The Controversial Influence of Cerebrovascular Risk Factors over Pathological Mechanisms of Late-Onset Alzheimer's Disease Dementia

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Cerebrovascular risk factors seem to play an important role in the pathogenesis of late-onset Alzheimer's disease dementia, but they are neither required nor sufficient for the development of amyloidogenic mechanisms [1]. Nonetheless, it is plausible that some cases of Alzheimer's disease dementia may be the result of chronic hypoperfusion of the brain due to intracranial or extra cranial atherosclerotic plaques, vascular lesions that are not exclusively linked to vascular dementia.

Recent studies have begun to shed more light on the role of cerebrovascular risk factors over onset and cognitive and functional decline of patients with Alzheimer's disease dementia. Unlike what was previously thought in the last decades, smoking is not protective, but rather a risk factor for Alzheimer's disease (even though it can prevent the development of other neurodegenerative diseases, such as Parkinson's disease and its complications) [2]. Other vascular risk factors that may play a role in the pathogenesis of Alzheimer's disease include arterial hypertension, diabetes mellitus, dyslipidemias, obesity and alcohol use [3]. Arterial hypertension and obesity seem to bring more morbidity when present in midlife, with opposite effects in late life, suggesting a possible role of these factors over the enhancement of cerebral perfusion when present only in late life; treatment of cerebrovascular risk factors throughout life may also reduce the incidence of vascular pathology and dementia syndromes [4].

The astrocyte-secreted apolipoprotein E is involved in the transport of cholesterol through cell membranes, in coronary atherogenesis and in amyloidogenic mechanisms [1, 5]. APOE is a moderately penetrant gene that is neither a prerequisite nor a sufficient agent for development of Alzheimer's disease, despite the fact that it is the most important genetic risk factor for incidence and earlier onset of late-onset Alzheimer's disease dementia [3]. Pooled vascular risk factors have been shown to synergistically increase the risk of Alzheimer's disease and lower the age at onset of dementia [6]. Isolated effects of cerebrovascular risk factors over the age at onset of dementia have not been demonstrated in all studies, despite the fact that obesity and smoking seem to be rather important in this regard [3]. Nonetheless, education, occupation and lifetime leisure activities enhance cognitive reserve regardless of APOE haplotypes, regulate the transcription of the APOE gene and prevent the onset of Alzheimer's disease dementia, but do not affect Alzheimer's disease pathology in the brain [7].

Although APOE haplotypes do not seem to have isolated effects over cognitive and functional decline, APOE4+ carriers have decreased participation in physical activities in late life, whereas APOE haplotypes may also act as risk modifiers in addition to vascular risk factors [8]. It has been shown that late life higher body mass index may slow cognitive and functional decline for males with Alzheimer's disease dementia, particularly for non-carriers of APOE4+ haplotypes [5]. Gender differences for obesity have also been demonstrated with regard to increased risk of Alzheimer's disease dementia only for females [9]. Hormonal effects over cognitive performance in such patients need to be studied in greater depth.

Isolated cerebrovascular risk factors have not been consistently shown to affect cognitive or functional decline in patients with Alzheimer's disease dementia, though their combinations may lead to cognitive stabilization or even improvement, possibly related to enhanced cerebral perfusion in late life [5-8]. On the other hand, late life variability in body mass index may affect cognition and functionality in these patients: increases in body mass index have been associated with rises in basic functionality and cognitive test scores for patients with Alzheimer's disease dementia, once again probably due to neurovascular protection related to enhanced cerebral perfusion [8].

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Despite the fact that carotid atherosclerosis leads to cerebral ischemia, thus inducing amyloidogenic pathways [1], other mechanisms could enhance cerebral perfusion and, thus, lead to neuroprotection against the development of dementia syndromes. The use of pacemakers has been shown to delay the onset of Alzheimer’s disease dementia, possibly by controlling heart rhythm and preventing thromboembolism to the brain [3]. Carriers of APOE4+ haplotypes have more neuropathologic lesions of Alzheimer’s disease and coronary artery atherosclerosis than non-carriers, an aspect that suggests an interrelation between Alzheimer’s disease and coronary heart disease [10]. Even though thromboembolic heart diseases may increase the risk of Alzheimer’s disease dementia, it seems that late life higher coronary artery disease risk may be protective against cognitive and functional decline in this dementia syndrome, particularly for carriers of APOE4+ haplotypes [5]. Since cerebral perfusion tends to decrease in late life, vascular risk factors could be neuroprotective for older people if they enhance cerebral perfusion and prevent amyloidogenesis.

The influence of cerebrovascular risk factors over neurodegeneration in late-onset Alzheimer’s disease dementia seems to be mediated by senescence, hormonal changes and genomic effects. Future studies should focus on biomarkers that lead to an objective assessment of dementia risk, thus providing better outcomes for all patients.

**Declaration of Conflicting Interests**

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