Atherosclerosis as a risk factor for dementia and Alzheimer's disease

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Abstract

The increasing prevalence of dementia, makes an urgent need to develop new approaches to mitigate the enormous social and economic impacts associated with it. Extensive research has proposed delimitation and control of the various, modifiable risk factors associated with its development and progress. While complex interactions of factors occurring during the lifetime of an individual, a growing number of studies has focused on their contribution to the degree of development. The role of cardiovascular risk factors, common in atherosclerosis and dementia, is important for cognitive impairment and vascular dementia, while, on the Alzcheimer's pathology is disputable even today. Considering that atherosclerosis is closely related to cardiovascular events, has made it the object of many studies, whether, its harmful impact on cerebral function leads to dementia and Alzheimer's disease. Furthermore, atherosclerosis is being studied and, as an independent risk factor, which may influence cognitive function, regardless of cerebral infarcts. Atherosclerosis, and in particular Alzheimer's pathology, may reflect a common underlying process that leads to a relationship between the two pathological conditions. Features common to both involve inflammation, macrophage infiltration, occlusion of the vasculature, amyloid accumulation, but also allelic variants in common genes including APOE.

Key words: atherosclerosis; dementia; AD; VaD; PAD; CAS; vessel calcification

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1. Introduction

Dementia and atherosclerosis are two conditions that cause the greatest burden on global public health.[1] Dementia, is a syndrome, mainly in the old age, which can be caused by a number of progressive degenerative diseases and other causes, affecting brain cells and influence cognitive, behavioral and other functions.[2] Alzheimer's disease (AD) is the main form of dementia, and characterized by the presence of extracellular senile plaques and intraneuronal deposition of neurofibrillary tangles but also cerebral vascular pathology.[3,4] Atherosclerosis or atherosclerotic vascular disease (AVD), is also a very common disorder of vessels in the elderly, and affects large and mediumsize arteries, of the entire cardiovascular system.[5,6] Ranges from primary arterial atheroma - inflammation and accumulation of cholesterol-laden macrophages in the walls of major arteries - to "plaque" formation and inflammation in the arterial wall.[7,8] It causes narrowing of the arteries' lumina, thereby reduces the blood flow for the supported region, while rupture of atherosclerotic plaques often leads to thrombosis that results in either occlusion of the vessel or thromboembolisms. Depending on the size of the embolus, it may cause lesions that range from "silent" infarcts or microinfarcts to large cerebral infarcts. "Silent" lacunar infarcts are not accompanied by any overt clinical symptoms, but double the risk of subsequent stroke and mainly vascular dementia.[5,6]

At a first glance two pathologies seems to be discrete, but clinical, experimental and epidemiological approaches suggest that these mutually interact, disrupting brain structure and function.[8] There is evidence for an association between the risk factors of atherosclerosis, in the middle age hypertension, diabetes (type-II), cardiovascular comorbidity, and AD, as regards both the predisposition for the development of the disease as well as to influence on its clinical course.[9]

It was estimated that cardiovascular risk factors may be responsible for up to half of the AD cases worldwide,[10] whilst cardiovascular health in general is now thought to be related not only with vascular dementia (VaD), but also with AD.[11,12,13]

In addition, there is accumulated evidence that subclinical atherosclerosis, may partly reflect lifetime exposure to cardiovascular risk factors.[14,15,16,17,18] Studies have shown that subclinical atherosclerosis, associated with a powerful risk of not only cardiovascular disease[19,20] and stroke,[21,22,23] but also cognitive and physical impairment,[9,24,25] while stroke doubles the risk of dementia.[26,27] By worse cognitive performance, the vessel larger atherosclerotic calcification volume was associated[28] whilst the calcified atherosclerotic plaques represent atherosclerotic process advanced stages and associated with markers of cerebrovascular disease.[29]

The link between atherosclerosis and dementia, however, may attenuated by the strongest association between atherosclerosis and mortality in prospective cohort studies with long follow-up periods.[24] Atherosclerosis and pathology of AD, as mentioned, may reflect a common underlying process leading to a relationship between the two pathologies.[30]

