literature. We included our results into a meta-analysis along with data available from seven published studies with 728 patients that looked into the role of ApoE ε4 in TLE. We found that ApoE ε4 carriers in our population had a non-significant earlier age of epilepsy onset than non-carriers. The meta-analysis confirmed this finding, showing that ApoE ε4 carriers had epilepsy onset almost 4 years earlier than non-carriers (mean difference 5.15 years; CI 95% 2.08—6.22; $p = 0.001$). In conclusion, the ApoE ε4 isoform is a genetic factor that might influence the age at onset of TLE.

1. Introduction

Gowers's *Epilepsy and other chronic convulsive diseases* book contained the first description of the silent interval occurring between a traumatic head injury and the subsequent onset of epilepsy (Gowers, 1881). Different dynamic, progressive structural, and functional changes may be occurring during this period, resulting years later in the clinical

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manifestations of epilepsy (Statler, 2006; Tani et al., 2007). These phenomena may have a role in Temporal Lobe Epilepsy (TLE), where a frequent but not necessary history of an early injury to the brain is followed years later by the recurrent and unprovoked seizures typical of this epileptic syndrome (Berg, 2008). However, the duration of the so-called silent interval, clinically and inaccurately inferred from the age of onset of epilepsy, is not uniform in all patients. The differences observed may depend on influences of genetic factors (Janszky et al., 2004).

Apolipoprotein E (ApoE) is a lipid transporter protein with a fundamental role in the maintenance and repair of neuron cell membranes (Mahley, 1988). The ApoE gene is polymorphic. Two single nucleotide polymorphisms result in three isoforms that differ in their abilities to accomplish ApoE critical functions (Morrow et al., 2000). ApoE ε4 is associated with a variety of neuropathological processes, such as Alzheimer's disease (Strittmatter et al., 1993), Multiple Sclerosis (Burwick et al., 2006), and Traumatic Brain Injury (Hiekkanen et al., 2009). Previous studies looked into the role of ApoE variants in Temporal Lobe Epilepsy (Briellmann et al., 2000; Cavalleri et al., 2005; Salzmann et al., 2008). Specifically, the results obtained regarding the role of the ApoE ε4 isoform as a modifier of the age of onset of epilepsy have been controversial so far (Kilpatrick et al., 1996; Tan et al., 2004).

In order to better explore the role of ApoE ε4 isoform as a modifier of the age at onset of TLE, we performed a molecular epidemiology study along with a systematic review and a meta-analysis of the evidence published on this subject.

2. Materials and methods

2.1. Molecular epidemiology study

2.1.1. Patients

Between August 2003 and July 2005, we recruited 78 MTE-HS patients (36 men, mean age 38.5 years) from the Epilepsy Clinic at the Neurology Division of the Ramos Mejia Hospital in Buenos Aires, Argentina. All patients were Buenos Aires residents. Previous studies have shown that the genetic contribution of Europeans to the gene pool of the population of Buenos Aires could be estimated at 67.55% (Martinez Marignac et al., 2004). The study was reviewed and approved by the local ethics committee and a written informed consent was obtained from each patient prior to any blood sample collection. All patients had a comprehensive diagnostic evaluation, including a detailed seizure history, neurological examination, neuropsychological testing, optimized MRI study, and surface EEG. Long-term video-EEG monitoring was performed in a subset of 47 patients. Findings from 26 of these video-EEGs are fully described elsewhere (Giagante et al., 2003). Data from all patients was consistent with the diagnosis of typical MTE-HS, without other additional etiologies. Thirty-five patients from this group additionally had a pathological diagnosis of HS when undergoing surgical treatment for their epilepsy. Thus, the diagnosis of MTE-HS was based mainly on the presence of typical temporal auras (epigastric in 85% of patients), interictal EEG discharges predominant over the temporal lobes (present in 65 subjects), along with typical MRI findings of HS, as assessed by a radiologist (in all 78 patients). We defined the age of epilepsy onset, retrospectively, as the age of the subject at his/her first unequivocal seizure, excluding febrile convulsions. Review of all the available information from the epilepsy clinic evaluation was blinded to the patient genotype.

2.1.2. Genotyping

Genomic DNA was isolated from whole blood using a Flexigene kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. ApoE genotypes were determined by PCR-RFLP, as previously described (Busch et al., 2007). The genotyping reactions were performed blinded to clinical features. No other polymorphisms were examined in our cohort.

2.1.3. Statistical analysis

Our cohort was stratified in two groups according to the presence of the ApoE ε4 allele. We compared the age of epilepsy onset between groups with the *t*-test. The level of significance was set at 5%.

