Apolipoprotein E "4 and testosterone interact in the risk of Alzheimer’s disease in men

This item was submitted to Loughborough University's Institutional Repository by the/an author.

Additional Information:

- This is a pre-print. This uncorrected proof was submitted to the journal, International Journal of Geriatric Psychiatry, 2002, © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Metadata Record: [https://dspace.lboro.ac.uk/2134/2544](https://dspace.lboro.ac.uk/2134/2544)

Please cite the published version.
This item was submitted to Loughborough’s Institutional Repository by the author and is made available under the following Creative Commons Licence conditions.

For the full text of this licence, please go to:
http://creativecommons.org/licenses/by-nc-nd/2.5/
Apolipoprotein E ε4 and testosterone interact in the risk of Alzheimer’s disease in men

E. Hogervorst*, D. J. Lehmann, J. McBroom and A. D. Smith

Oxford Project To Investigate Memory and Ageing, Department of Pharmacology, Radcliffe, Infirmary, Oxford, UK

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 antiseraum. 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
(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 ε2 (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 testosterone: 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, 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, among other factors, lowers testosterone in male controls and low testosterone, whether or not due to APOE4 status, contributes to the onset of AD. Another interpretation is that APOE4 lowers testosterone in controls and that AD results in a lowering of testosterone levels for other reasons. This study cannot distinguish between these interpretations. Prospective studies are needed to resolve these issues.

Low testosterone is potentially a modifiable risk factor. At present, no long-term studies have investigated 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 APOE4-positive controls had lower levels in the present 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 testosterone replacement therapy in APOE4 carriers who are at risk of AD.

**ACKNOWLEDGEMENTS**

This work was supported by grants from The Alzheimer’s Association (NIRG 00-2258), the Takayama Foundation, the Norman Collisson Foundation and Bristol-Myers Squibb. E. Hogervorst is a Margaret Pelly Fellow of Somerville college, Oxford.

We would like to thank Professor M. Dowsett at the Department of Biochemistry, Royal Marsden NHS Trust in London for the oestradiol assay, and D. Quantrill and M. Gales at the Clinical Biochemistry Department of the John Radcliffe Infirmary for the testosterone and SHBG assays. We would also like to thank the members and participants of OPTIMA for making this study possible.

**REFERENCES**


Author Query Form (GPS/714)

Special Instructions: Author please write responses to queries directly on Galley proofs and then fax back. Alternatively please list responses in an e-mail.

Q1: Author: Reword as structured summary. Query to Pr. Ed—or leave as is as very shot paper?