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Menopause and the brain

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ABSTRACT

Estrogen may have a beneficial effect on the risk and course of Alzheimer's disease (AD) through several mechanisms, including improvement of cerebral blood flow, stimulation of the neuron, or gliacyte and interaction with genetic factors. In this paper, the therapeutic and etiologic research of the role of estrogen in cognitive function and dementia is reviewed. Findings to date are promising but far from conclusive. In therapeutic research, interpretation of studies is hampered by the small sizes of the studies and differences in methodology. Most etiological studies have been limited to retrospective studies in which the history of estrogen use was obtained from an informant. Follow-up studies conducted to date have yielded controversial results. Further research is needed to elucidate the role of estrogen in the pathogenesis and progression of dementia. Subjects genetically susceptible for AD may prove to be an important high-risk group to target in preventive, therapeutic and etiologic research.

INTRODUCTION

In the past decades, important advances have been made in understanding gonadal steroid effects on brain and behavior[1]. Effects of estrogen on axonal outgrowth, connectivity and function have been described in several brain regions[1]. Although the potential has been recognized for a long time[2–7], there is growing interest in the role of estrogen in the pathogenesis of dementia and Alzheimer's disease as well as the potential of estrogen in the treatment of dementia. In experimental animal studies, oophorectomy has been shown to stimulate neuronal regeneration and modulate long- and short-term synaptic function[8]. Furthermore, gonadal hormones have been related to learning and memory function[9]. Ovarian steroid deprivation results in a reversible learning impairment and compromised cholinergic function in Sprague-Dawley rats[10], while estrogen has been found to counteract the effect of scopolamine in rats[11]. Here, the empirical evidence for a role of estrogen in cognitive function and dementia in women will be reviewed. The Alzheimer pathology will be discussed briefly in light of the role of estrogen. The focus of this review will be on the empirical findings of therapeutic and etiologic research of cognitive function and Alzheimer's disease.

ESTROGEN AND ALZHEIMER PATHOLOGY

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by a progressive decline in intellectual functions. The pathological characteristics of AD include the deposition of β-amyloid in parenchymal senile plaques and cerebral blood vessel walls and accumulation of neurofibrillary tangles within neurons. Furthermore, there are pronounced neurochemical deficits of the cholinergic, serotoninergic and monoaminergic systems. It has long been recognized that genetic factors are implicated in AD[12]. In the relatively rare early-onset dominant forms, several major genes have been implicated including the amyloid precursor gene and the presenilin genes. The most important genetic factor that plays a role

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in both the early- and late-onset form of AD is the apolipoprotein E gene. The genetic etiology of late-onset AD is complex in that multiple genetic and environmental factors may play a role[12]. In the majority of cases the disease most likely results from the interplay between several genetic and environmental factors.

Estrogens may be implicated in Alzheimer's in several ways. Direct stimulation of neurons and/or cholinergic markers, improvement of cerebral blood flow, development of gliacytes and suppression of apolipoprotein E have been suggested[13,14]. Through the involvement in cerebral blood flow and other vascular factors, estrogen use may not only be relevant for AD but also for vascular dementia. Although these observations are of great import, past experience on other factors has taught that the relevance for AD pathogenesis or treatment remains to be proven in empirical research in humans.

ESTROGEN AND COGNITIVE FUNCTION

The potential of a beneficial effect of estrogen on the brain was already recognized in the late 1970s[3–7]. Prevention of loss of cognitive function has been studied in a considerable number of trials. Results of these studies have been equivocal. Although in the majority, improvements in memory and/or cognition after treatment with estrogen was found[3–5,15,16] other trials failed to show any beneficial effect[6,7,17]. Conflicting findings may be explained for a large part by differences between studies in psychometric tests and estrogen regimens. Furthermore, the number of subjects studied varied considerably between studies and the duration of treatment was limited[18].

Arguing against the hypothesis of a protective effect of estrogen for cognitive decline are the findings of a 15-year follow-up study of 800 women aged 65–95 years[18]. No consistent evidence for an effect of estrogen on cognitive function could be shown[18]. A problem in the interpretation of such long-term follow-up studies is the high mortality, which may be associated with cognitive function and/or estrogen use.

ESTROGEN AND THE TREATMENT OF AD

The information on the potential of estrogen in the treatment is limited to a number of uncontrolled studies in AD patients. Trials performed up to date are small ($n = 4–7$) and controlled double-blind trials are not available. A beneficial effect of estrogen was shown in two studies[19,20]. However, worsening of the dementia after estrogen treatment has also been reported[21]. Conclusions based on these observations are far from definitive given limitations in study design. The role of estrogen in treatment in AD is an issue that remains to be resolved.

ESTROGEN AND THE RISK OF AD

Empirical findings of epidemiological studies of the effect of estrogens on the risk of AD have been controversial[22–30]. Two retrospective studies and one prospective follow-up study based on anamnestic data suggested a protective effect of estrogen replacement therapy[27–30].

