Review

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Non-psychiatric comorbidity associated with Alzheimer's disease

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Summary

The burden of medical comorbidity in individuals with Alzheimer's disease is greater than that observed in matched individuals without dementia. This has important implications for all clinicians and healthcare providers who deal with this common condition. The prevalence of vascular risk factors and vascular disease is particularly high. Additionally, associations with a number of other chronic medical conditions have been described, including thyroid disorders, sleep apnoea, osteoporosis and glaucoma. This review gives an overview of evidenced medical (non-psychiatric) comorbidity associated with Alzheimer's disease and briefly explores the underlying mechanisms that may account for these associations.

Introduction

In Alzheimer's disease, cognitive impairment influences the presentation and recognition of other medical conditions and the outcome of treatment. In turn, many physical health factors contribute to cognitive decline.

The burden of medical comorbidity in Alzheimer's disease is greater than matched individuals without Alzheimer's disease.[1] Higher medical comorbidity is significantly associated with lower cognition on mini-mental state examination taking into account age, gender, education and care setting.[2] Higher medical comorbidity is also significantly associated with poorer self-care, decreased mobility and greater incontinence, adjusted for the same demographic factors and cognition. Therefore, not only are medical comorbidities implicated in cognitive decline but also, independently of cognition, they may adversely affect function and independence. Moreover, an understanding of the non-psychiatric associations of Alzheimer's disease may shed light on poorly understood pathophysiological mechanisms of this condition.

This article reviews the medical (non-psychiatric) comorbidity of Alzheimer's disease. Medical conditions with an evidenced association with Alzheimer's disease were identified through interrogating PubMed, Embase and Medline using a number of search terms including 'Alzheimer's', 'association' and 'comorbidity'. The review briefly explores the underlying mechanisms that may account for these associations and will be of practical use to clinicians dealing with patients with Alzheimer's disease.

Vascular disease and Alzheimer's dementia

There is a particularly strong association between Alzheimer's disease and vascular disease as well as vascular risk factors. The pathological hallmark

of Alzheimer's disease is accumulation of β-amyloid plaques and the formation of neurofibrillary tangles,[3] while vascular dementia is characterized by ischaemic damage and multiple infarctions due to occlusion of cerebral blood vessels. Although these two diseases have long been considered separate entities, increasing evidence has shown that the ischaemic damage known to cause vascular dementia is also responsible for the development of Alzheimer's dementia, which could explain the overlap of the presence of both these diseases, known as mixed dementia.

In animal models, ischaemia results in increased amyloid deposition in the brain cortex,[4,5] and it is likely similar to processes that occur in humans.[6] Ischaemic damage disrupts the blood–brain barrier which is protective against the deposition of β-amyloid in the neurones and finally cause an up-regulation of apolipoprotein E that binds to β-amyloid causing conformational change in the peptide, which renders it neurotoxic. There is upregulation of the expression of amyloid precursor protein and amyloid beta in response to ischaemic damage to the brain.

Elevated blood pressure is established as a strong risk factor for vascular dementia. The relationship between blood pressure and Alzheimer's disease is more complicated. Evidence shows that elevated blood pressure in midlife is a strong risk factor for Alzheimer's disease.[7] However, hypotension in later life, defined as a diastolic blood pressure <70 mmHg, has a similar effect. This relationship was described in the Chicago Health and Ageing Project,[8] where low later life blood pressure was related to higher incidence of Alzheimer's disease. This can be explained by the fact that hypotension in later life leads to ischaemic conditions that promote neuronal death.[9] The decreasing auto-regulatory capacity of the brain in later life causes the brain to be more vulnerable to ischaemic insults when systemic blood pressure falls beyond a critical level to maintain adequate perfusion.[10]

In a prospective study of 3734 Japanese-Asian men followed up for 25 years, there was a strong association between midlife hypertension and Alzheimer's and vascular dementia.[11] This effect was most pronounced in men not treated with anti-hypertensives. Data from autopsy and neuroimaging findings from the same study demonstrated that elevated systolic blood pressure in midlife caused a vasculopathic change along with reduced brain weight and a significant amount of neuritic (β-amyloid) plaques in the neocortex and hippocampus.[7] Similar findings have been observed in a Finnish study.[12]

Elevated blood pressure causes the blood–brain barrier disruption around the capillaries in the brain which in turn cause the dysfunction of subcortical vessels.[13] This subsequently impairs critical nutrient delivery to the brain, especially glucose which in turn impairs its performance. Hypertension also causes endothelial damage which has a 2-fold effect on the brain. First, it leads to impaired nitric oxide production resulting in the generation of free radicals.[14] Second, it triggers an inflammatory response that promotes neuritic plaque formation.[15] Extreme hypoxia has also been shown to cause amyloid precursor protein accumulation and its subsequent cleavage to amyloid.[16]