2.2. Systematic review and meta-analysis

2.2.1. Search strategy and inclusion criteria

MEDLINE, EMBASE, BIOSIS, and EpiGad (http://www.epigad.org) databases were searched with no language restrictions from their inception to July 1st, 2009. The search strategy was: *Epilepsy, Temporal Lobe [MeSH Terms], or Seizures [MeSH Terms], or Temporal lobe epilepsy, or seizures, and Apolipoprotein E4 [MeSH Terms], or Apolipoprotein E, or ApoE*. All references in these studies and published reviews were explored to identify additional studies not indexed by the selected databases. Whenever multiple publications from the same study group were found, we selected the one with the most complete and recent results. Eligible studies had to meet all of the following criteria: (a) original data from independent studies; (b) publication in a peer-reviewed journal; (c) enough data to calculate the gene variant effect on age at onset of TLE; (d) investigation of the ApoE ε2, 3, and 4 polymorphisms; (e) description of the genotyping method or its reference; and (f) inclusion of patients with a diagnosis of TLE. Authors were contacted whenever there were queries about their studies.

2.2.2. Data extraction

Two investigators (M.K. and D.G.M.) independently extracted the following data from each publication: author, country of origin, patient selection and features, demographic information, ethnic origin of the study population, number of eligible and genotyped subjects; number of subjects with each ApoE genotype, and mean age at onset of epilepsy for each genotype. Disagreements were settled by consensus.

2.2.3. Quality score assessment

Methodology quality was independently assessed by two reviewers (M.K. and D.G.M.) according to a set of predefined criteria (Supplementary Table 1), based on the scale of Thakkinstian et al. (2004). Disagreements were settled by consensus. Scores ranged from 0 (lowest) to 7 (highest).

2.2.4. Statistical analysis

Since we detected heterogeneity among studies, summary effects and the corresponding 95% CI were estimated by random effect meta-analysis using the ''metan'' command in the Stata package (Version 9.0; StataCorp LP, College station, TX). The pooled effect size is presented as the standardized difference (SD; *Cohenĭs d*) in the outcome variable (age at onset of epilepsy), which was defined as the mean difference (between carriers and not carriers of ApoE ε4 allele) divided by the common within-group standard deviation by the method of Cohen. Since the outcome variable was equally measured by all investigators, i.e., in years, we also estimated the pooled mean absolute difference. We explored potential causes of heterogeneity by adjusting a meta-regression model. A *Q*-test for heterogeneity was performed. Publication bias was assessed using Egger's and Begg-Matzumdar tests. The level of significance was set at 5%. Forest plots were also generated.

Table 1 Summary of study included in the meta-analysis.

First author	Cases (HS), *n*	Country	Year	ApoE4[a], *n*	AOE 4 y (sd)	No ApoE4[b], *n*	AOE 23 y (sd)	Quality
Briellmann	43(31)	Australia	2000	10	5 (5)	33	14.9 (10)	4
Mercier	48(9)	France	2000	19	4.1 (2.43)≈	29	13.8 (2.43)≈	5
Yeni	47(47)	Turkey	2004	8	7.44 (6.13)	39	8.75 (7.61)	3
Gambardella	138(24)	Italy	2005	24	26.2 (20.1)	114	33.9 (20.7)	6
Cavalleri	181(141)	UK	2005	30	13.7 (10)	151	16.7 (11)	6
Busch	87(64)	USA	2007	22	13.82 (9.29)	65	14.26 (10.13)	5
Salzmann	106(86)	France	2008	26	10.54 (6.36)	80	16.5 (9.9)	5
Kauffman	78(78)	Argentina	2009	23	14.3 (12.13)	55	16.5 (12.54)	7

[a] ApoE4 carriers.
[b] ApoE4 non-carriers. AOE 4 mean age at onset of epilepsy in ApoE4 carriers. AOE 23 mean age at onset of epilepsy in APOE4 non-carriers.
≈ DS estimated from age at onset range.

3. Results

3.1. Effect of the ApoE ε4 allele in our population

The distribution of ApoE genotypes was consistent with what is typically observed in the general population and did not deviate from Hardy—Weimberg equilibrium. At least one ApoE ε4 allele was present in 29.9% of the patients ($n = 23$; ε2/ε4 = 4, ε3/ε4 = 17, ε4/ε4 = 2) and was absent in the remaining ($n = 54$; ε2/ε2= 0, ε2/ε3 = 3, ε3/ε3 = 51).