However, others including a prospective study based on computerized pharmaceutical records did not show evidence for a relationship[22–26]. An important methodological problem which hampers the validity of the follow-up study that failed to show an association is the fact that the diagnosis of AD at follow-up was based on mortality records[4]. However, the potential of bias in the studies with positive findings has also been substantial. Selection bias may have occurred due to mortality in patients related to estrogen use, e.g. mortality from breast cancer. As information cannot be obtained from a demented patient, assessment of risk factor exposure has often been based on surrogate informants, which may be an important source of error[27,28]. The strongest evidence for an effect of estrogen on the risk and age at onset of AD is derived from a short-term follow-up study (1–5 years) of 1124 elderly women[29]. This study reported a twofold reduction in risk in women using estrogen after onset of menopause. The decrease in risk was stronger in those using the estrogen for a longer period. A methodological point to consider in short-term follow-up studies is the problem that women may have been cognitively impaired at baseline in this follow-up study and selectively forgot to report their medication. Furthermore, studies of estrogen replacement therapy are liable to selection bias, in that women receiving estrogen may be more healthy in general and may subsequently have a reduced risk of Alzheimer. In particular the fact that women using estrogen are in general better educated and of higher socio-economic status is important. As both

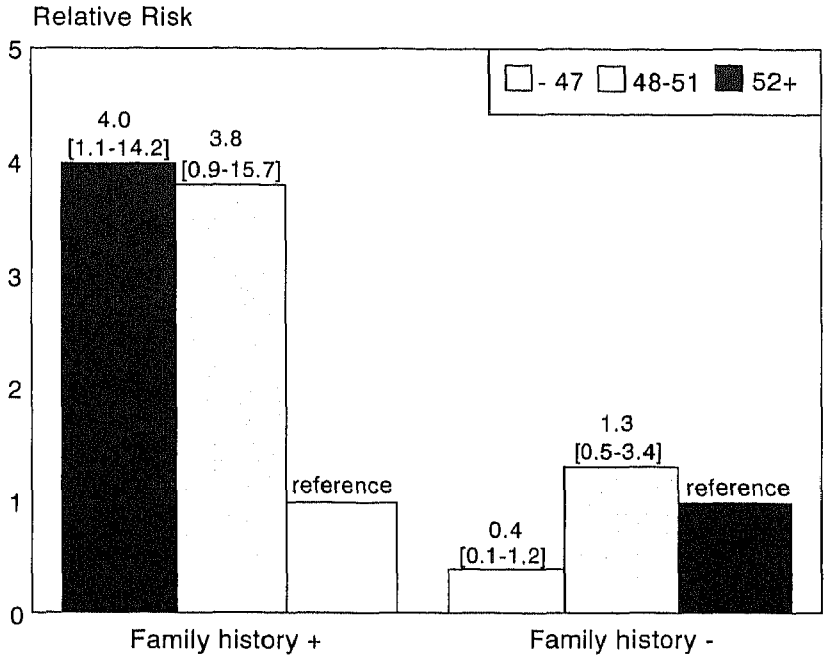

Figure 1 Age at menopause and the risk of Alzheimer's disease by family history of dementia

factors have been associated with a decreased risk of AD and dementia[12], it is not straightforward which factors contributes to the decreased risk of AD[12].

MENOPAUSE AND THE RISK OF AD

Although there is some evidence for a beneficial effect of estrogen, up to date no evidence was found for a relationship to age at menopause. Findings on the role of menopause in AD are of limited validity and not straightforward to interpret. Overall, no association to age at menopause could be shown[27,31]. However, there is some evidence for a role of menopause in those with a positive family history of disease[31]. In a population-based series of 124 patients with early-onset AD (≤ 65 years), an early age at menopause (before age 47 years) was associated with a significantly increased risk of AD in those with a positive family history of dementia (OR 4.0; 95% CI: 1.0–15.4; see Figure 1)[31]. No consistent relationship was found in those without a family history of dementia. When studying age at menopause in a series of 19 families in which AD appeared to segregate as an autosomal dominant disorder, age at menopause was significantly earlier in Alzheimer patients with a natural menopause than in controls with a natural menopause from the same family (difference 2.6 years; standard error of the difference 0.67; $p < 0.05$). The finding of an earlier menopause in women of families with an autosomal dominant form of AD is of interest in light of the prevention of the disease in this high risk population. An issue to resolve in this subgroup is the possibility that the early menopause is a consequence of the Alzheimer pathology.

CONCLUSION

The putative beneficial effect of estrogen on cognitive function and the risk of AD and dementia is important in light of the limited knowledge of the pathogenesis of these common disorders and the lack of therapy. However, findings to date are far from conclusive and more research is needed. Double-blind controlled trials are needed in light of the potential preventive and/or therapeutic use of estrogen in dementia patients. Data on effective dose and duration are needed for therapeutic and preventive strategies. At present, no such information is available on which to base therapeutic or preventive actions. Long-term follow-up studies on risk factors for AD and dementia, that are currently ongoing, will most likely provide some answers with regard to the role of estrogen in the etiology of dementia and AD. Non-response, competing mortal-

ity and comorbidity complicating the diagnosis will be challenges to overcome in these studies. Subjects genetically susceptible for AD may prove to be an important high-risk group to target in preventive, therapeutic and etiologic research. The progress in the understanding of the genetics of Alzheimer's disease and other types of dementia has opened new possibilities for population-based and/or clinic-based studies of the interaction of genetic factors with non-genetic factors such as postmenopausal estrogen treatment.

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