There is debate on whether an increased atherosclerosis in patients with AD is due to a result of the first, on the pathology of the second, or simply an additive effect of the two individual pathologies in cognitive function.[24] Evidence for cardiovascular risk factors predisposing to AD includes premature presence of senile plaques in individuals with coronary artery disease and an association of both senile plaques and neurofibrillary tangles with a history of hypertension.[31] Additionally, large-vessel atherosclerosis has been found to be associated with frequency of neuritic plaques, a major pathological feature of AD.[32] An autopsy study of specimens who met the neuropathological criteria for AD showed that those with infarcts had poorer cognitive function and a higher prevalence of dementia than those without infarcts.[33]

While AD has a long preclinical period, and atherosclerosis in general begins much earlier in life, the time relevance for some researchers, shows that atherosclerosis can cause or accelerate AD and not vice versa.[34]

2. Mechanisms Linking Atherosclerosis, Dementia and AD

Pathways of connection include common cardiovascular risk factors,[9] with hypercholesterolemia, oxidative stress and inflammation to dominate,[35] but also subclinical cerebrovascular disease, small vessel disease, including silent brain infarcts, white matter disease and cerebral hypoperfusion.[12,13,36] Arterial stiffness is a well-established risk factor for white matter disease and also associated with evidence of microvascular brain

damage. Recent studies also show blood pressure and arterial stiffness are associated with brain Aβ deposition in elderly adults.[37]

Autopsy studies provide strong evidence that most patients with AD show small vessel brain disease that includes infarcts, microinfarcts, microbleeds, demyelinization, and axonal damage.[26] In *vivo* imaging studies have shown that MRI-markers of small vessel disease, such as white matter lesions and lacunar infarcts are associated with the risk of dementia.[26,36,38]

On the other hand, atherosclerotic calcification all four large vessels, the coronary arteries, aortic arch, and intracranial and extracranial carotid arteries seem to be strongly associated with MRI-markers of subclinical vascular brain disease.[39] Chronic brain hypoperfusion and hypoxia, as a result of atherosclerotic stenosis, atherosclerotic stiffness, and increased vascular resistance of the small and large vessels, has been linked to pathophysiologic cascade leading to AD pathology, and may be able to explain the relationship between two diseases. The hypoperfusion, due to structural changes in cerebral vessels caused by atherosclerosis, may cause disruption of the blood-brain barrier and worsening of the amyloid pathology apart from subclinical vascular disease.[26,40,41] This evolution could allow deposition or reduced clearance of beta amyloid protein and the formation of amyloid plaques, as well as hyperphosphorylation of tau protein, but also this in turn, may promote cerebrovascular atherogenesis, such as formation of atherosclerotic lesions through vascular oxidative stress and endothelial dysfunction, leading to further vascular damage, thus resulting in a vicious cycle.[1,42]

According to Vagnucci and Li (2003), the hypothesis that vascular endothelial cells play a central role in progressive destruction of neurons in AD is supported. Endothelial dysfunction, which is one of the most important pathophysiological links between exposure to cardiovascular risk factors and the development of atherosclerotic disease, could play a role in the secretion of the precursor substrate of the neurotoxic A beta-protein leading to the destruction of cortical neurons in AD.[43,44] In addition, endothelial lesions in AD, have been related to the location and number of senile plaques,[45] but also it has been reported that beta amyloid could interact with vascular endothelial cells to produce an excess of free radicals.[46] The possibility of apolipoprotein E (APOE) genotype association with both pathological conditions is also contemplated. Allelic variants in common genes, including APOE predispose to both diseases.[4] Apolipoprotein E is a plasma lipoprotein, which plays a basic role in the degradation of particles rich in cholesterol and triglycerides.[47] ApoE polymorphism modulates susceptibility to many diseases with an important role in neurodegenerative disorders and atherosclerotic artery disease.[48] This genotype is considered to be the main genetic determinant risk factor of AD: People carrying the e4 allele are at increased risk.[49] On the other hand, ε4 allele that is associated with higher low density lipoprotein cholesterol (LDL-C) is considered to be proatherogenic.[48]

When compared to allele E3, allele E2 is associated with lower LDL levels, whereas allele E4 with higher LDL levels. Thus allele E2 exhibits a protective role, whereas allele E4 is associated with a high risk factor for premature developming of atherosclerosis.[47]

