VIEW POINT

Alzheimer disease in post-menopausal women: Intervene in the critical window period

Nayer Jamshed, Fouzia Firdaus Ozair[1], Praveen Aggarwal, Meera Ekka

Department of Emergency Medicine, All India Institute of Medical Sciences, [1]Department of Forensic Medicine, Hamdard Institute of Medical Sciences and Research, New Delhi, India

ABSTRACT

Alzheimer disease (AD) is a crippling neurodegenerative disorder. It is more common in females after menopause. Estrogen probably has a protective role in cognitive decline. Large amount of research has been carried out to see the benefits of hormone replacement therapy with regards to Alzheimer still its neuroprotective effect is not established. Recent studies suggest a reduced risk of AD and improved cognitive functioning of post-menopausal women who used 17 β-estradiol in the critical period. Use of 17 β-estradiol in young and healthy post-menopausal women yields the maximum benefit when the neurons are intact or neuronal stress has just started. Hence intervention in the critical period is key in the prevention or delay of AD in post-menopausal women.

Key Words: 17 β-estradiol, Alzheimer disease, critical period, post-menopausal

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease, accounting for more than 50% of all dementia types.[1] Its twice more common in females which could be due to increased longevity and sex difference in brain size.[2] Estrogen has neurotrophic action in areas involved in memory and cognition. Post-menopausal women are at increased risk than their male counterpart. Women with Alzheimer have lower endogenous estrogen level which lead to the hypothesis that estrogen could be neuroprotective. Hormone replacement therapy (HRT) has been extensively studied in the past, but results were inconclusive. Recent studies suggest that 17 β-estradiol based therapies may provide the most beneficial neuroprotective effect. Early introduction and prolonged therapy preferably for <5 years with 17 β-estradiol prevents AD.

ROLE OF ESTROGEN THERAPY IN AD

Observational studies have examined both HRT and estrogen replacement therapy (ERT), in relation to AD. ERT was associated with moderately reduced risk for development of AD.[3] An inverse relationship was seen for the duration of ERT and risk for Alzheimer.[4] Increased risk of Alzheimer is seen with younger age at oophorectomy (bilateral or unilateral). These findings suggest that earlier age of surgical menopause increases the risk of cognitive impairment.[5] In Women's Health Initiative Memory Study (WHIMS), investigators enrolled 7479 post-menopausal women. A total of 4532 women with natural menopause were randomized into a trial comparing conjugated equine estrogen (CEE) with medroxyprogesterone (MPA) versus placebo. However, the trial was discontinued before completion due to unexpected adverse health risks. Study revealed that women who received CEE with MPA demonstrated greater cognitive decline compared with the placebo group. Additional analysis revealed that risk for dementia was doubled for women who received CEE with MPA compared with the placebo group. Taken together, data from the WHIMS demonstrated a higher incidence of dementia and greater cognitive decline among hormone user.[6,7] Hence combination therapies that include progestin may actually ameliorate the beneficial effects of estrogen.[8] Predominant estrogen in premenopausal women is estradiol and its decline is more than estrone in post-menopausal age.

Address for Correspondence: Dr. Nayer Jamshed, Department of Emergency Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. E-mail: jamshednayer@gmail.com

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CEE contains predominantly estrone rather than estradiol; it also contains other hormones which are not desired. In contrast 17 β-estradiol, administration achieved a hormone state close to that observed prior to menopause.

