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.

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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 determined.2 An effect of estrogen in this group of patients will strengthen the evidence for a beneficial role of estrogen in Alzheimer’s disease. The aim of this population based study was to investigate whether estrogen use is related to early onset Alzheimer’s disease.

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.3 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.4 Data for APOE typing were available for 82% of the patients and 73% of the controls.

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.1 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.1 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.4 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.

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

<table>
<thead>
<tr>
<th>Estrogen use</th>
<th>Cases (n=109)</th>
<th>Controls (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>In matched individuals (n=208)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>98</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>86</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% v 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 APOE*3 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
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