ApoE4 associated with hyperlipidemia, and hypercholesterolemia, which lead to atherosclerosis, coronary heart disease and stroke.[49] A meta-analysis by Zhu et al. (2015), showed that APOE4 gene carriers compared to carriers APOE3 gene were more prone to clinical atherosclerosis incidence, whereas APOE4 gene may be a risk factor for clinical atherosclerosis.[50] From previous studies, APOE e4 genotype, was considered to be a risk factor for cardiovascular disease, while in combination synergistically with atherosclerosis, peripheral vascular disease, or diabetes (type II), may contribute to increased risk for AD.[51,52] Evidence suggests that patients with AD carrying the APOE e4, have higher carotid intima-media thickness (cIMT), than patients with AD non-carriers.[53]

3. Linking localized and generalized atherosclerosis with dementia risk

3.1 Systemic Atherosclerosis

Both a low ankle-brachial index (ABI) and an increased cIMT, are considered as markers of systemic atherosclerotic disease.[54] Systemic atherosclerosis has also been suggested to play a role in cognitive impairment in the elderly,[55,56] and studies have shown that it can increase directly AD pathology.[12,32,57,58,59]

In a study of Bos et al., (2015), in 2364 nondemented

participants of the Rotterdam study on which the atherosclerotic calcification of coronary arteries, aortic arch, and intracranial and extracranial carotid arteries were measured, it was found that atherosclerotic calcification in multiple vessels, was associated with a higher risk of dementia. It seems rather that the generalized atherosclerosis, which probably is a better reflection of one's vascular status rather than localized atherosclerosis, is associated with dementia.[60]

3.2 Peripheral Artery Disease (peripheral artery disease PAD)

Low ankle-brachial index considered as a marker for generalized PAD.[18] Cardiovascular disease associated with an increased incidence of dementia and AD, with the highest risk observed in individuals with PAD, suggesting that the extended peripheral atherosclerosis is a risk factor for dementia.[61,62] In the Rotterdam study, the presence of PAD was associated with worse cognitive performance.[63]

3.3 Atherosclerosis Intracranial Arteries

Postmortem studies have demonstrated that people with AD have significantly more atherosclerotic stenosis of intracranial arteries.[58,59,64,65] Cerebral arteriosclerosis, focal constrictions and stiffening of the vessel wall may lead to increased collagen fibres and extracellular matrix components result in loss of distensibility/elasticity/arterial stiffness that would affect brain perfusion.[37,66] Elderly participants, in the study Baltimore Longitudinal Study of Aging (BLSA), have been studied on the relationship between atherosclerosis and dementia. In this study, it was shown that the presence of intracranial atherosclerosis uniquely increased the odds of dementia regardless Alzheimer's pathology or cerebral infarcts.[30] For Zheng et al (2013), cerebral arteriosclerosis was positively correlated with microinfarcts but not with AD pathology.[67]

A mechanism that may link the intracranial atherosclerosis and dementia may be common, and include toxic β-amyloid peptide (Aβ),[68,69] inflammation,[70,71,72] oxidative stress,[73,74] white matter disease.[75] Large vessel intracranial atherosclerosis could be a marker for dysfunction of small cerebral vessels and their endothelium. This is probably the main cause of cognitive decline, either through disruption of the communication between neurons and blood vessels, or through disruption of the blood-brain barrier.[30]

Cycle of Willis. According to many studies, there is an association between atherosclerosis in the cycle of Willis and AD.[59,76,77] In post-mortem demented and no demented samples, atherosclerotic occlusion in the circle of Willis arteries, was most extensive in patient group compared to the control group (no dementia).

