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New cardiovascular targets to prevent late onset Alzheimer disease

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ABSTRACT

The prevalence of dementia rises to between 20% and 40% with advancing age. The dominant cause of dementia in approximately 70% of these patients is Alzheimer disease. There is no effective disease-modifying pharmaceutical treatment for this neurodegenerative disease. A wide range of Alzheimer drugs that appeared effective in animal models have recently failed to show clinical benefit in patients. However, hopeful news has emerged from recent studies that suggest that therapeutic strategies aimed at reducing cardiovascular disease may also reduce the prevalence of dementia due to Alzheimer disease. This review summarizes the evidence for this link between cardiovascular disease and late onset Alzheimer dementia. Only evidence from human research is considered here. Longitudinal studies show an association between high blood pressure and pathological accumulation of the protein amyloid-beta$_{42}$, and an even stronger association between vascular stiffness and amyloid accumulation, in elderly subjects. Amyloid-beta$_{42}$ accumulation is considered to be an early marker of Alzheimer disease, and increases the risk of subsequent cognitive decline and development of dementia. These observations could provide an explanation for recent observations of reduced dementia prevalence associated with improved cardiovascular care.

1. Introduction

An estimated 5% of the general population aged 65 to 70 years has dementia. This number increases to 20% above the age of 80 and reaches a plateau over age 90. The dominant cause of dementia in approximately 70% of these patients is Alzheimer disease. There is no effective disease-modifying pharmaceutical treatment for this neurodegenerative disease. A wide range of Alzheimer drugs that appeared effective in animal models have recently failed to show clinical benefit in patients. However, hopeful news has emerged from recent studies that suggest that therapeutic strategies aimed at reducing cardiovascular disease may also reduce the prevalence of dementia due to Alzheimer disease.

This review will discuss recent relevant human studies that have investigated the link between cardiovascular disease and Alzheimer. The wide range of animal studies on this topic will not be included here, because translational evidence is not yet available for most of the investigated mechanisms and translational failure is unfortunately very common in the field of Alzheimer disease.

It is important to note that cardiovascular disease may cause cognitive impairment in the absence of Alzheimer disease, through direct vascular neuronal injury, for example in cortical stroke, lacunar infarction, small vessel disease, microbleeds and intracranial hemorrhage (Wiesmann et al., 2013). These causes of dementia are classified as vascular dementia, that represents up to 20% of all dementia. Cardiovascular disease may also cause cerebrovascular disease that contributes to the cognitive disorder in a patient with Alzheimer disease (or any other neurodegenerative disease); these cases are covered in the classification of vascular cognitive impairment (VCI), a term that encompasses all patients in whom cerebrovascular lesions significantly contribute to their cognitive decline (Wiesmann et al., 2013). It is obvious that prevention of cardiovascular disease will impact the prevalence of vascular cognitive impairment and vascular dementia, and these topics will therefore not be covered in this review. In addition, diabetes may also directly, or through cerebrovascular disease, lead to cognitive decline and dementia other than Alzheimer disease (Rawlings et al., 2014). This is also beyond the scope of this review, which will focus on the most common cause of dementia: late onset Alzheimer disease. When reading this review, it must be kept in mind that control of cardiovascular disease and diabetes will have a broader beneficial effect on the prevalence of dementia

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that reaches beyond its impact on Alzheimer disease.

2. Alzheimer disease

A clear definition of Alzheimer disease is an essential starting point for this review of potential cardiovascular targets to prevent this condition.

2.1. Late onset Alzheimer disease versus familial (genetic) early-onset Alzheimer disease

2.1.1. Alzheimer disease and Alzheimer dementia

Alzheimer disease is a progressive neurodegenerative disease that starts with an asymptomatic phase (preclinical Alzheimer disease), where neuronal loss does not lead to symptoms because of compensation. This phase may last 5–15 years based on recent studies, but gradually advances to a phase with mild cognitive and behavioral impairments but maintained ability to function independently. With further loss of cognitive function due to progression of Alzheimer disease, independent functioning becomes impaired, and this phase is defined as dementia. Presently, dementia is divided into three stages (mild, moderate and severe). In mild dementia, patients can live outside institutional care with support from professional and family caregivers. Some patients for example maintain the ability to cook, shop, and even to drive a car. In severe dementia, 24 h care is needed as patients require assistance in almost all basic functions (getting dressed, eating, washing) and there is loss of urinary and often fecal continence.

