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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 (APOEε4) 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 APOEε4 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 1®, 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 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 APOEε4 × testosterone interaction (OR = 1.28, 95% CI = 1.07–1.54) were significantly associated with AD, which suggested that the presence of the APOEε4 allele modified the risk of AD associated with low testosterone levels. Entering APOEε4 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 × APOEε4 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 APOEε4-positive controls than in those without APOEε4; second, in men without APOEε4, testosterone levels were lower in AD than in controls. One of the lowest testosterone levels
against the development of AD. Short-term studies
investigated the possibly protective effects of testosterone
factor. At present, no long-term studies have investi-
gated the possibly protective effects of testosterone
against the development of AD. Short-term studies
with testosterone replacement therapy in non-
dermented men have given mixed results (Wolf et al.,
1999). A possible explanation could be that, since
APOE4-positive controls had lower levels in the pre-
sent study than those without the allele, perhaps only
APOE4-positive men would profit from testosterone
replacement therapy. Future, long-term studies should
investigate the possibly protective effect of testoster-
one replacement therapy in APOE4 carriers who are
at risk of AD.

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Hogervorst E, Williams J, Budge M, Barnetson L, Combrinck M,
Smith AD. 2001. Serum total testosterone is lower in men with

COMMENT
Table 1 illustrates two important results. First,
APoE4 is associated with lower testosterone levels
in men, but only significantly so in controls. Second,
testosterone levels are higher in controls than in AD,
but only in men without APoE4. These results are
open to various interpretations. One is that APoE4
and other factors, lowers testosterone in male con-
trols and low testosterone, whether or not due to
APoE4 status, contributes to the onset of AD. Another interpretation is that APoE4 lowers testos-
terone in controls and that AD results in a lowering of
testosterone levels for other reasons. This study can-
not distinguish between these interpretations. Pros-
spective studies are needed to resolve these issues.

Low testosterone is potentially a modifiable risk
factor. At present, no long-term studies have investi-
gated the possibly protective effects of testosterone
against the development of AD. Short-term studies
with testosterone replacement therapy in non-
dermented men have given mixed results (Wolf et al.,
1999). A possible explanation could be that, since
APoE4-positive controls had lower levels in the pre-
sent study than those without the allele, perhaps only
APoE4-positive men would profit from testosterone
replacement therapy. Future, long-term studies should
investigate the possibly protective effect of testoster-
one replacement therapy in APoE4 carriers who are
at risk of AD.

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>Mean±</th>
<th>p (t-test)</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>&lt;0.001</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>&lt;0.001</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.
cTestosterone, 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
higher 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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