Also statistically significant differences between control and AD groups were observed with regard to Braak stage (stages in which the progressive development of pathological alterations in AD has divided), total score of amyloid plaque, total score of neurofibrillary tangles, total white matter rarefaction score, brain weight, Mini-Mental State Examination scores, and apolipoprotein E allelic frequencies.[34] Also in previous relevant study in postmortem specimens, atherosclerosis in the Circle of Willis was more severe in subjects with AD and VaD than in control subjects. In fact, the atherogenic degree was associated, in direct proportion to an increase in the odds ratios for the diagnoses of both AD and VaD, and also increased the odds ratios for both increased neuritic plaque density and higher Braak neurofibrillary tangle stage.[64] In the study of Yarchoan et.al (2012), it was found that more than 77% of AD subjects had grossly apparent circle of Willis atherosclerosis, a rate which was significantly higher than that normal subjects (47%) or of subjects with non-AD disease (subjects with other neurodegenerative diseases) (43-67%).[77]

3.4 Carotid Atherosclerosis (carotid atherosclerosis CAS)

Clinical studies have shown a positive relationship between carotid atherosclerosis and dementia while the increased in its prevalence has been observed in patients with a diagnosis of dementia and AD.[66,78] Carotid atherosclerosis, including cIMT, carotid plaque and carotid stenosis were associated with accelerated cognitive decline in patients with AD,[79,80] as well as in healthy elderly.[81]

In the Rotterdam study, in 4.971 individuals, from the middle age to 94 years, showed that the presence of carotid plaques was associated with worse cognitive function, regardless the age and educational level.[63] In 6.647 participants, also from the Rotterdam study, with mean follow-up of 9 years, which examined multiple measures of atherosclerosis, cIMT, carotid plaques, and

peripheral artery disease/measured as ankle-brachial index, was found that mainly carotid atherosclerosis was associated with increased risk of dementia during short follow-up. This association attenuated with longer follow-up, likely because of the strong association between atherosclerosis and mortality.[24]

Multiple measures of carotid atherosclerosis, were associated with the prospective risk of dementia in Baltimore Longitudinal Study of Aging participants, more than 14 years of follow-up. In particular at higher risk were found to be people with upper quintile of carotid IMT (more than 2.5 times) and with bilateral carotid plaque (nearly 2.0 times), while no correlation was found between carotid plaque and this risk.[9] In Cardiovascular Health Study, highest quartile of cIMT, was associated with a significantly increased risk of dementia and AD, after 5 years of follow up.[61] In 2.364 participants from the Rotterdam study, were measured, coronary arteries atherosclerotic calcification, aortic arch and intracranial and extracranial carotid arteries. Larger volume of calcification in the extracranial carotid arteries was associated with a higher risk of dementia and cognitive impairment (in individuals without dementia).[60] In addition, in 2.414 nondemented people from the Rotterdam Study, which was investigated brain changes on magnetic resonance imaging (MRI), researchers found that extracranial and intracranial carotid calcification volumes related to smaller white matter volumes.[28] Recent study by Kao et al. (2015) also showed a significant effect of intracranial internal carotid artery calcification in cognitive impairment with directly proportional manner.[82] In a study by Yue et al. (2016), which investigated possible associations between the carotid artery stenosis, and cognitive impairment in patients with acute ischemic stroke, was found that a high degree of carotid artery was associated with higher risk of cognitive impairment.[83] Also study in elderly Chinese population without stroke, investigated the effects of the IMT and carotid artery stenosis in cognitive function. Patients with severe carotid artery stenosis (≥ 70%) had a lower Mini-Mental State Examination score in comparison to mild to moderate (40-70%). Cognitive performance differed between patients with left and right carotid artery stenosis, but no differences were observed among patients in severe stenosis.[84]

3.5 Coronary Arteries Atherosclerosis

In the study by Rosano et al. (2005), it was found that the elderly with higher levels of coronary arteries calcification, were more likely to develop serious brain abnormalities, including white matter as well as cognitive impairment.[85] In AGES-Reykjavik study, subjects with higher coronary artery calcification were more likely to have dementia and lower cognitive scores, lower white matter volume, lower gray matter volume, and total brain tissue, and to have more cerebral infarcts, cerebral microbleeds, and white matter lesions. Lower scores in each of the cognitive domain was closely associated with atherosclerotic burden, mainly the quantity of calcium concentration in coronary arteries.[86] Furthermore in the study of Reis et al. (2013), greater subclinical atherosclerotic coronary arteries calcification, in middle-aged individuals without heart disease, or stroke, associated with worse performance in each test of cognitive function.[29] In contrast no association was found in the study of Dolan et al., (2010), and Bos et al., (2015), wherein the coronary atherosclerosis did not increase the potential risk of dementia.[30,60] Lack of association between coronary artery calcification and dementia, may reflect increased mortality, and the high risk of cardiac events, including cardiac death.[87]

