Estrogen use and early onset Alzheimer’s disease: a population-based study

Arjen J C Slooter, Juliana Bronzova, Jaqueline C M Witteman, Christine Van Broeckhoven, Albert Hofman, Cornelia M van Duijn

Abstract
Estrogen use may be protective for Alzheimer’s disease with late onset. However, the effects on early onset Alzheimer’s disease are unclear. This issue was studied in a population based setting. For each female patient, a female control was matched on age (within 5 years) and place of residence. Information on estrogen use and other risk factors were, for cases (n=109) and controls (n=119), collected from the next of kin by structured interview. The strength of the association between estrogen use and early onset Alzheimer’s disease was studied using conditional logistic regression with adjustment for age and education level. There was an inverse association between estrogen use and early onset Alzheimer’s disease (adjusted odds ratio 0.34; 95% confidence interval 0.12–0.94). The study therefore suggests that estrogen use is beneficial to Alzheimer’s disease with early onset.

(J Neurol Neurosurg Psychiatry 1999;67:779–781)

Keywords: Alzheimer’s disease; estrogen; dementia

In recent years, there has been substantial interest in the effect of estrogen use on Alzheimer’s disease. However, all studies until now have reported on patients with late onset Alzheimer’s disease.1 Early onset Alzheimer’s disease is thought to be more often genetically related to early onset Alzheimer’s disease.1 The aim of this population based study was to investigate whether estrogen use is related to early onset Alzheimer’s disease.

Subjects and methods
STUDY POPULATION
Patients were derived from a population based study of early onset Alzheimer’s disease. Details concerning ascertainment of the patients have been published elsewhere.3 All patients diagnosed between 1980 and 1987, from two regions in the Netherlands, were included. The diagnosis of early onset Alzheimer’s disease was made according to a standard protocol similar to NINCDS-ADRDA criteria.4 Inclusion criteria for entering this study were female sex, age of onset before 65 years, and a slowly progressive decline of intellectual functions. In addition, the score on the clinical dementia rating scale should be greater than 0.5, the score on the short portable mental status questionnaire less than 20 (out of 30), and the score on the Hachinski scale should be 7 or lower (out of 18). Exclusion criteria were abnormalities other than cerebral atrophy on CT, and evidence of focal dysfunction on EEG. Furthermore, the dementia syndrome should not be the result of vascular or metabolic disorders, alcoholism, or depression. For each patient, a control subject was selected matched for age (within 5 years), sex, and place of residence. These controls were selected at random (within each age and sex category) from the municipal population register. Overall, in 52% of cases, the first consenting person served as a control, in 34% it was the second selected person, in 12% the third, and in 2% the fourth. Cognitive function in the controls was tested by short portable mental status questionnaire and none showed symptoms of dementia.6 Informed consent was obtained from all participants. After excluding women with missing data on estrogen use (n=15 cases; n=5 controls) the study population comprised 109 patients with early onset Alzheimer’s disease and 119 controls.

DATA COLLECTION
Information on estrogen use, age at menopause, vascular pathology, and education level was obtained by structured questionnaire. For both cases and controls, the next of kin was interviewed to collect the data symmetrically, as described in detail elsewhere.7 Patients who received estrogen were at the moment of intake all non-demented. A history of myocardial infarction, hypertension, and hypercholesterolemia was recorded. The presence of at least one of these three conditions was considered as vascular pathology. Age at onset was defined as age when memory failure or changes in behaviour were first noted. APOE genotyping was performed on coded DNA samples without knowledge of the diagnoses, as described earlier.8 Data for APOE typing were available for 82% of the patients and 73% of the controls.
Table 1  Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=109)</th>
<th>Controls (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (y (SD))</td>
<td>57.9 (6.4)</td>
<td>58.2 (6.7)*</td>
</tr>
<tr>
<td>Age at menopause (y (SD))</td>
<td>49.6 (4.1)</td>
<td>49.4 (4.4)</td>
</tr>
<tr>
<td>Estrogen use:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (10%)</td>
<td>24 (20%)+</td>
</tr>
<tr>
<td>No</td>
<td>98 (90%)</td>
<td>95 (80%)</td>
</tr>
<tr>
<td>APOE genotype‡:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE*2</td>
<td>10 (10%)</td>
<td>23 (25%)</td>
</tr>
<tr>
<td>APOEε3εε3 or APOEε2εε3</td>
<td>37 (37%)</td>
<td>44 (48%)</td>
</tr>
<tr>
<td>APOE*4</td>
<td>54 (53%)</td>
<td>24 (26%)+</td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary only</td>
<td>96 (88%)</td>
<td>90 (76%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>13 (12%)</td>
<td>29 (24%)+</td>
</tr>
<tr>
<td>Vasculcar pathology:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>29 (27%)</td>
<td>47 (39%)+</td>
</tr>
<tr>
<td>Absent</td>
<td>80 (73%)</td>
<td>72 (61%)</td>
</tr>
</tbody>
</table>

*Age in controls.
†p<0.05.
‡APOE genotypes were missing in eight cases and 28 controls.
§APOE*2, and APOE*4. There were no women more often used estrogen than those with primary education only (among the controls: n=16; 28% vs n=8; 18%), although not significantly (χ²=1.3; df=1; p=0.25).

