Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age

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SHORT REPORT

Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age

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We examined the relation between oestrogen containing hormone therapy (HT) used for more than 6 months and Alzheimer's disease (AD) risk in 971 postmenopausal women (426 AD patients, 545 relatives without dementia). There was a significant interaction between age and HT use on AD risk (p = 0.03). In stratified analyses, a significant protective association was seen only in the youngest age tertile (50–63 years; odds ratio = 0.35, 95% confidence interval = 0.19 to 0.66). Results must be considered cautiously in light of recent clinical trial evidence that oestrogen plus progestin increases dementia incidence in older postmenopausal women. However, our observational findings are consistent with the view that HT may protect younger women from AD or reduce the risk of early onset forms of AD, or that HT used during the early postmenopause may reduce AD risk.

The Women's Health Initiative Memory Study (WHIMS), a randomised double blind placebo controlled primary prevention trial in women 65 years of age or older, reported that oestrogen plus progestin increases overall dementia risk.[1] This seminal finding in older postmenopausal women contrasts starkly with observational research that oestrogen containing hormone therapy (HT) is associated with a lower risk of Alzheimer's disease (AD).[2] Few studies have considered HT effects in younger postmenopausal women. Moreover, most observational studies have not reported on possible confounding or effect modification by other AD risk factors, because relevant data were not collected or sample sizes were too small for meaningful analyses. We evaluated the relation between HT and AD with data from AD probands and their relatives in the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) Study. We found that HT was associated with reduced AD risk, but this effect was apparent only among younger women.

METHODS

Subjects

As described elsewhere,[3] MIRAGE probands meet criteria for probable or definite AD. Controls are first degree relatives or spouses of probands, whose age was censored at the year of proband symptom onset to guard against bias from temporal patterns in prescribing medications. Controls provided written informed consent; patients provided written consent or assent with proxy informed consent. Studies were approved by institutional review boards at participating sites. A total of 532 female AD patients and 819 female controls without dementia were available for analysis.

Risk factor data were collected from primary informants of AD patients, with verification from secondary informants and medical records where possible. Controls without dementia provided their own risk factor information. We studied female MIRAGE participants who were postmenopausal, or, if "unsure" of menopausal status, were at least 60 years of age. Oestrogen exposure was based on the question: "Did you ever take an oestrogen medication or an oestrogen replacement therapy (for example, Premarin, Estradiol, Ortho-Novum, etc) for birth control, menopausal symptoms, osteoporosis, or any other reason on a daily basis for more than 6 months?". Exposed participants (i) responded "yes" and provided a specific valid oestrogen drug or failed to specify a particular oestrogen, and (ii) initiated HT at least 1 year prior to dementia onset/censored age or failed to specify a start date for HT. Unexposed participants (i) responded "no", or (ii) responded "yes" but failed to initiate HT before dementia onset/censored year. Birth control medication when used before age 36 was not considered a valid oestrogen; women who reported birth control medication after age 35 or responded "yes" but provided an invalid oestrogen were excluded. One purpose of this analysis was to evaluate potential interactions between oestrogen and apolipoprotein E (ApoE) genotype,[4,5] and the final sample was limited to 426 patients and 545 controls without dementia (13 mothers, 316 sisters, 53 daughters, and 163 spouses of male probands) where oestrogen use, age, education, ethnicity, and ApoE genotype were known.

Other factors evaluated as possible confounders or modifiers of the effect of HT on AD risk were alcohol use (nine with missing data), cigarette smoking (one missing), daily use of non-steroidal anti-inflammatory drugs (NSAIDs) for more than 6 months (20 missing), and prior hysterectomy or oophorectomy (11 missing) (table 1).

