Maturitas 94 (2016) 98–105

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Alzheimer's disease, apolipoprotein E and hormone replacement therapy

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ARTICLE INFO

Article history:
Received 13 March 2016
Received in revised form 5 August 2016
Accepted 13 September 2016

Keywords:
Alzheimer's disease
Hormone therapy
APO lipoprotein

ABSTRACT

Alzheimer's disease is the most frequent cause of dementia in older patients. The prevalence is higher in women than in men. This may be the result of both the higher life expectancy of women and the loss of neuroprotective estrogen after menopause. Earlier age at menopause (spontaneous or surgical) is associated with an enhanced risk of developing Alzheimer's disease. Therefore, it is postulated that estrogen could be protective against it. If so, increasing exposure to estrogen through the use of post-menopausal hormone replacement could also be protective against Alzheimer's disease. The results of the clinical studies that have examined this hypothesis are inconclusive, however. One explanation for this is that estrogen treatment is protective only if it is initiated in the years immediately after menopause. Another possibility is that the neuroprotective effects of estrogen are negated by a particular genotype of apolipoprotein E. This protein plays an important role in cholesterol transport to the neurons. Studies that have examined the link between estrogen replacement therapy, Alzheimer's disease and the E4 allele of ApoE are inconclusive. This article reviews the literature on the influence of hormone replacement therapy on the incidence and progression of Alzheimer's disease.

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http://dx.doi.org/10.1016/j.maturitas.2016.09.009
0378-5122/

1. Introduction

Dementia is a clinical syndrome characterized by progressive loss in functionalities of daily living due to changes in cognition, emotions and behavior [1]. Its prevalence increases exponentially with age, from 1.5% of the general population aged 60–69 years, to 40% among those aged 90–99 years. In 2010, it was estimated that, globally, 35.6 million people were living with dementia [2]. However, recent studies suggest that the prevalence of dementia is stabilizing or even decreasing [3,4].

Dementia is usually caused by a neurodegenerative disease such as Alzheimer's disease (AD), vascular atherosclerosis, Lewy body disease, Parkinson's disease, frontotemporal disease or Creutzfeldt-Jacob disease [5]. Other causes of dementia include metabolic disorders (vitamin deficiency such as thiamin deficiency leading to Korsakov syndrome, thyroid disease), infections (HIV, syphilis) and toxins (e.g. alcoholic dementia). The most common form of dementia in the elderly is AD [2].

Different studies have shown an increased risk of AD in women older than 80 [6–8]. Andersen et al. found that the cumulative risk of AD by the age of 95 is 0.22 for 65-year-old women compared with 0.09 for men of the same age [6]. Suggested reasons for this are controversial and heterogeneous, and include life expectancy, social factors, educational differences as well as hormonal influences. Three large studies have shown the protective effect of estrogen in postmenopausal women [9–11]. In many publications 'dementia' is used as a synonym for AD, which makes it difficult to compare their conclusions [12–14]. The strongest known genetic risk factor for the development of AD is the E4 allele of the apolipoprotein E gene [15]. Carriers of the E4 allele are more likely to develop AD than non-carriers [16,17]. This article reviews the relation between AD, estrogen and apolipoprotein E (ApoE).

2. Pathogenesis of Alzheimer's disease

The pathogenesis of AD is not yet fully understood. The neuropathological hallmark of AD is the combined presence of β-amyloid plaques and hyperphosphorylated tau-containing neurofibrillary tangles [18–20].

The β-amyloid plaques arise from an extracellular deposition of amyloid beta protein [21]. This protein is formed after cleavage of the amyloid precursor protein (APP) by the β- and γ-secretase enzymes [22]. In AD there is an overproduction and/or decreased clearance of amyloid beta peptides [23]. The accumulated amyloid beta peptides can aggregate into oligomers [24] and form plaques [16]. The amyloid cascade hypothesis [25] states that these oligomers and plaques induce inflammation and other reactions that damage the neurons, especially at the level of the synapses [26].