STATISTICAL ANALYSIS
The strength of the association between early onset Alzheimer’s disease and estrogen use was studied as an odds ratio (OR) in a conditional logistic regression analysis, and presented with a 95% confidence interval (95% CI). The dependent variable was case-control status, and the predictor variables were estrogen use (present or absent), age (in years) and education level (primary education only or more). Stratified analyses according to the APOE genotype were done with unconditional logistic regression, a more powerful technique, as models did not converge with a conditional approach. Disregarding matching in an unconditional logistic regression will produce narrower confidence intervals, but the estimated odds ratios may be biased towards unity.

We used a product term for estrogen use and APOE*2 (which included the APOEε2ε2 and APOEε2ε3 genotypes), a product term estrogen use and APOE*4 (which included APOEε3ε4 and APOEε4ε4) in a model that further included the terms estrogen use, APOE*2, and APOE*4. There were no women with the APOEε2ε4 genotype. Categorical variables were studied with the χ² test, whereas for normally distributed, continuous variables, the two sample t test was used. Based on 109 cases and 119 controls, a significance level of 0.05, and a statistical power of 80%, the smallest detectable decrease in risk of EOAD was 0.34.

Table 2  Odds ratio for early onset Alzheimer’s disease associated with estrogen use

<table>
<thead>
<tr>
<th>Estrogen use</th>
<th>In matched individuals (n=208)</th>
<th>In matched pairs (n=104)</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>6 98</td>
<td>1 5</td>
<td>Yes 1</td>
<td>0.29 (0.11–0.80)</td>
<td>0.34 (0.12–0.94)</td>
</tr>
<tr>
<td>No</td>
<td>18 86</td>
<td>17 81</td>
<td>No 17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age and education level using conditional logistic regression.

Results
Descriptive statistics of the study population are presented in table 1. Estrogen use was reported less often for patients (10%) than for controls (20%). The age distribution was similar for patients and controls. Moreover, cases and controls did not differ in age at menopause. Table 1 further shows that patients with early onset Alzheimer’s disease were less educated than the non-demented controls. Education level seemed to be related to estrogen use as well, as higher educated women more often used estrogen than those with primary education only (among the controls: n=16; 28% vs n=8; 18%), although not significantly (χ²=1.3; df=1; p=0.25).

As shown in table 2, a significant, inverse association between estrogen use and prevalence of early onset Alzheimer’s disease was found using only matched case-control pairs (adjusted OR 0.34; 95% CI 0.12–0.94). This relation held when restrictions were made to those without vascular pathology (adjusted OR 0.16; 95% CI 0.02–1.31). The inverse association between estrogen use and early onset Alzheimer’s disease seemed to be stronger in APOE*4 (adjusted OR 0.37; 95% CI 0.08–1.58) and APOE*2 carriers (OR 0.25; 95% CI 0.02–3.63), than in women with the APOEε3ε3 genotype (adjusted OR 0.60; 95% CI 0.19–1.88). However, the early onset Alzheimer’s disease genotype did not significantly modify the association between estrogen use and early onset Alzheimer’s disease, as the test for statistical interaction between estrogen use and APOE*4 or APOE*2 yielded p values of 0.36 and 0.53 respectively.

Discussion
This is the first study on estrogen use and Alzheimer’s disease with early onset. We found an inverse association, which held when restrictions were made for those without vascular pathology. A limitation of the study is that the design was observational and data on estrogen use had to be obtained by informants due to memory problems in the patients. Informants were unfortunately not able to specify the type and duration of estrogen use. Misclassification of estrogen use might thus have occurred. However, it should be noted that in the period of data collection (1980–7), the effects of estrogen use were largely unknown to the general population. It seems unlikely that relatives of the cases reported estrogen use less often, compared with informants for controls. Therefore, any misclassification was probably random, and resulted in an underestimation of the true relation. Although the cases were not demented at the moment of estrogen administration, mild memory deficits may have been present, and we cannot exclude the possibility that this resulted in a lower chance of estrogen prescription. It can be hypothesised that the cases were less likely to use estrogen because they developed Alzheimer’s disease before, or soon after menopause. However, the menopause occurred, on average, 8.3 (SD 8.1) years before dementia onset and therefore this does not
Estrogen use and early onset Alzheimer's disease

781

Financial support for this study came from The Netherlands Organization for Scientific Research (NWO), the Netherlands Institute for Health Sciences (NIHES), the Euro的局面 European Union Concerted Action on dementia, the Flemish Biotechnol- ogy Program, and the Fund for Scientific Research—Flanders, Belgium (FWO-F). We thank Drs W Schulte, T Tanja, R Haaxma, A Lamers, and R Saan for assisting with case diagno- sis. Helen de Bruijn, Micheline de Haes, Jeanette Kamman, Hilda Kornman, Hanneke van Meurs, and Caroline Valkenburg for their help in data collection, and Barbara Benard for advice with statistical analysis. Hubert Bachnowens, Marc Cruts, Mar- leen Van den Broeck, and Sally Serneels are acknowledged for their help in data collection, and Barbara Benard for advice with statistical analysis. Hubert Bachnowens, Marc Cruts, Mar- leen Van den Broeck, and Sally Serneels are acknowledged for APOE genotyping.