We observed a non-significant difference in the age at onset of epilepsy between ApoE ε4 carriers and non-carriers. Patients with the ε4 allele had an earlier age at onset of epilepsy than patients without the ε4 allele (14.13 ± 12.13 years in carriers vs. 16.5 ± 12.54 years in non-carriers; Cohenǐs $d = -0.18$; $T = -0.71$; $p = 0.47$). The power of our sample was 0.53. The low frequency of patients carrying two copies of the ε4 allele prevented us from assessing a dosage effect for this allele on the age at onset of epilepsy.

There were no differences in other variables. A previous history of febrile seizures and a family history of epilepsy were similar between carriers and non-carriers of the ε4 allele.

3.2. Meta-analysis

The combined search yielded 74 studies. Of these, 54 were excluded by reading their titles and abstracts. Thus, 20 references were left for analysis to ensure agreement with inclusion criteria. Subsequently, nine studies were excluded because they did not investigate the association between ApoE polymorphisms and TLE clinical features. Two other articles were not included because of incomplete data (Blumcke et al., 1997; Kumar et al., 2006). Out of two studies (Gambardella et al., 1999, 2005) from Gambardella et al., we selected the one with the largest and most recent sample size (Gambardella et al., 2005). The studies from Busch et al. (2007) and Chapin et al. (2008) involved the same population of patients. For that reason, we selected the first one. Eventually, seven references met our inclusion criteria (Table 1). Therefore, data from these studies, along with the results obtained in our population, totalled a

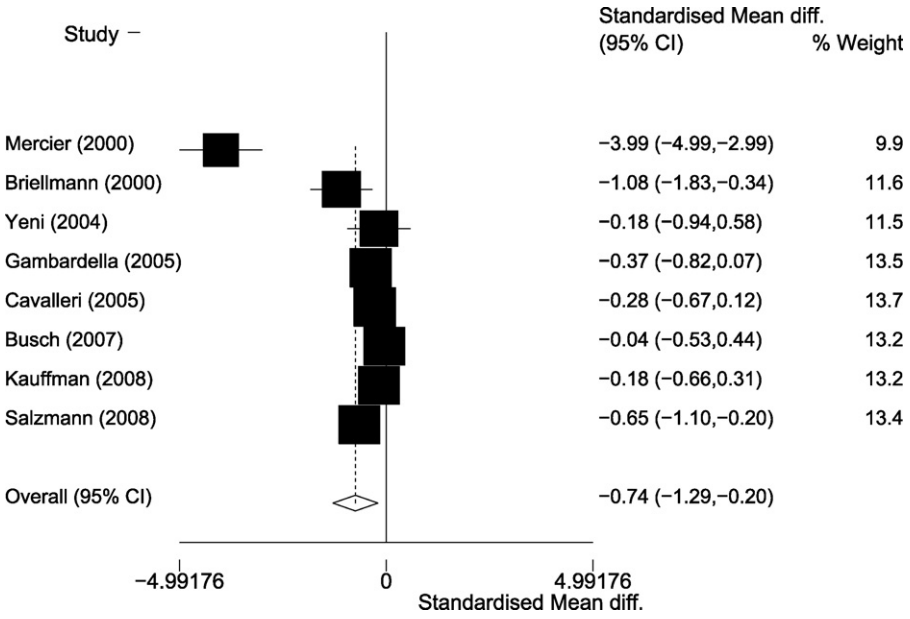

Figure 1 Forest Plot of the summary effect of the ApoE4 allele on TLE age at onset.

sample of 728 patients. Hippocampal sclerosis was reported in 480 (66%) patients. All studies were carried out in populations from Turkey, USA, Italy, Australia, United Kingdom, France, and Argentina. The quality of the studies ranged from 3 to 7, being seven the maximum score. A summary of the data analyzed is presented in Table 1.

The age at onset of epilepsy was significantly lower in ApoE ε4 carriers. Patients with the ε4 allele had an age of onset of epilepsy 5 years earlier, on average, than patients without the ε4 allele (mean difference 5.15 years; CI 95% 2.08—6.22; $p = 0.001$; standardized mean difference −0.74; CI 95% −1.29 to −0.20; $p = 0.007$) (Fig. 1).

Additionally, we performed an influential analysis in order to test the robustness of our findings. This analysis showed that no single study appeared to be excessively influential on the results. Exclusion from the analysis of each of the two studies (Briellmann et al., 2000; Mercier and Lucotte, 2000) with the largest effect size resulted in no more than a 20%, or a 1 year, reduction in the gene effect (Supplementary Figure 1).