3.6 Aortic atherosclerosis

The study of Reis et al. (2013) examined the calcification of the abdominal aorta and cognitive function in middle-aged individuals without heart disease or stroke. Greater calcification was associated with worse performance in every test of cognition, but mostly of verbal memory.[29]

4. Conclusions

Evidence suggests that atherosclerosis either systemic or localized, has an effect on brain health, as an independent risk factor, but also closely related to cardiovascular events, reflecting an overall vascular profile. The contribution of atherosclerosis, cognitive impairment and dementia are also important, but need stronger evidence for the relationship with the AD pathology. Considering, the effects of atherosclerosis

and other risk factors in the middle age, several years before the clinical onset of dementia mainly AD, any efforts to prevent or control atherosclerosis very early in life may lead to delays in cognitive impairment related to aging and potentially dementia in later life.

Conflict of Interest

All authors declare no conflict of interest.

Abbreviations

β: β-amyloid ABI: ankle-brachial index, AD: Alzheimer's disease APOE: Apolipoprotein E, AVD: atherosclerotic vascular disease, CAS: carotid atherosclerosis, cIMT: carotid intima-media thickness CT: computed tomography, LDL: low density lipoprotein cholesterol MRI: Magnetic Resonance Imaging, PAD: peripheral artery disease VaD: vascular dementia

Περίληψη

Η αθηροσκλήρωση ως παράγοντας κινδύνου άνοιας

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Ο αυξανόμενος επιπολασμός της άνοιας, καθιστά επιτακτική την ανάγκη να αναπτυχθούν νέες προσεγγίσεις για τον μετριασμό των τεράστιων κοινωνικών και οικονομικών επιπτώσεων που σχετίζονται με αυτήν. Η εκτεταμένη έρευνα έχει προτείνει οριοθέτηση και έλεγχο των ποικίλων τροποποιήσιμων παραγόντων κινδύνου που σχετίζονται με την ανάπτυξη και την πρόοδό της. Και ενώ πολύπλοκες αλληλεπιδράσεις των παραγόντων λαμβάνουν χώρα κατά τη διάρκεια ζωής του ατόμου, ένας αυξανόμενος αριθμός μελετών έχει εστιάσει στη συνεισφορά τους στο βαθμό ανάπτυξης. Ο ρόλος των καρδιαγγειακών παραγόντων κινδύνου, κοινών σε αθηροσκλήρωση και άνοια, είναι σημαντικός επί της γνωστικής εξασθένισης και της αγγειακής άνοιας, ενώ επί της παθολογίας της νόσου Alzheimer είναι μέχρι σήμερα συζητήσιμος. Δεδομένου δε, ότι η αθηροσκλήρωση συνδέεται στενά με καρδιαγγειακά συμβάματα, έχει αποτελέσει αντικείμενο πολλών μελετών, το κατά πόσο η επιβλαβής επίδρασή της στην εγκεφαλική λειτουργία οδηγεί σε άνοια και νόσο Alzheimer. Επιπλέον, μελετάται και σαν ένας ανεξάρτητος παράγοντας κινδύνου, που μπορεί να επηρεάσει την γνωστική λειτουργία ανεξάρτητα από τα έμφρακτα του εγκεφάλου. Η αθηροσκλήρωση και η παθολογία ειδικότερα της νόσου Alzheimer, μπορεί να αντανακλά μια κοινή υποκείμενη διαδικασία που οδηγεί σε μια σχέση μεταξύ των δύο παθολογικών καταστάσεων. Κοινά σημεία και στις δύο, αποτελούν μεταξύ άλλων η φλεγμονή, η διήθηση μακροφάγων, η απόφραξη των αγγείων, η συσσώρευση του Αβ αμυλοειδούς στον εγκέφαλο, αλλά και παραλλαγές σε κοινά γονίδια, συμπεριλαμβανομένου του APOE.

Λέξεις ευρετηρίου: αθηροσκλήρωση, άνοια, νόσος Alzheimer, αγγειακή άνοια, ασβεστοποίηση αγγείων, PAD, CAS

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