ROLE OF 17 β-ESTRADIOL IN AD

Studies suggest that 17 β-estradiol significantly improved the verbal memory by enhancing verbal information processing and decreased forgetfulness. It reduced the errors in memory tasks. 17 β-estradiol increased the metabolism in receptive language and auditory association area.[9] For getting the desired result, a minimum of 3 months of therapy with no upper cut off is needed.[10] β-amyloid and tau proteins are involved in the structural changes that lead to AD pathology, particularly in the hippocampus, medial temporal, parietal and frontal cortical regions.[11] Evidence has shown that estrogen particularly 17 β-estradiol provides protection against β-amyloid induced damage and tau-related changes.[12] Neuroimaging outcomes have also been supportive of the benefits of 17 β-estradiol, particularly in the brain regions that show preclinical abnormalities in individuals who are at risk for AD. 17 β-estradiol, increases the blood flow to the hippocampus and superior temporal gyrus and it also activates left middle, superior frontal cortex and inferior parietal cortex during verbal memory encoding task on functional magnetic resonant imaging.[13,14] 17 β-estradiol also reduces the level of amyloid precursor protein (APP) through enhanced alpha secretase processing resulting in marked reduction of APP-C terminal fragment, amyloid beta and plaque burden. It also enhances the level of transthyretin in the brain, which inhibits the aggregation of amyloid βeta into plaque.[15] 17 β-estradiol also promotes the growth and survival of cholinergic neurons, increases the density of hippocampal neurons and increases the synaptic plasticity in the hippocampus which enhance the short and long term memory.[16]

HYPOTHESIS OF HEALTHY CELL BIAS

17 β-estradiol benefits most to those post-menopausal women who are cognitively intact. It selectively benefits healthy neurons (healthy cell bias) or when neuronal stress has just started.[17] In degenerating neurons particularly in the presence of apolipoprotein E_4, it is not helpful even at higher doses.[18]

HYPOTHESIS OF CRITICAL PERIOD

There are studies which suggest that there may be a "critical period" for post-menopausal women during which 17 β-estradiol selectively provides a beneficial effect. Its benefit is more when cholinergic system is intact or transiently disrupted. Younger post-menopausal women have higher density of muscarinic receptor than an older one. 17 β-estradiol in early post-menopausal women significantly decreased the anticholinergic induced verbal memory task.[19,20] In Cache County Study investigators enrolled 1768 women between 1995 and 2006 at the age of menopause who were given HRT particularly17 β-estradiol without progesterone. When started within a critical period of 5 years post-menopausal, it decreased the incidence of AD by 30%.[21]

WHEN AND HOW TO GIVE 17 β-ESTRADIOL

Ideally 17 β-estradiol should be started within a critical period of 5 years post-menopause in a dose of 50 μg/day transdermally. Transdermal route byepasses the hepatic metabolism and hence results in steady state plasma concentration of estradiol. It also maintains 1:1 estrone to estradiol ratio which is normally observed in selected phases of the menstrual cycle. Duration of therapy with 17 β-estradiol can vary from 3 months to 10 years. Favorable results are noted from both short and long term therapy.[21,22] Food and Drug Administration recommends HRT at lowest possible dose for the shortest duration but in 2013 British and International Menopause Society put no arbitrary limit on duration of HRT. If symptoms persist, the benefits of hormone therapy outweigh the risk.[23] The major concern with estrogen therapy is increased risk of venous thrombosis, coronary artery disease, breast and endometrial carcinoma, dysmenorrhea, abnormal vaginal bleeding and hypersensitivity. Screening of patients who are at risk to develop above complications and mammography should be done in every case. Regular annual follow-up for early detection of complication is advisable just like any other HRT.

CONCLUSION

Neuroprotective role of estrogen containing hormone therapy is useful but controversial. Recent studies suggest that estrogen particularly 17 β-estradiol has a positive effect in increasing blood flow, stimulating dendrites, protecting against oxidative stress and modulating neurotransmitters. There appears to be a critical window (window of opportunity) between 50 and 60 years of age, ideally within first 5 years of menopause during which estrogens have this positive effect but thereafter the cells deteriorate and estrogen may accelerate cell damage, the so called "healthy cell bias". So it is advised to start 17 β-estradiol in early menopause for longer duration as an inverse relation exists between HRT and risk for AD. Additional research is needed to optimize hormone therapy to delay, prevent and treat AD and to prevent estrogen related complications such as carcinoma and venous thrombosis.

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