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Cardiovascular Risk Factors and Alzheimer's Disease: a Mini Review

George P. Paraskevas[1]*, Vasilios C. Constantinides[1], Panagiotis G. Paraskevas[2], Elisabeth Kapaki[1]

[1]Cognitive and Movement Disorders Clinic and Neurochemistry Unit, 1st Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, Eginition Hospital, Greece.
[2]Technological Educational Institute of Crete, School of Health and Welfare Services, Nursing Department, Heraklion, Greece

***Corresponding Authors:** George P. Paraskevas, MD, PhD, Associate Professor of Neurology, 1st Department of Neurology, National and Kapodistrian University of Athens, Eginition Hospital, Greece.*

ABSTRACT

Alzheimer's disease is a neurodegenerative disorder characterized by extracellular deposition of beta amyloid and intraneuronal tangle formation in the brain. Common and modifiable cardiovascular risk factors such as mid-life hypertension, dyslipidemia, diabetes, mid-life obesity, smoking and physical inactivity seem, to be risk factors of AD, through many interrelated mechanisms associated with beta amyloid formation and deposition and tau-protein hyperphosphorylation. Controlling such factors during mid-life results in a delay of Alzheimer's disease symptom onset, which in turn may potentially result in a decrease of disease prevalence by millions of patients worldwide.

Keywords: *Alzheimer's disease, cardiovascular risk factors, hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, physical exercise.*

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1], followed by vascular cognitive impairment [2].Major risk factors for AD include increasing age, female sex and the ε4 allele of the apolipoprotein E gene (*APOE4*) [1,3,4]. However such risk factors are non-modifiable. During the last two decades, it has been clearly shown that with increasing age, there is an increase in the percentage of patients with AD presenting with concomitant cerebrovascular pathology [5], whilst more than half of the patients with vascular cognitive impairment have additional AD-type pathology [6]. In fact, this type of mixed dementia in the elderly may be more common than pure AD or pure vascular cognitive impairment and more common than expected by coincidence [7], leading to the hypothesis that common and modifiable cardiovascular risk factors may also play some role in AD [8]. This mini review aims to summarizing current evidence on the effects of classical cardiovascular risk factors on AD and the possible favorable effect of modifying such factors on AD epidemiology.

HYPERTENSION

Although not clearly [9], available data indicate a possible association of hypertension, especially midlife diastolic hypertension, with AD [10,11,12]. The adverse effects of hypertension may be related, at least partly, to beta amyloid accumulation in the brain[13,14]due to increased vessel wall stiffness, alterations in blood brain barrier function and hypoxia-induced oxidative stress and neuroinflamation, resulting in protein miss folding, increased beta amyloid deposition and reduced beta amyloid clearance [11,15,16]. Tau deposition with tangle formation has also been described[17,18].Whatever the biochemical mechanism, diastolic hypertension during the 4th to 6th decade of life is associated not only with imaging biomarkers of vascular disease (white matter hyper-intensities) but also of AD, including hippocampal atrophy [19], decreased metabolism in AD-related areas such as temporal and parietal lobes [20] and with increased risk of AD after the age of 65 [3,11].However, it must be noted that late-life hypertension or active hypertension during the

dementia stage of AD may be related to a slower progression of cognitive decline [9,21,22].

Antihypertensive medication use seems to reduce the risk of dementia [23].Data from various studies are inconsistent, probably due different methodologies, different definitions and tests for the diagnosis of cognitive impairment/dementia, inadequate samples and low effect sizes, necessitating further well-designed studies in larger samples. Over activity of the pressor axis of the renin-angiotensin system may play some role in AD [24] and angiotensin-converting enzyme inhibitors may have a beneficial effect, especially in *APOE4* carriers [25].In one meta-analysis, angiotensin receptor blockers were superior to other antihypertensives in preventing cognitive decline [26], while in another, thiazide or potassium sparing diuretics either alone, or in combination with angiotensin receptor blockers were able to reduce the risk of Alzheimer's disease [27]. In addition to restoring normotension, it has been hypothesized that some antihypertensive drugs may have specific neuroprotective effects including decreased amyloidogenesis and maintained calcium homeostasis (calcium channel blockers), enhanced amyloid elimination, reduced tau hyperphosphorylation and reduced excitotoxicity (angiotensin II receptor blockers) and maintenance of normal potassium levels (potassium-sparing diuretics) [11]. Whatever the mechanism and despite the inconsistencies between the various studies and meta-analyses, the general feeling is that early treatment of hypertension is a good practice to reduce the risk of, or delay cognitive decline [9,11]. However, late-life hypotension or overtreatment with antihypertensives may result in an increased risk of AD [3].