2.1.2. Prevention of Alzheimer disease versus prevention of Alzheimer dementia

The distinction between Alzheimer disease and dementia due to Alzheimer disease (where dementia essentially describes a stage of advanced Alzheimer disease) clarifies that efforts towards prevention can have two goals. The first goal is prevention of the disease, i.e. prevention of the neurodegenerative disorder, which is the most idealistic but also least feasible goal, as we will see later. The second goal is prevention of progression of the disease from asymptomatic or mild symptomatic to dementia. With this second goal, the neurodegenerative disease per se is not prevented, but progression is slowed down or the impact of neurodegeneration on cognitive function is reduced, for example due to prevention of (cerebrovascular) co-morbidity. Although the second goal may seem less powerful, on a societal level, postponing the age of onset of dementia leads to substantial reductions in disease burden (Sloane et al., 2002). This review will address both goals for prevention.

2.1.3. Late onset Alzheimer disease

When we consider efforts to prevent Alzheimer disease or dementia due to Alzheimer disease it is important to distinguish late onset Alzheimer disease from the familial (genetic) early onset form of this disease. Both are characterized by progressive accumulation of the protein amyloid-beta$_{42}$ in oligomers and in large aggregates known as plaques, with early involvement of brain areas involved in memory. Genetic Alzheimer disease is a rare ($<5\%$ of all cases), autosomal dominant disease caused by mutations in a single gene in each family. Several genes have been identified thus far. These mutations occur in genes that are involved in the processing of amyloid-beta$_{42}$ and lead to overproduction of this protein (Tanzi, 2013; Tanzi et al., 1996). The age of onset of dementia is <60 years, and mutations lead to development of disease in nearly 100% of those affected. Much of Alzheimer research is based on models based on familial disease, with animal models based on the known mutations.

In contrast, the common ($>95\%$) late onset Alzheimer disease, also described as sporadic Alzheimer disease, is not linked with single dominant genetic changes, but is thought to result from several factors (genetic and environmental) that lead to an imbalance in production and clearance of amyloid-beta$_{42}$. Although several genetic variants have been associated with late onset Alzheimer disease, these explain less than 50% of this disease. Compared with the familial form, late onset Alzheimer disease has a much larger variation in age of onset and rate of disease progression.

3. Cardiovascular factors and late onset Alzheimer disease

3.1. Epidemiological evidence

Even though Alois Alzheimer reported atherosclerosis in cerebral blood vessels in the post-mortem examination of his 55 year old index patient with Alzheimer disease (Alzheimer et al., 1995), Alzheimer disease and vascular disease have historically been considered separate entities. This distinction was enforced by clinical criteria for the diagnosis of dementia due to Alzheimer disease. For familial Alzheimer disease, this separation seemed valid, because its dominant genetic cause and young age of onset left little room for contributions of vascular disease. However, epidemiological studies of late onset Alzheimer disease identified hypertension, diabetes mellitus, atherosclerosis, atrial fibrillation, coronary artery disease, smoking, obesity, and the metabolic syndrome as risk factors for dementia due to Alzheimer disease (Biessels et al., 2006; Kalaria et al., 2012; Kalaria and Ihara, 2013). Many studies have shown the association between increased blood pressure in mid-life and cognitive decline or Alzheimer dementia in later life (Kivipelto et al., 2001; Skoog et al., 1996). Among all vascular risk factors, hypertension seems to be the most powerful risk factor for Alzheimer dementia (Kennelly et al., 2009). Although these associations do not prove causality between cardiovascular disease and Alzheimer disease, these studies have challenged the historical distinction between these two conditions.

The epidemiological studies have in most cases relied on clinical diagnoses of dementia due to Alzheimer disease. They therefore risk misclassification (e.g. misclassification of vascular dementia as Alzheimer dementia in studies where neuroimaging was not available) and, in addition, they provide no information on the relationship between vascular disease and earlier stages of Alzheimer disease, i.e. the preclinical or mild cognitive impairment stage. Recent advances however have made it possible to study these early stages of disease.

3.2. Vascular disease and amyloid-beta$_{42}$ accumulation

Whereas earlier studies had to rely on post-mortem examination of the brain to demonstrate amyloid plaques to confirm Alzheimer disease, it is now possible to reveal accumulation of amyloid-beta$_{42}$ in vivo. Using nuclear imaging with a radioactively labeled ligand that binds to amyloid-beta$_{42}$, uptake of tracer, reflecting deposits of amyloid-beta$_{42}$, can be quantified, a technique described as amyloid imaging. In asymptomatic elderly, amyloid imaging indicates abnormally high levels of amyloid-beta$_{42}$ in an estimated 30% in age 65–69, increasing to 55% at age >80–84 (Jack et al., 2014). The current hypothesis is that these so-called amyloid-positive but asymptomatic elderly represent preclinical Alzheimer disease. Longitudinal studies are underway to test this hypothesis, but preliminary data suggest that these amyloid-positive elderly show a decline in cognitive function on follow-up compared to amyloid-negative controls (Wirth et al., 2013). The

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