Early menopause, later start to hormone therapy may increase risk of Alzheimer's disease

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Women are more likely than men to develop Alzheimer's disease (AD), with women making up two-thirds of the population living with AD. A

new study, led by Mass General Brigham researchers, sheds light on the relationship between the risk of Alzheimer's disease and age of menopause and use of hormone therapy (HT). The results, published in *JAMA Neurology*, indicate that early age at menopause may be a risk factor for AD dementia, but that women who were prescribed HT around the age of menopause onset did not show increased risk.

"HT is the most reliable way to ameliorate severe menopause symptoms, but over the last few decades, there has been a lack of clarity on how HT affects the brain," said corresponding author Rachel Buckley, Ph.D., of the Department of Neurology at Massachusetts General Hospital (MGH), a founding member of the Mass General Brigham health care system.

"We found that the highest levels of tau, a protein involved in Alzheimer's disease, were only observed in hormone therapy users who reported a long delay between age at menopause onset and their initiation of hormone therapy. The idea that tau deposition may underlie the association between late hormone therapy intervention and Alzheimer's disease dementia was a huge finding, something that hadn't been seen before."

Premature menopause, defined as menopause that occurs spontaneously before the age of 40 or due to surgical intervention before the age of 45, has been associated with increased risk of AD dementia. HT improves many severe symptoms related to menopause and has been hypothesized to also prevent cognitive impairment.

However, two decades ago, the seminal Women's Health Initiative (WHI) study found that HT use was associated with a nearly two-fold higher incidence of dementia compared to a placebo among women aged 65 years and older, possibly due to the initiation of HT many years after menopause onset. To better understand these findings, Buckley and

colleagues used positron emission tomography (PET) neuroimaging to study how the presence of two proteins involved in AD dementia, β-amyloid and tau, related to age at menopause and HT use.

While previous studies examined symptoms of cognitive decline in menopausal women, few investigations analyzed the biological factors underlying these changes, which may be at play in determining risk of Alzheimer's disease.

"When it comes to hormone therapy, timing is everything," said co-author JoAnn Manson, MD, MPH, DrPH, one of the lead investigators of the WHI and chief of the Division of Preventive Medicine at Brigham and Women's Hospital, a founding member of the Mass General Brigham health care system. "Our previous findings from the WHI suggested that starting HT early in menopause, rather than late initiation, provides better outcomes for heart disease, cognitive function, and all-cause mortality—and this study suggests that the same is true for tau deposition."

The researchers used data from the Wisconsin Registry for Alzheimer's Prevention (WRAP), one of the few longitudinal studies on AD dementia that includes detailed information on menopause and HT use as well as PET neuroimaging. They analyzed PET scans from 292 cognitively unimpaired adults to determine levels of amyloid and tau in seven regions of the brain. Tau, which is known to be present in greater quantities in women compared to men in these brain regions, was the primary focus of the investigation, as its presence may offer insight into the sex-specific aspects of AD dementia and the risks that post-menopausal women may experience, even before they begin to display symptoms of cognitive decline.

As expected, women had greater levels of tau compared to men of the same age, especially in cases where they also had elevated β-amyloid.

But the researchers also found that the association between abnormal levels of β-amyloid and tau was much stronger in women who had earlier menopause onset, even after adjusting for known causes of premature menopause, such as smoking and oophorectomy, and even genetic risk factors for AD dementia. Notably, tau levels were high in the entorhinal and inferior temporal regions, which are located close to the memory-center of the brain and are known to be involved in the progression of AD dementia.

Given that many women who undergo premature menopause use HT, the researchers examined whether HT use was associated with β-amyloid and tau. While they did confirm this association, they observed that late initiation of HT—five years or more after menopause—drove this relationship. Many women in the late-HT-initiation group began HT close to a decade after menopause.

Going forward, the researchers are continuing to study sex-specific risk factors for AD dementia by analyzing biological signatures, including sex hormones, in blood plasma and on the X-chromosome. They are also continuing to engage in efforts to understand the unique role that tau plays in women compared to men, its impact on the brain, and why earlier menopause and late HT initiation may be associated with increased tau, even in cognitively unimpaired women.

"Up to 10% of women experience premature or early menopause, and our findings suggest that earlier age at menopause may be a risk factor for AD dementia," said first author Gillian Coughlan, Ph.D., of the MGH Department of Neurology. "Hormone therapy can have negative effects on cognition, but only if initiated several years after age at menopause. These observational findings support clinical guidelines that state hormone therapy should be administered close to menopause onset, but not several years after."

More information: Association of Age at Menopause and Hormone Therapy Use With Tau and β-Amyloid Positron Emission Tomography, *JAMA Neurology* (2023). DOI: 10.1001/jamaneurol.2023.0455. jamanetwork.com/journals/jaman … cle-abstract/2802791

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