DIABETES MELLITUS

In various studies, diabetes was associated with increased relative risk not only of vascular dementia or all-cause dementia, but also of clinically diagnosed Alzheimer's disease, although the usual pathology is mixed (vascular *and* neurodegenerative) [3,28,29].Most studies concerned type 2 diabetes [29], but type 1 diabetes may also increase the risk AD [30] . Young/middle life type 2 diabetes may be associated with an increased risk of AD in older age [31] and, insulin resistance even in childhood may increase the risk of developing neurodegeneration later in life [30,32]. Carriers of genetic polymorphisms associated with type 2 diabetes may show faster progression from MCI to probable AD [33].

Diabetes is related to neuroimaging findings of neurodegeneration or decreased metabolism in areas compatible with AD (entorhinal cortex, temporal lobe, fusiform gyrus) [34].Insulin provokes neuronal release of beta amyloid [35]. Insulin resistance has been incriminated for reduced clearance of beta amyloid and phosphorylated tau [36]. The metabolic derangements induced by diabetes lead also to activation of glycogen synthase kinase 3 (GSK-3), an enzyme related to production of beta amyloid [37], but also responsible for tau hyperphosphorylation [38]. Another protein which is co-secreted with insulin by the pancreas, namely amylin, has been shown to induce beta amyloid aggregation [39,40]. Thus, diabetes, through overproduction and decreased clearance, leads to both biochemical/ pathological characteristics of AD, i.e. amyloid plaque formation and tangle formation but,since beta amyloid further increases insulin resistance, a complex vicious circle is initiated,resulting in a cascade of events leading to oxidative stress, mitochondrial dysfunction, apoptosis, synaptic dysfunction and neuronal loss [40].

Despite methodological differences and inconsistent results, some studies show evidence for beneficial effects of controlling type 2 diabetes on cognitive function [41]. However, the preventive potential of drugs such metformin, sulfonylureas and thiazolidinediones is not proven;it may be due to vascular rather than AD-related mechanisms and may vary among patients, necessitating large-scale studies [42].

It should be pointed that,besides the vascular component of the diabetes-related cognitive decline, the neurodegenerative component is not always AD.In a recent positron emission tomography study [43],patients diagnosed clinically with diabetes-related AD, were indeed tau and amyloid positive. However, of the patients diagnosed as diabetes-related dementia, only 29% showed both amyloid and tau positivity (indicating AD), whilst 19% were negative for both tau and amyloid; most interesting 52% were positive for tau only, either in the medial temporal lobe or extensively in the neocortex [43].

DYSLIPIDEMIA

High total cholesterol has been shown to increase the risk of developing clinical AD 30

years later [44] and mid-life hypercholesterolemia is considered an independent risk factor for AD later in life [45,46]. Hyperlipidemia is associated with hypometabolism in cortical areas related to AD [34]. Elevated cholesterol may reduce the non-amyloidogenic alpha secretase activity and promote the amyloidogenic beta-site cleavage, leading to the formation of amyloid beta [47,48] and amyloid plaques [49]. In addition, among the other cardiovascular factors, hypercholesterolemia may be the most significant predictor of tau accumulation in the entorhinal cortex [34].

Early control of dyslipidemia with statins seems to decrease the risk of development or progression of AD later in life [46,50]. Reduction of beta amyloid formation may be an important effect, but reduction of neuroinflammation and oxidative stress may be additional beneficial mechanisms [46].