Diabetes mellitus may also be a contributing risk factor for Alzheimer's disease. Several large studies have shown that diabetes is associated with cognitive impairment.[17–21] A positive association has also been found between impaired glucose tolerance and Alzheimer's disease.[22–24] Leibson et al.[21] concluded that adult onset diabetes mellitus increased the risk of Alzheimer's disease by 37% in women and 127% in men. These findings are largely supported by results of other studies—the Rotterdam study showed a link between diabetes and Alzheimer's disease with a relative risk of 1.3.[22,25] Patients with diabetes have also been shown to have greater degrees of whole-brain atrophy and hippocampal atrophy.[26,27]

The association between diabetes mellitus and Alzheimer's disease probably involves several mechanisms. Peripheral hyperinsulinemia seen in type 2 diabetes results in blood–brain barrier dysfunction and decreased insulin transport to the brain.[28,29] Reduced brain insulin signalling causes increased tau phosphorylation and β-amyloid levels in a streptozin mouse model of diabetes.[30] Insulin receptors are found in high concentration in areas associated with memory functions such as the hypothalamus and limbic system, perhaps explaining the strong association between peripheral hyperinsulinemia and impaired cognition.[31] Hyperinsulinemia also provokes increase in central inflammation.[32] Animal studies have shown that this leads to neurodegeneration and cognitive deficits. In a study of diabetic rats, hyperglycaemia caused an upregulation of amyloid precursor protein, neuronal loss and neuritic degeneration.[33]

Obesity is the primary cause of insulin resistance. Lobo et al.[34] showed that 80% of obese individuals are insulin resistant. The public health implications of the growing number of obese individuals in the population may extend to exacerbate the predicted future rise in prevalence of dementia. Both a recent meta-analysis and a newly published twin study confirmed that obesity in midlife is a significant

risk factor for both Alzheimer's and vascular dementia,[35,36] though this association may disappear or even become reversed in later life.[35] Obesity results in free fatty acid elevation and inhibition of enzyme metalloprotease, which facilitates clearance of β-amyloid and normal insulin signalling.[37] Free fatty acid further stimulates the aggregation of amyloid and tau proteins as shown in the Honolulu Asia Ageing study.[38] Elevated free fatty acid produces a pro-inflammatory state with a rise in TNF-α,[39] which may contribute to Alzheimer's dementia.[40] Elevated midlife total cholesterol level is associated with a 2- to 3-fold increased risk of Alzheimer's disease.[41] Cholesterol plays a large role in β-amyloid aggregation. Cholesterol-derived aldehydes promote Schiff's base formation, accelerating the early stages of amyloidogenesis.[42,43] Cerebral atherosclerosis is strongly linked to neuritic plaque formation[44,45] and cholesterol has also been implicated in their pathogenesis.[46,47]

Thyroid

Both hypothyroidism and hyperthyroidism are well-recognized as potentially reversible causes of cognitive impairment. There is also a link between thyroid function at the higher and lower ends of the normal clinical range and risk of dementia.[48]

Kalmijn *et al.*[49] demonstrated a 3-fold increased risk of Alzheimer's disease with sub-clinical hyperthyroidism >2 years. In the 2009 Honolulu-Asia ageing study, thyroxine (but not thyrotropin) concentration was associated with increased risk of Alzheimer's disease in their male sample over a mean follow-up period of almost 5 years.[50] The authors found a higher Alzheimer's pathology load in those with higher free thyroxine in a sub-sample at post-mortem. A large sample of original Framingham cohort participants demonstrated an association between both high and low thyroid-stimulating hormone levels and dementia in females only.[51] Tan and Vasan[48] suggest that thyroid abnormalities are more likely causative of Alzheimer's pathology than consequence. Suggested mechanisms include effects on amyloid and tau deposition,[50] cholinergic function, or neuronal survival, or alternatively the indirect mediation of risk via vascular factors.[50,51]

Sleep apnoea

Sleep apnoea is more common in the elderly than in younger individuals,[52] and various small studies demonstrate increased prevalence in Alzheimer's disease.[53,54] Various neuropsychological deficits have been described in sleep apnoea patients without dementia. However, the deficits are mild and dissimilar in pattern to Alzheimer's disease and to vascular dementia.[55] In sleep apnoea, continuous positive airway pressure (CPAP) has been shown to improve cognitive functions in several domains.[56] A group investigating the effect of CPAP for sleep apnoea in Alzheimer's disease patients found improved sleep patterns[56] and cognition.[57,58] Deficits in cholinergic neurotransmission have been suggested as a cause for sleep apnoea in Alzheimer's disease. Moraes *et al.*[59] found that oxygen saturation, REM sleep duration and cognition improved with donepezil in a small group of Alzheimer's patients compared to placebo controls.

However, across studies the magnitude of difference of rates of sleep apnoea in Alzheimer's disease compared to controls has been generally small,[60,61] and other studies have failed to confirm an association.[62] Sleep apnoea overlaps with multiple medical conditions linked to impaired cognition, including hypothyroidism and hypertension. An association with apoE4 has been demonstrated.[63] Overall, the relationship between cognition and sleep apnoea remains unclear. To clarify the mechanisms involved, Alzheimer's disease and other types of cognitive impairment in sleep apnoea should be examined separately.

