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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.

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...
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gate the possibly protective effects of testosterone

spective studies are needed to resolve these issues.

Another interpretation is that

APOE

but only in men without

APOE

among other factors, lowers testosterone in male con-

controls.

We also examined two other alleles, apolipoprotein

Eε2 (APOEε2) 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

APOEε2-positive controls to have higher steroid

levels than those without APOEε2 (e.g. for testoster-
one: 20.2 nmol/l (n = 11) vs 16.5 nmol/l (n = 42),

p = 0.1, t-test).

COMMENT

Table 1 illustrates two important results. First,

APOEε4 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 APOEε4. These results are

open to various interpretations. One is that APOEε4,

among other factors, lowers testosterone in male con-

trols and low testosterone, whether or not due to

APOEε4 status. Another interpretation is that APOEε4 lowers testos-

erone 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-
demented men have given mixed results (Wolf et al.,

1999). A possible explanation could be that, since

APOEε4-positive controls had lower levels in the pre-

sent study than those without the allele, perhaps only

APOEε4-positive men would profit from testosterone

replacement therapy. Future, long-term studies should

investigate the possibly protective effect of testoster-
one replacement therapy in APOEε4 carriers who are

at risk of AD.

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