Statistical analyses

Patients and controls were compared with t tests or Wilcoxon rank sum tests (continuous measures) and χ^2 tests (categorical measures). Crude odds ratios (ORs) were calculated for categorical variables, which were compared to Mantel-Haenszel ORs to evaluate potential confounding. The Breslow Day statistic was used to evaluate whether ORs differed among groups. Multivariate modelling used generalised estimating equations specifying the logit link function for binary responses. The generalised estimating equations procedure accounts for correlation among subjects within families (694 families in this study) and incorporates information from singletons. An independence working correlation structure was assumed; standard errors were calculated using the empirical variance estimator. Marginal expectations for the logarithm of the odds of AD were modelled as a linear function of predictor variables. ORs were

Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E; CI, confidence interval; HT, hormone therapy; MIRAGE, Multi-Institutional Research in Alzheimer Genetic Epidemiology; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; SD, standard deviation; WHIMS, the Women's Health Initiative Memory Study

Table 1 Characteristics of Alzheimer cases and family controls without dementia*

	Alzheimer cases (n = 426)	Controls without dementia (n = 545)	Probability†
Age, years	71.1 (SD 8.1)	65.0 (SD 8.6)	<0.0001
Education, 12 years or more	218 (53%)	384 (69%)	<0.0001
Ethnicity, African American	162 (35%)	125 (23%)	<0.0001
Oestrogen use for more than 6 months	87 (21%)	192 (35%)	0.0007
ApoE, at least one ε4 allele	281 (66%)	201 (37%)	<0.0001
Alcohol, more than 0.25 drinks/day	106 (25%)	163 (27%)	0.7
Smoking history, current or past	149 (37%)	196 (35%)	0.3
NSAID use for more than 6 months	20 (5%)	86 (16%)	<0.0001
History of hysterectomy or oophorectomy	141 (35%)	231 (42%)	0.016

*Values are given as mean (standard deviation, SD) or as number (percent, adjusted for age tertile).
†Probability values are from a generalised estimating equations model that accounts for familial correlation and adjusts for age.
ApoE, apolipoprotein E genotype; n, number; NSAID, non-steroidal anti-inflammatory drug.

Table 2 Age stratified risk of Alzheimer's disease associated with prior use of hormone therapy

	Number of Alzheimer cases	Number of controls without dementia	Crude OR (95% CI)	Adjusted OR (95% CI)*
Entire sample (ages 50–99)				
No HT	339	353	Reference	Reference
HT	87	192	0.47 (0.35 to 0.63)	0.70 (0.51 to 0.95)
First age tertile (50–63 years)				
No HT	58	135	Reference	Reference
HT	17	112	0.35 (0.19 to 0.64)	0.35 (0.19 to 0.66)
Second age tertile (64–71 years)				
No HT	105	127	Reference	Reference
HT	28	52	0.65 (0.39 to 1.1)	0.86 (0.50 to 1.5)
Third age tertile (72–99 years)				
No HT	176	91	Reference	Reference
HT	42	28	0.78 (0.47 to 1.3)	0.97 (0.57 to 1.6)

*Adjusted for age, education, and ethnicity.
CI, confidence interval; HT, oestrogen containing hormone therapy.

adjusted for age, education, and race. Cross product terms were incorporated into models to evaluate statistical interactions. Analyses used SAS software version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

AD patients in comparison to controls were older, less well educated, more likely to be African American, and more likely to possess at least one copy of the ApoE ε4 allele, but less likely to have used HT or NSAIDs (table 1). Conjugated oestrogens were the most commonly reported HT preparation (61%). In analyses adjusting for age, education, and race, HT was associated with a 30% reduction in AD risk (table 2). There was no interaction between HT use and education or race (p's$\geqslant$0.5), but the interaction with age was significant ($p = 0.03$), indicating that the protective association of HT was age dependent.

In analyses stratified by age tertiles, HT was significantly associated with reduced risk in the youngest tertile (OR = 0.35) but not in the second and third tertiles, where ORs were similar (table 2). Risk estimates were essentially unchanged in analyses that adjusted for alcohol use, smoking history, NSAID use, and hysterectomy/oophorectomy status as possible confounders. There were no significant interactions between HT use and these factors (data not shown).

