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Review Article

Epidemiology of estrogen and dementia in women with Down syndrome☆

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ABSTRACT

Several lines of investigation have shown a protective role for estrogen in Alzheimer's disease through a number of biological actions. This review examines studies of the role of estrogen-related factors in age at onset and risk for Alzheimer's disease in women with Down syndrome, a population at high risk for early onset of dementia. The studies are consistent in showing that early age at menopause and that low levels of endogenous bioavailable estradiol in postmenopausal women with Down syndrome are associated with earlier age at onset and overall risk for dementia. Polymorphisms in genes associated with estrogen receptor activity and in genes for estrogen biosynthesis affecting endogenous estrogen are related to age at onset and cumulative incidence of dementia, and may serve as biomarkers of risk. To date, no clinical trials of estrogen or hormone replacement therapy (ERT/HRT) have been published for women with Down syndrome. While findings from clinical trials of ERT or HRT for dementia have generally been negative among women in the neurotypical population, the short interval between menopause and onset of cognitive decline, together with a more positive balance between potential benefits and risks, suggests an opportunity to evaluate the efficacy of ERT/HRT for delaying or preventing dementia in this high risk population, although questions concerning the optimal formulation and timing of the hormone therapy are not yet resolved.

1. Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia in the elderly. Clinically, AD is characterized by a progressive deterioration of cognitive and functional skills that begins during middle-age (early onset AD) or late in life (late-onset AD). AD is associated with a characteristic pattern of neuropathology, including the deposition of extracellular beta amyloid (Aβ) in neuritic plaques, intracellular accumulation of neurofibrillary tangles, neuronal loss and gross atrophy [1].

Down syndrome (DS), defined cytogenetically by trisomy 21 (in full or in part), is the most common chromosomal disorder associated with intellectual disability, occurring in approximately 1/700 live births [2]. Virtually all individuals with DS develop the characteristic pattern of neuropathology found in neurotypical adults with AD by the time they reach 40 years of age [3], with clear risk for clinical progression to AD beginning in the mid- to late 40s. Triplication and overexpression of the gene for amyloid precursor protein (*APP*), located on chromosome 21, is believed to play a significant role in the increased risk of dementia in DS which may be mediated by an increased production of Aβ peptides [4]. However, despite the nearly universal occurrence of AD pathology by age 40, there is wide variation in age at onset of dementia and in dementia related phenotypes such as levels of Aβ peptides. The average age at onset of dementia in adults with DS is between 50 and 60 years of age, with an approximate range from the late 30s to 70 years. This together with the fact that not all individuals with DS will develop dementia during their lifetime, suggests that additional genetic, biological and environmental factors may influence the rate and degree of Aβ deposition or clearance and may be important modifiers of risk that accelerate or slow disease progression [5].

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2. Neuroprotective effects of estrogen

Several lines of investigation have shown a protective role for estrogen in AD through a number of biological actions [6,7]. Biologically, estrogen promotes the growth and survival of systems and processes associated with AD. Estrogen promotes the health of cholinergic neurons [8–10], increases cholinergic activity [11], has antioxidant and anti-inflammatory properties [12–14], decreases ischemic damage [15,16], promotes the nonamyloidogenic metabolism of the amyloid precursor protein [9,17–20], and protects against the toxicity of Aβ [9,21–23]. The loss of estrogen following menopause may play a role in the cognitive declines associated with AD and estrogen's protective effects have been investigated in the neurotypical population through several lines of research, although findings are not consistent. These include studies relating (a) age at menopause to cognitive decline and age at onset of dementia [24,25], (b) levels of endogenous hormones in postmenopausal women to cognitive decline and risk for dementia [26–35], (c) variants in genes involved in estrogen receptor activity and estrogen biosynthesis to risk of AD [36], and (d) studies of the beneficial effects of hormone replacement therapy on dementia risk [37,38]. Inconsistent results may be related to differences between studies in the age range of participants, the hormones assessed, whether or not study participants took hormone replacement therapy during the peri-menopausal period, and variation in adjustment for comorbid conditions and other risk factors in the analysis.

3. Menopause and risk for dementia in women with DS

Menopause is characterized by dramatic declines in estrogen levels. Women with DS have onset of menopause between 44 and 46 years of age [39–44], while the median age at menopause is around 51 years for women with neurotypical development [45]. When women with DS with onset of menopause below the median age were compared with women with DS with onset of menopause above the median age, earlier age at menopause was associated with earlier age at onset of AD and an approximately two- to three-fold increase in risk of AD [41,46,47]. Further, when cognitive function in women with DS without dementia, aged 21–57 years, was compared with cognitive function in age-matched men with DS, premenopausal women performed better than men, while postmenopausal women performed more poorly than men and showed significant declines in cognitive function [48]. These findings suggest that cognitive declines in postmenopausal women with DS are associated with reduced estrogen availability as well as with age [48].

