Short communication

Negative evidences in association between apolipoprotein E polymorphism and panic disorder

S. Martínez-Barrondo a,*, P.A. Sáiz a, B. Morales b, M.P. García-Portilla a, E. Coto b, V. Álvarez b, M.T. Basarán a, M. Bousoño a, J. Bobes a

a Department of Psychiatry, School of Medicine, University of Oviedo, Julian Clavería 6, 3, 33006 Oviedo, Spain
b Laboratory of Molecular Genetics, Hospital Universitario Central de Asturias, Oviedo, Spain

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Abstract

The aim is to investigate the association between apolipoprotein E (ApoE) and panic disorder (PD). Genotyping 92 PD patients [Diagnostic Statistic Manual IV (DSM IV) criteria] and 174 controls no differences were found between both groups. Variation in the ApoE-gene was not associated with the development of PD.

Keywords: Genetic association; Panic disorder; Apolipoprotein E

1. Introduction

Apolipoprotein E (ApoE) is a protein, and a major component of lipoproteins [18–20]. Specifically ApoE, mediates the cholesterol homeostasis in the body and is a major lipid carrier in the brain. It plays and important role in intraneuronal cholesterol transport, neuronal growth and in central nervous system response to injury, particularly in the hippocampal region [15], which has also been associated to panic disorder (PD) [5,8].

Several studies [4,9,12–14] indicate that chronic increases of cholesterolemia, lead to increases of ApoE mRNA levels. Some of them [12] even find in vitro changes in ApoE segregation, with decrease of ApoE cellular and secreted levels as long as long-term treatment with statins goes on.

PD patients have consecutively show high cholesterol blood levels [3,7,10]. Although results are not totally consistent [16,18], Feder [6] suggested a relationship between PD and hypercholesterolemia with presence of common genetic markers. As ApoE is involved in lipids metabolism and PD shows elevated cholesterol blood levels, we decide to genotype ApoE in PD patients. No investigations are found about PD and its relationship with ApoE.

In order to clarify the possible association between the variation at the ApoE-gene and PD, we genotyped a group of PD patients and matched controls.

2. Subjects and methods

2.1. Subjects

Out of 102 PD out-patients screened, 92 [mean age (S.D.): 35.87 (12.38) years; 30.4% males (28 patients); mean onset of PD (S.D.): 30.98 (10.47) years; mean duration of the disorder (S.D.): 4.34 (7.91) years] were enrolled in the study, 9.8% withdrew the inform consent. All patients had a diagnosis of PD according to DSM-IV criteria.

One hundred and seventy-four healthy volunteers [mean age (S.D.): 38.40 (8.94) years; 38.5% males (67 subjects)], matched with patients for age and ethnicity, were also genotyped.

Evaluation of both groups was made using the structured clinical interviews Mini International Neuropsychiatric Interview (MINI), and Structured Clinical Interview for DSM-IV II (SCID-II). Among the 92 patients, excluding agoraphobia, which represented 97.8% of comorbidity, 28.3% had another comorbid disorder (18.5% a mental disorder related to sub-
The study was conducted according to the provisions of the World Medical Association Declaration of Helsinki, ethical approval of the study was granted [22], and all participants gave their informed consent.

2.2. ApoE genotyping

ApoE-genotyping was performed as follows [21]. Genomic DNA was extracted from leukocytes in 10 ml of peripheral blood. 100 ng of genomic DNA were polymerase chain reaction (PCR)-amplified with primers 5′ TCCAGGAGCTG-CAGGCGGGCA 3′ and 5′ ACAGAATTCGCCCCGGC-CTGGTACACTGCCA 3′. After 35 cycles of amplification, reactions were digested with the restriction enzyme CfoI, and digested-fragments were separated by electrophoresis on a 4% ethidium bromide-stained agarose gel. Allele assignment was based on the presence or absence of CfoI cutting sites in the amplified sequence.

2.3. Statistical analysis

Differences between allele and genotype frequencies were assessed using $\chi^2$-test, and two-tailed Fisher’s exact test. $P \leq 0.05$ was considered as significant. Odds ratio (ORs) and their confidence intervals (95% CIs) were also calculated.

4. Results

We genotyped 92 PD out-patients (DSM IV criteria). The ApoE genotypes distribution is summarized in Table 1. $\varepsilon3\varepsilon3$ were the more common genotypes in PD and controls. However, genotype frequencies did not differ between both groups (two-tailed Fisher’s exact test = 5.660, $P = 0.161$). $\varepsilon3$ allele frequency was also the more common in both groups, and no differences were found comparing them ($\chi^2 = 3.648, df = 2, P = 0.161$) (Table 2).

5. Discussion

The association between PD and ApoE has not been studied before. Our investigation shows negative conclusions.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PD</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varepsilon2\varepsilon3$</td>
<td>13 (14.13)</td>
<td>21 (12.07)</td>
</tr>
<tr>
<td>$\varepsilon2\varepsilon4$</td>
<td>0 (0)</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>$\varepsilon3\varepsilon3$</td>
<td>60 (65.21)</td>
<td>131 (75.29)</td>
</tr>
<tr>
<td>$\varepsilon3\varepsilon4$</td>
<td>18 (19.57)</td>
<td>21 (12.07)</td>
</tr>
<tr>
<td>$\varepsilon4\varepsilon4$</td>
<td>1 (1.09)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>174</td>
</tr>
</tbody>
</table>

Two-tailed Fisher’s exact test = 5.660, $P = 0.161$. Values in parentheses are in percentages.

Table 2

Allele frequencies of ApoE in PD patients and controls

<table>
<thead>
<tr>
<th>Allele</th>
<th>PD</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varepsilon2$</td>
<td>13 (7.07)</td>
<td>22 (6.3)</td>
</tr>
<tr>
<td>$\varepsilon3$</td>
<td>151 (82.07)</td>
<td>304 (87.4)</td>
</tr>
<tr>
<td>$\varepsilon4$</td>
<td>20 (10.86)</td>
<td>22 (6.3)</td>
</tr>
<tr>
<td>Total</td>
<td>184</td>
<td>348</td>
</tr>
</tbody>
</table>

$\chi^2 = 3.648, df = 2, P = 0.161$. Values in parentheses are in percentages.

There is not a more frequent ApoE genotype or allele frequency related to PD. The negative results might be explained by the presence of high cholesterol levels in PD patients related with specific endophenotypes of the disorder, such as fear for dying [17] and sleep panic [2]. As ApoE seemed to be related to cholesterol levels, further investigations are needed comparing ApoE genotypes and cholesterol levels in these subtypes.

PD has a high comorbidity with depression. Agargun et al. [1] found low cholesterol levels in PD associated with major depression. Comorbidity could be another factor to include in statistical analyses in next studies of ApoE genotypes and PD, because it might be a confusional factor for the results of our investigation.

Another possible explanation for our negative results is a hypotheses, recently published [11], where changes of cholesterololemia are related to a serotoninergic dysfunction in anxiety disorders and major depressive disorder, and it would not have any relation to ApoE.

In conclusion, the results of our study do not support the role of ApoE genotype or allele frequency in PD. However, further studies with endophenotypes of PD (nocturnal pattern or peripheric neurovegetative pattern), comorbidity disorders, and measuring cholesterololemia are needed to clarify it.

References