DISCUSSION

Similar to previous observational reports,[2] HT in the MIRAGE Study was associated with a reduction in AD risk. However, the protective association was modified by age and was limited to younger woman (65% reduction for women aged 50–63; table 2). The relation between HT and AD risk was not confounded by education, race, ApoE genotype, alcohol use, smoking history, NSAID exposure, or hysterectomy/oophorectomy status, nor were there significant interactions between oestrogen use and these variables. Strengths of the MIRAGE Study are large sample size, high HT exposure rate (35% among controls), and the ability to adjust for a number of factors that might confound or modify the relation between HT and AD.

A limitation of the MIRAGE Study is that case control studies are susceptible to selection bias. Information on progestin use was not ascertained, and we were therefore unable to distinguish effects of unopposed oestrogen from those of oestrogen plus progestin. HT exposures were not validated against pharmacy or prescription records. Use of a proxy informant for cases but not controls introduced the possibility of exposure misclassification; however, within the MIRAGE Study there is very good agreement between proxy responses and index subject responses for most exposures, including HT.[6] Sons and brothers are somewhat less reliable in reporting HT use,[6] and in post hoc analyses excluding 48 cases with brother or son informants, age remained a significant modifier of the oestrogen effect on AD risk ($p = 0.04$). The protective association of oestrogen was still apparent in the lowest age tertile (OR = 0.37, 95% CI = 0.19 to 0.70) but not in the two higher tertiles (OR = 0.88, 95% CI = 0.60 to 1.3).

HT was reported to protect against AD in a population based study of AD with age at onset less than 65 years.[5] However, an association between HT and AD risk limited to younger postmenopausal women has not been reported previously. This finding differs from, but does not directly conflict with, results of the WHIMS primary prevention trial, where women aged 65 or older given oestrogen plus progestin faced an increased incidence of dementia apparent 1 year after treatment assignment.[1] We found no overall increase in AD risk in this older age range (table 2), but confidence intervals overlap with those reported in the WHIMS trial, and we have no valid data on when these older women initiated HT.

Effect modification by age could represent a chance finding, or unrecognised bias or confounding. Another interpretation is that protective effects of oestrogen containing HT decline with advancing age as deleterious effects of HT and competing risks assume greater prominence. Younger women exposed to HT necessarily used HT at an early age, but for older women exposure could have occurred at any age. Therefore, another consideration for MIRAGE findings is that HT might influence AD risk when initiated or used during a critical window in the early postmenopause.[7] After ovariectomy, for example, oestrogen effects on synaptic density may depend on treatment timing,[8] and the ability of oestrogen to enhance memory performance is reduced in older animals compared to younger animals.[9] The so called critical window hypothesis should be addressed in cohorts with better information on timing and duration of HT exposures. Finally, pathogenetic mechanisms differ for early and late onset AD,[10] and MIRAGE results may be germane only for relatively uncommon early onset disease.

Women commonly begin HT for bothersome climacteric symptoms and discontinue therapy within several years.[11] In this regard, most studies that have examined the relation between HT and AD have included substantial numbers of former users, and one cohort study reported a protective association specifically among former users.[12] Prior reports of greater AD risk reduction with longer durations of HT exposure[4 12–14] are also consistent with the view that early HT may be protective, since longer HT use is associated with a younger age of HT initiation.[15]

Data from the MIRAGE Study do not help us decide among alternative explanations for effect modification by age, since reliable information was unavailable on the duration and timing of HT. However, our results raise the possibility that the protective association of HT might be confined to a subgroup of women characterised by younger age or early HT use. These possibilities can eventually be confirmed or refuted in appropriately designed randomised clinical trials. For the present, adverse findings on dementia from WHIMS in older women[1] and other recognised health risks of HT[16] dictate that HT should not be recommended for AD prevention at any age.

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