4. Endogenous estrogen and risk for AD in women with DS

Individual differences in estrogen levels after menopause and during the period when AD is developing may play an important role in the pathogenesis of AD and influence age at onset and risk for AD. Studies in the Ts65Dn mouse model of DS found that estrogen treatment improved cognitive and cholinergic function [49,50]. Treatment with 17β estradiol for 60 days in postmenopausal female trisomic mice 11–15 months of age improved learning in a T-maze task [49]. In a related study, female trisomic mice 9–15 months of age treated with 17β estradiol for 60 days showed improved cholinergic and dendritic markers in the hippocampus and increased levels of APP in the striatum [50]. In a cross-sectional analysis, women with DS who were demented had elevated levels of serum sex hormone binding globulin (SHBG) compared with women with DS without dementia, but similar levels of total estradiol, suggesting that bioavailable estradiol is most importantly associated with cognitive decline and dementia risk [46]. In a follow-up longitudinal study in a cohort of women with DS, lower baseline levels of bioavailable estradiol were associated with a four-fold increased risk of developing AD and with an earlier age at onset [51]. These findings support the hypothesis that loss of biologically active estrogen following menopause may accelerate the development of dementia.

In postmenopausal women, body mass index (BMI) influences the level of estrone, the principal source of estrogen. Higher BMI is associated with increased levels of serum estradiol and estrone, and therefore peri- and post-menopausal obesity might have a beneficial effect on cognition [52]. In a retrospective analysis, increased body weight in women with AD was correlated with better performance on two measures of global cognitive function [53]. When estrone levels were examined in healthy postmenopausal women with DS, estrone levels were 66.9% higher in obese (BMI $\geq$ 30) compared with non-obese women with DS and 136% higher in obese than in non-obese premenopausal women with DS [52]. Among postmenopausal women with DS, obese individuals performed significantly better than non-obese individuals with DS on measures of verbal memory and on an overall measure of neuropsychological function. Among premenopausal women with DS, however, there were no similar differences in performance by obesity status [52]. Thus, higher endogenous estrogen levels after menopause, but not before, were associated with enhanced cognitive performance in women with DS who were not demented, complementing the finding that reduced endogenous levels in post-menopausal women are associated with increased risk for AD [51].

Overall, findings of studies that have examined the relationship between age at menopause or levels of endogenous estrogen and risk of dementia are more consistent in women with Down syndrome than the findings in women in the neurotypical population. One factor that may be related to differences in the consistency of findings in these two populations is that the interval between menopause and onset of dementia in women in the neurotypical population is relatively long compared with the short interval between menopause and onset of dementia in women with Down syndrome. Thus, among women in the neurotypical population, onset or changes in other risk factors during that interval may play a more important role. In addition, epidemiological studies have consistently shown that cardiovascular risk factors increase the risk of late onset Alzheimer's in the neurotypical population. History of diabetes and metabolic syndrome [54–57], stroke [58], hypertension [59], low HDL [60], smoking [59,61] and midlife central obesity [62] alone or in the aggregate have been associated with greater risk [59,63]. These cardiovascular risk factors increase with age and play an important role in risk for dementia among women in the neurotypical population, but are of lower prevalence among women with Down syndrome [64–68].

5. Genetic variants in estrogen: estrogen receptors

Prior research supports a role for genetic factors that affect the bioavailability of estrogen within the brain in modifying age at onset and risk of AD. Estrogen activity in the brain is mediated by two receptors belonging to a family of nuclear receptors, ERα and ERβ. These receptors are found in regions affected in AD, including the hippocampus, basal forebrain and amygdala [69–72]. Both ERα and ERβ appear to have a role in the preservation of cholinergic activity [73,74] and ERβ may mediate the effects of estrogen on hippocampal synaptic plasticity [75]. The neuroprotective effects of estrogen against Aβ induced toxicity appear to be mediated by ERα, which may act by blocking Aβ-induced apoptosis [23,76–78], and polymorphisms in *ESR1*, the gene coding for ERα, have been linked to risk for cognitive decline among women in the neurotypical population [10,79–87]. ERβ is expressed in the cerebral cortex, hippocampus, anterior olfactory nucleus, dorsal raphe, substantia nigra, midbrain ventral tegmental area and cerebellum [69,88], and polymorphisms in *ESR2*, the gene coding for ERβ, have been associated with cognitive impairment and risk for AD among women in the neurotypical population [10,84,89–92].

5.1. *ESR1*

Among women in the neurotypical population, two tightly linked