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

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SHORT REPORT

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

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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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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.

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[5] should be greater than 0.5, the score on the short portable mental status questionnaire[6] less than 20 (out of 30), and the score on the Hachinski scale[7] 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.[8] 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.[9] Patients who received estrogen were at the moment of intake all non-demented. A history of myocardial infarction, hypertension, and hypercholesterolaemia 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.[10] Data for APOE typing were available for 82% of the patients and 73% of the controls.

Table 1 Characteristics of the study population

	Cases (n=109)	*Controls (n=119)*
Age at onset (y (SD))	57.9 (6.4)	58.2 (6.7)*
Age at menopause (y (SD))	49.6 (4.1)	49.4 (4.4)
Estrogen use:		
Yes	11 (10%)	24 (20%)†
No	98 (90%)	95 (80%)
APOE genotype‡:		
APOE*2	10 (10%)	23 (25%)
APOE3ε3	37 (37%)	44 (48%)
APOE*4	54 (53%)	24 (26%)†
Education:		
Primary only	96 (88%)	90 (76%)
Secondary	13 (12%)	29 (24%)†
Vascular pathology:		
Present	29 (27%)	47 (39%)†
Absent	80 (73%)	72 (61%)

*Age in controls.
†p< 0.05.
‡APOE genotypes were missing in eight cases and 28 controls; proportions are based on the available information; APOE*2 denotes APOEε2ε2 or APOEε2ε3; APOE*4 indicates APOEε3ε4 or APOEε4ε4.

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,[11] 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.[12] An unconditional logistic regression analysis was also performed to test for statistical interaction between estrogen use and the APOE genotype. 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 χ^2 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

	Estrogen use							
	In matched individuals (n=208)		*In matched pairs (n=104)*					
					Controls		*Crude OR (95% CI)*	*Adjusted OR* (95% CI)*
	Yes	*No*			*Yes*	*No*		
Cases	6	98	Cases	Yes	1	5	0.29 (0.11–0.80)	0.34 (0.12–0.94)
Controls	18	86		No	17	81		

*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 (χ^2=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

seem to be a likely explanation. An advantage of this study is the population based approach that minimises selection bias.

In our study population, the administration of estrogens took place more than 10 years ago when vascular diseases were among the contraindications.[13] To evaluate confounding by contraindication, we restricted the analyses to those without vascular pathology at the moment of the study. As this is a chronic condition, the absence of vascular pathology at the moment of the study implies absent vascular pathology at the moment of administration. We could still detect an inverse association of estrogen use with early onset Alzheimer's disease in these women, which suggests that our findings are not due to confounding.

Estrogen may be implicated in Alzheimer's disease through several mechanisms. It may be protective for atherosclerosis,[14] and may increase cerebral blood flow.[15] As vascular factors seem to be implicated in Alzheimer's disease,[16] estrogen use may thus have a beneficial effect on its development. Secondly, estrogen was found to have neurotrophic effects. Estrogen may promote the activity of growth factors,[17] increase neuron viability,[17] and maintain neuronal interconnections in brain areas associated with cognition.[18] It further affects several neurotransmitter systems, in particular the cholinergic system.[19] Thirdly, estrogen may favourably modify the processing of amyloid precursor protein, thereby reducing the accumulation of β-amyloid.[17] In addition, the putative exitotoxic effects of β-amyloid may be diminished by estrogen.[20] Other possible mechanisms include the reversal of glucocorticoid damage, and anti-inflammatory effects.[17]

Epidemiological studies of estrogen use and late onset Alzheimer's disease have been inconsistent.[1] Up to now, 11 observational studies on estrogen use and the risk of dementia have been published, four suggested an increased risk, and seven a decreased risk of dementia.[1 21] A meta-analysis of 10 of these investigations reported a 29% decreased risk of developing dementia associated with estrogen use.[1] There were, however, striking differences in methodology across these studies: two used a cohort design and eight a case-control approach. Different diagnostic criteria were used, and several studies were subject to recall bias. It should be noted that in the, methodologically superior, prospective follow up studies a decreased risk was seen,[22 23] which is plausible given the results from experimental studies mentioned above. The present study provides further evidence that estrogen use has a protective effect on Alzheimer's disease, as we could detect an inverse association with the early onset type, which is thought to be less environmentally determined than late onset Alzheimer's disease.

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