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Apolipoprotein E ε4 and testosterone interact in the risk of Alzheimer’s disease in men

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SUMMARY

The apolipoprotein E ε4 allele (APOE ε4) is a well-established risk factor for Alzheimer’s disease (AD), but the mechanisms for this association are not well understood. In addition, other risk and protecting factors are needed to explain the causality of the disease. Sex steroid hormones, such as estradiol and testosterone, are thought to exert protective mechanisms in the brain (Lee and McEwen, 2001). Lower levels of total estradiol and total testosterone in men with AD have been found (Hogervorst et al., 2001; Rasmuson et al., 2002). The current study examined relations between APOE ε4 and levels of total testosterone and total estradiol in the risk of AD in men. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer’s disease; testosterone; apolipoprotein E ε4 allele; risk

SUBJECTS, METHODS AND RESULTS

We examined 116 male Caucasians from the Oxford Project To Investigate Memory and Ageing (OPTIMA). Fifty-one were autopsy confirmed CERAD AD cases (mean age at episode: 75.3 years, range: 58.8–89.5 years), 10 were diagnosed ‘probable AD’ by NINCDS/ADRDA criteria (69.8 years, range: 57.4–88.8 years) and 55 were without cognitive impairment and with CAMCOG scores ≥ 80 (73.6 years, range: 39.9–94.7 years). All had given their informed consent prior to the study (Clarke et al., 1998).

We analysed total testosterone using a competitive enzyme immunoassay (Bayer®, Bayer Cooperation, Tarrytown, NY, USA) in non-fasting blood serum samples that had been stored at −70°C. Serum had been collected between 10 and 12 am. For total estradiol, duplicate serum samples were extracted with ether. Estradiol was then assessed by radioimmunoassay using a highly specific rabbit antiserum. SHBG levels were investigated using an immuno-enzymometric assay (IEMA). Subjects were genotyped by standard PCR methods for APOE ε4 and for the butyrylcholinesterase K variant.

Using a logistic regression model with age and SHBG as co-variables, low testosterone (odds ratio (OR) = 0.86, 95% confidence intervals (CI) 0.75–0.99) and the APOE ε4 × testosterone interaction (OR = 1.28, 95% CI = 1.07–1.54) were significantly associated with AD, which suggested that the presence of the APOE ε4 allele modified the risk of AD associated with low testosterone levels. Entering APOE ε4 by itself as a risk factor for AD, gave an OR of 7.72 (95% CI = 3.63 to 16.48, p < 0.01). In a model where estradiol replaced testosterone, neither estradiol alone nor the estradiol × APOE ε4 interaction was a significant predictor of AD.

Table 1 presents the results of analyses stratified by diagnosis. The two main results were: first, testosterone levels were lower in APOE ε4-positive controls than in those without APOE ε4; second, in men without APOE ε4, testosterone levels were lower in AD than in controls. One of the lowest testosterone levels
with testosterone replacement therapy in non-
against the development of AD. Short-term studies
gated the possibly protective effects of testosterone
factor. At present, no long-term studies have investi-
spective studies are needed to resolve these issues.
not distinguish between these interpretations. Pro-
testosterone levels for other reasons. This study can-
APOE another interpretation is that
APOE but only in men without
APOE among other factors, lowers testosterone in male con-
testosterone levels are higher in controls than in AD,
APOE Table 1 illustrates two important results. First,
COMMENT
Table 1. Sex steroid levels in AD and in controls, by APOE4 status

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Subgroup (n)</th>
<th>APOE4 status (n)</th>
<th>Meana</th>
<th>p (t-test)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>AD (61)</td>
<td>With (44)</td>
<td>13.9 ±5.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (17)</td>
<td>15.0 ±4.8*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (53)</td>
<td>With (12)</td>
<td>11.3 ±7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (41)</td>
<td>19.1 ±5.4*</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>AD (60)</td>
<td>With (43)</td>
<td>69.8 ±28.7</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (17)</td>
<td>94.9 ±28.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (55)</td>
<td>With (12)</td>
<td>70.6 ±42.4</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (43)</td>
<td>107.8 ±34.9</td>
<td></td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; APOE4, apolipoprotein E 4; NS, not significant.
aTestosterone levels are in nmol/l and estradiol in pmol/l.
bAll subgroups were normally distributed; equal variances could be and were assumed in all cases.
Testosterone, APOE4-negative AD cases vs APOE4-negative controls: p = 0.009 (t-test).

(1.6 nmol/l) was in the only control who was an
APOE4 homozygote. With estradiol, levels were
lower in APOE4 carriers, both in AD cases and in
controls.
We also examined two other alleles, apolipoprotein
E 2 (APOE2) and the butyrylcholinesterase K
variant (BCHE-K). No significant association was
found between either allele and either steroid in any
analysis. Only a weak tendency was seen for
APOE2-positive controls to have higher steroid
levels than those without APOE2 (e.g. for testoster-
one: 20.2 nmol/l (n = 11) vs 16.5 nmol/l (n = 42),
p = 0.1, t-test).

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