Whereas β-amyloid remains mainly in the extracellular matrix, tau is an intracellular protein, necessary for the stabilization of microtubules that form the neuronal cytoskeleton. Hyperphosphorylation of tau arises from activation of different protein kinase and phosphatase enzymes [27]. The hyperphosphorylation of tau leads to structural changes in the tau protein, affecting its binding with the microtubules. Hyperphosphorylated tau proteins aggregate and form neurofibrillary tangles, and the neuronal cytoskeleton disintegrates [28].

However, as it has been shown that an abnormal number of β-amyloid deposits does not necessarily induce the clinical presentation of AD [29], it has been suggested that a dementia syndrome, due to underlying Alzheimer's neuropathology, is a consequence of multiple factors (including genetic, environmental and vascular) [30].

3. Influence of apolipoprotein E on Alzheimer's disease

The E4 allele of the apolipoprotein E gene is the strongest known genetic risk factor for the development of Alzheimer's disease.

3.1. Function of ApoE

ApoE is an important protein for the regulation of cholesterol transport [31]. Lipids (triglycerides, cholesteryl esters, phospholipids and cholesterol) are transported through the body packaged in lipoproteins – chylomicrons, and four groups classified by density: very low, low, intermediate and high density lipoproteins (VLDL, LDL, IDL and HDL, respectively). Lipoproteins are complexes that comprise the lipids themselves and proteins (the apolipoproteins). The apolipoproteins function as structural components of the membrane of lipoproteins and as ligands for receptors present on the surface of cells in the liver and those peripheral tissues that take up cholesterol [32]. ApoE works as a ligand for LDL receptors [33,34]. It is produced mainly by the liver and seldom by the macrophages. In the central nervous system it is synthesised mainly by the astrocytes and the microglia and sometimes by the neurons [34]. ApoE regulates cholesterol transport to the neurons [16], where it is required for synapse development, dendrite formation, long-term potentiation (a persistent strengthening of synapses and suspected to be a foundation of memory) and axonal guidance (the process by which neurons send out axons to reach targets). Lack of cholesterol delivery causes structural and functional problems in the central nervous system [33].

3.2. ApoE structure

ApoE is a protein composed of 299 amino acids. The N-terminal domain is the region that binds with the LDL receptors, whereas the C-terminal domain is the lipid-binding region. The ApoE gene is located on chromosome 19. There are different alleles of the ApoE gene. The major alleles result in three different apolipoproteins, called ApoE2, ApoE3 and ApoE4. These three proteins differ by one amino acid at position 112 and one at position 158 [34]. These differences affect the structure of the ApoE protein and alter its ability to bind to lipids, receptors and β-amyloid [16]. The most common allele is that coding for ApoE3 (77%). ApoE2 is the least common (8%). The prevalence of the apoE4 allele is 15% in the general population but this rises to 40% in patients with AD [22].

3.3. ApoE4 as a genetic risk factor for AD

The apoE4 allele is associated with a higher risk of AD and a lower age of onset [16,17,35]. Compared with homozygous ApoE3 individuals, heterozygous ApoE4 (E2E4, OR 2.6; E3E4, OR 3.2) and homozygous ApoE4 (E4E4, OR 14.9) individuals have a higher risk of AD. The ApoE2 allele, alone and in combination, has a protective effect (E2E2, OR 0.6; E2E3, OR 0.6) against AD in comparison with homozygous ApoE3 individuals. The mean age of clinical onset is 68 years in homozygous ApoE4 individuals, 76 years in heterozygous ApoE4 individuals and 84 years in E4 non-carriers [16]. Although the type of ApoE gene relates to vulnerability to AD, it does not mean that homozygous ApoE4 individuals necessarily develop AD.

The prevalence of the ApoE4 allele is dependent on ethnicity but is in general around 15–20% [36]. The ApoE4 allele occurs most frequently in northern Europe and least frequently in southern Europe and Asia [37].

3.4. ApoE4 mechanisms

Why ApoE influences the risk of AD is not completely understood. It is postulated that both amyloid-β dependent and