Meta-regression analysis was used to assess possible causes of heterogeneity for three predefined potential sources of variance between studies: quality score, study size, and proportion of HS patients included in each population. We found the proportion of HS patients as a significant source of heterogeneity ($p = 0.003$).

We also performed two sensitivity analyses. When excluding studies with a low quality score (<5) (Briellmann et al., 2000; Yeni et al., 2005), we did not find significantly different estimates (mean difference 4.97 years; CI 95% 1.35—8.58; $p = 0.001$). Secondly, when we excluded studies involving low numbers of HS patients (Mercier and Lucotte, 2000; Gambardella et al., 2005), we did not find significantly different estimates either (mean difference 3.97 years; CI 95% 1.20—6.73; $p = 0.005$). Finally, the funnel plot for overall results was symmetric, without evidence of publication bias in the Begg test ($p = 0.2$).

4. Discussion

Overall, our results show that the ApoE ε4 allele is associated with an earlier onset of TLE. Patients with the ε4 allele had an onset of epilepsy 5 years earlier, on average, than patients without the ε4 allele. This finding may contrast with previous studies (Cavalleri et al., 2005), as well as with the analysis in our own population, although it is similar to the results of the first research on this topic performed by Briellmann et al. (2000). However, this apparent contradiction is found very often in the field of the genetics of complex disorders (Hattersley and McCarthy, 2005). Conflicting findings may be due to multiple causes such as differences in the populations analyzed, difficulties with the phenotype definition, or a low-power design to detect small genetic effects (Zondervan and Cardon, 2004). We believe that conflicting findings, such as those in our population, are mainly due to the latter. However, this problem could be solved, at least in part, by carrying out a systematic review of the literature and a meta-analysis (Lin et al., 2006; Munafo, 2006). Accordingly, all of the populations analyzed showed a trend for a lower age at onset of epilepsy in ApoE ε4 carriers when compared with non-carriers, thus underscoring the meta-analysis greatest power to reveal this gene effect.

The variability in the age at onset of epilepsy may be a reflection of the duration of the silent interval in TLE. Furthermore, there is evidence that the extent of this period could depend on genetic influences (Janszky et al., 2004). Different epileptogenic processes that take place during the silent interval may be under the influence of genetic factors such as ApoE. The ApoE ε4 isoform has been found to play a role in different neurodegenerative processes, such as disruption of neuronal cytoskeleton, increase in β amyloid protein deposits (Holtzman et al., 2000), and apoptosis potentiation (Ji et al., 2002). These phenomena have also been observed in TLE. Most of the patients with MTE-HS have cytoskeletal abnormalities in their hilar cells (Thom et al., 2002). An increase in β amyloid deposits was found in a number of MTE-HS patients (Gouras et al., 1997). Finally, the expression of different apoptotic markers such as caspases, p53, and FAS was upregulated in hippocampal tissue from patients with this epileptic syndrome (Xu et al., 2007). Therefore, our findings seem to be biologically plausible, highlighting the ApoE gene as a candidate to influence the epileptogenetic processes occurring in TLE. However, since MTE-HS does not always involve a discrete traumatic injury and the age at seizure onset is a rough proxy for the time between a traumatic injury and seizure onset, other unexplored factors besides the extent of the silent interval could explain the findings of our study. For instance, among potential candidates we can mention that previous studies have associated the nature and severity of memory impairments with the age at onset of TLE (Lespinet et al., 2002).

We must interpret these results with caution. The data set analyzed is of relatively small magnitude. About 1 year of the gene effect estimation could be accounted for by one small study (Mercier and Lucotte, 2000). The results of our meta-regression analysis may be pointing out lack of homogeneity of the pooled populations. Furthermore, the quality of the different studies is uneven. Not all investigators provided appropriate descriptions of the criteria for the identification and selection of cases. The limited number of patients carrying two copies of the ε4 allele prevented us from investigating a ''dosage effect'' for this allele, as it is seen in Alzheimeŕs disease (Strittmatter et al., 1993). Moreover, other variables that were not fully analyzed such as age, ethnicity, gender, and epilepsy etiology may be a source of bias for our results. Future studies with meta-analyses of a higher number of cases, better quality designs, and especially individual patient data meta-analysis are needed in order to provide a better estimate of the effect of this polymorphism on the age at onset of this disorder.

In summary, ApoE ε4 isoform is a genetic factor that might influence the age at onset of TLE.

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None of the authors has any other financial disclosure.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eplepsyres.2010.05.007.

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