Other Factors and Combinations

Cardiac arrhythmias, coronary heart disease and congestive heart failure have been shown to be associated with AD imaging biomarkers [34]. Various studies have shown that mid-life obesity is associated with increased risk for all-cause dementia, including AD [3].However, in late life, a higher body mass index is associated with decreased risk, whilst weight loss is associated with increased risk of AD [51,52]. Despite earlier opinions for a protective role in cognition, smoking is associated with amyloid positivity in positron emission tomography [53] and with an increased risk of dementia, including AD [3]. Physical inactivity is also a risk factor for all-cause dementia and AD [3].

Many patients suffer of combinations of the above factors. The so-called metabolic syndrome, characterized by various combinations of inter-related factors such as dyslipidemia, increased body-mass index, insulin resistance, hypertension and diabetes [54] and the concept of decreased "vascular health" in general [34], are considered to be a risk factors of AD, due to amyloid-predominant (amyloid beta formation, amyloid oligomers) and/or tau-predominant mechanisms [55]. In addition to drug treatment, nutritional interventionsand physical exercise may offer significant non-pharmacological methods of prevention,targeting many mechanisms, including oxidative stress, neuroinflammation, insulin resistance, obesity, dyslipidemia and possibly inducing neurogenesis and improve brain perfusion [56,57].

Preventive Potential

In an elegant study a few years ago, Barnes and Yaffe reviewed many studies and meta-analyses and calculated AD cases attributable to various modifiable risk factors and preventable by reduction of such factors [3]. They found that, of total AD cases worldwide, 5% are attributable to mid-life hypertension, 2% to diabetes, 2% to mid-life obesity, 13% to physical inactivity and 14% to smoking. Reduction of the above factors by 25% could potentially result in a worldwide reduction of AD prevalence by 100,000, 200,000, 166,000, 1,000,000 and 1,000,000 cases respectively. Adding two additional preventable factors, namely depression and cognitive inactivity, up to 50% of AD cases worldwide may be attributable to the combination of the above factors and, combined 25% reduction of all modifiable factors could result in a reduction of AD prevalence by 3,000,000 cases globally.

In a recent, equally elegant study from Europe, Mayer *et. al.*, hadsimilarfindings [58]. Attributable percentage of cases was 6.8% for mid-life hypertension, 3.1% for diabetes, 4.1% for midlife obesity, 20.3% for physical inactivity and 13.6% for smoking. Adding depression and low education, 31.4% of European AD cases were attributable to the combination of the above factors. Reduction of these risk factors by 20% could result not only ina 6.5% reduction of vascular dementia prevalence but, additionally, in a 6.4% reduction of AD prevalence (40,000 AD cases) in Italy.

Conclusion

Alzheimer's disease is a neurodegenerative disorder characterized by extracellular deposition of beta amyloid and intraneuronal tangle formation in the brain [1]. Symptoms are usually of senile onset, but there is a long asymptomatic period of 1–2 or even 3 decades [59]. During this asymptomatic period, the subject is unaware of any neurological abnormality, yet amyloid formation and deposition as well as tau hyperphosphorylation and tangle formation are ongoing and, when the first vague symptoms appear, the biochemical and pathophysiological characteristics of the disease are already well established [59]. The various cardiovascular risk factors described above, act during the asymptomatic phase and seem responsible for accelerating the biochemical processes of AD in 30%–50% of cases [3,58]. Controlling of such factors during the dementia stage of AD may be too late. It is

during the long asymptomatic period (mid-life) that such factors should be controlled, in order to achieve a delay in the biochemical progress of AD and in symptom onset. Cessation of smoking, a healthy diet, physical exercise and preservation of a normal body-mass index should be practiced by the general population during mid-life (or younger) as well as pharmacological treatment of hypertension, dyslipidemia or diabetes when needed, in order to delay symptom onset of AD, or progress from the mild cognitive impairment stage to full-blown dementia. This, in turn, seems to decrease the prevalence of AD by millions of patients worldwide.

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