Estrogens and Alzheimer disease risk

Is there a window of opportunity?

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Alzheimer disease (AD) is largely a disorder of old age, yet factors that influence risk may operate years before the disease is clinically manifest. There is increasing consensus that interventions to reduce the burden of AD will be more successful if implemented during middle age rather than later in life.

Endogenous and exogenous estrogens are widely believed to influence AD risk in women, yet the magnitude—or even the direction—of their effects remains controversial. In this issue of *Neurology*®, Shao et al.[1] provide new evidence from the Cache County, Utah, cohort study on the effects of estrogen-containing hormone therapy and the risk of late-onset AD. Findings suggest that effects may depend on timing, varying according to whether initiation occurs close to menopause or later in life.

Direct evidence regarding exogenous estrogens on dementia comes from the Women's Health Initiative Memory Study (WHIMS). In this ancillary study of the landmark Women's Health Initiative, postmenopausal women were randomly allocated to placebo or conjugated estrogens, which for women who had not undergone hysterectomy were combined with medroxyprogesterone acetate. WHIMS participation was restricted to women 65 to 79 years of age. For women receiving combined hormone therapy, the risk of dementia was doubled.[2] For women who had undergone hysterectomy, the between-group difference was not significant, although overall dementia risk was elevated in pooled analyses of the 2 hormone groups.[2] AD was not reported as a separate outcome because of small numbers.

Before the WHIMS, a robust observational literature had suggested protective associations between "ever-use" of hormone therapy and AD later in life. Meta-analyses estimated risk reductions of approximately one-third. Competing, but not mutually exclusive, explanations for the jarring discrepancy between experimental and observational findings focus on unrecognized confounding and nongeneralizability.[3] Compared with nonusers, hormone users tend to be healthier and to engage in healthier lifestyle practices. These differences on their own could account for the observed protective association. Conversely, WHIMS participants were not representative of women in observational studies, where most hormone use was for menopausal symptoms. Based on age, most women classified as hormone users in observational studies would have been ineligible for WHIMS enrollment at the time of their hormone use.

In earlier analyses from Cache County, past use of hormone therapy was associated with a two-thirds reduction in the risk of late-onset AD, whereas current use did not affect risk.[4] Shao et al.[1] now provide new evidence that strengthens the critical window, or timing, hypothesis as it pertains to AD risk. Between 1995 and 2006, 176 cohort members developed AD. Compared with women who reported no use of hormone therapy, women who initiated therapy within 5 years of menopause had a 30% lower incidence of AD (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.49–0.99). In contrast, risk was unaltered among hormone users who began treatment more than 5 years after menopause (HR 1.03, 95% CI 0.68–1.55). In secondary analyses, the greatest risk was among women who started combined therapy (estrogen plus progestogen) within 3 years of cohort inception, when women were at least 65 years of age (HR 1.93, 95% CI 0.94–3.96). This risk estimate is similar to that of WHIMS participants allocated to combined therapy.[2]

Excluding women with cognitive impairment at baseline had no substantial effect on these analyses, helping to address concerns regarding recall bias. Strengths of this study include the population basis, prospective collection of detailed information on hormone use and reproductive factors, and validated techniques for case ascertainment. Unrecognized confounding remains a potential limitation.

Other observational research since WHIMS, which tends to support Cache County inferences,

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and research involving other health outcomes provide a framework for interpreting Cache County results.

In the Multi-Institutional Research on Alzheimer Genetic Epidemiology case-control study of 971 postmenopausal women, age interacted significantly with hormone use in predicting AD risk.[5] Hormone therapy was associated with reduced risk in younger, but not older, postmenopausal women. In the youngest age tertile, the risk was 65% lower. In the Northern California Kaiser Permanente managed health care consortium, self-reported hormone use among midlife women was linked to a 26% reduction in late-onset dementia. In contrast, prescriptions for hormones among older women who had not reported earlier use were associated with a 48% increase.[6]

AD and coronary heart disease share common risk factors. In the Women's Health Initiative, women assigned to hormone therapy close to menopause had reduced risk of coronary heart disease, whereas women assigned to hormone therapy later in life had increased risk.[7] Age or proximity to menopause, however, do not seem to modify the deleterious effects of standard-dose hormone therapy on risk of ischemic stroke,[8] and it is not yet known whether timing influences hormone effects on cognition. Clinical trial data show that hormone initiation in late life does not improve cognitive skills.[9] Within the next year, findings from 2 large randomized clinical trials (ELITE, ClinicalTrials.gov identifier NCT00114517; KEEPS, ClinicalTrials.gov identifier NCT00623311) will provide clearer evidence regarding hormone effects on cognition in younger postmenopausal women.

Premature loss of endogenous estrogens may increase dementia risk,[10] and exogenous estrogens that prolong midlife exposure might plausibly ameliorate risk. Cache County findings support the possibility that young age or temporal proximity to menopause represents a window during which relatively short-term hormone use might reduce long-term AD risk. Yet these new results do not resolve lingering issues of unrecognized confounding and nongeneralizability, and they do not provide a sufficient foundation for new clinical recommendations. Convincing evidence will be difficult to achieve. A new trial involving young postmenopausal women, randomly assigned to placebo or an estrogen and followed for up to 3 decades for incident AD, seems unfeasible. Partial answers will continue to accrue from other well-designed cohort studies.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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