Osteoporosis

A number of studies have demonstrated an association between low bone mineral density and both cognitive decline[64] and Alzheimer's disease.[65,66] Alzheimer's disease patients are more prone to osteoporosis, falls and fractures than non-demented subjects, with poorer outcomes following fracture. The health of bones is therefore important for disability and mortality in Alzheimer's disease patients since bone mineral density strongly predicts fracture. Weller and Schnatzer[67] found a prevalence of osteoporosis of 27% in nursing home residents with Alzheimer's disease cases compared to 16% in those without dementia. The Alzheimer's disease group also suffered higher rates of falls and an excess of hip fractures, even after accounting for the higher number of falls. The authors suggest that a further independent factor must account for the higher rates of fracture in Alzheimer's disease. However, their study design involved use of a questionnaire to identify the presence of osteoporosis and would have failed to identify undiagnosed bone loss.

More recently, an association has been demonstrated between low bone mineral density and brain atrophy in early Alzheimer's disease.[68] A

further paper by the same authors demonstrated reduced volume in the hypothalamus specifically in early Alzheimer's disease, again associated with low bone mineral density.[69] The authors propose that neurodegeneration leads to bone loss through neural or hormonal mechanisms. Alternatively, factors including weight loss, reduced soft tissue and nutritional deficiencies may underlie the relationships between cognition, bone mass and fractures.

Glaucoma

Increased prevalence with age and neurodegenerative pathology are common factors in both Alzheimer's disease and glaucoma. Studies have demonstrated higher rates of glaucoma in Alzheimer's disease,[70] which are not explained by a shared factor of apoE4.[71] A study of 112 nursing home residents with Alzheimer's disease revealed an occurrence rate of 25.9% compared to 5.2% in matched non-demented controls.[70] Glaucoma is characterized by retinal ganglion cell death. Raised intraocular pressure is typically seen in glaucoma, but studies demonstrate that the disease can occur in the absence of raised pressure indicating the role of other pathological mechanisms. Considerable evidence supports the presence of the characteristic pathological mechanisms of Alzheimer's disease, of β-amyloid accumulation, neuronal apoptosis and cell loss, in glaucoma.[72–75] Optic nerve degeneration and loss of retinal ganglion cells have also been found in Alzheimer's disease. However, this has been found to occur in the absence of retinal or optic nerve amyloid or tau pathology.[76,77] Wostyn *et al.*[78] proposed low CSF pressure occurring in Alzheimer's disease as a factor leading to increased risk of glaucoma. While further research is required to clarify overlapping disease processes in glaucoma and Alzheimer's disease, existing work raises some interesting possibilities for therapy. Guo *et al.*[73] investigated treatments targeting β-amyloid for glaucoma, with some success.

Cancer

Not all conditions are more prevalent in Alzheimer's disease. There is mounting evidence of a protective effect of Alzheimer's disease against developing cancer. One population-based prospective study found a slower rate of developing cancer in Alzheimer's disease, and also reduced risk of Alzheimer's disease in cancer.[79] The same investigating group failed to demonstrate an association between cancer and vascular dementia, indicating a link with neurodegenerative disease specifically.[79]

Disruption to biological mechanisms regulating cell apoptosis may be crucial to both cancer and Alzheimer's disease. One enzyme involved in cellular signalling, Pin1, appears to be over-expressed in many cancers and downregulated in Alzheimer's disease.[80]

Rheumatoid arthritis and NSAIDs

Epidemiological studies have also demonstrated lower rates of Alzheimer's disease in rheumatoid arthritis.[81] Non-steroidal anti-inflammatory drugs (NSAIDs) are a mainstay of treatment for arthritis, and theoretical models implicate inflammation as key to Alzheimer's disease pathogenesis. Consequently, there has been considerable research interest into the role of NSAIDs in Alzheimer's disease. Substantial evidence from longitudinal observation studies supports a protective role for NSAIDS against Alzheimer's disease.[81,82] NSAIDs appear to delay Alzheimer's disease onset[83] and supporting evidence has demonstrated diminished risk reduction with increasing age.[84] However, clinical trials have failed to demonstrate benefit.[85] A plausible explanation is that studies did not involve intervention at a sufficiently early stage. There is general agreement that sustained treatment of >2 years duration is required[86] and that NSAID ingestion must occur at least several years before the onset of Alzheimer's disease for risk reduction.[82,87]

Most traditional NSAIDs inhibit both COX1 and COX2 enzymes. COX1 is implicated in the activation of microglia in Alzheimer's disease, and the theoretical rationale for the use of NSAIDS targeting this enzyme is supported by epidemiological work.[85,88] Some clinical trials have investigated the newer selective COX 2 inhibitors such as celecoxib, finding no benefit. Results from animal models and epidemiological studies also support a lack of efficacy for selective COX2 inhibitors in reducing Alzheimer's disease risk.[85] However, NSAIDs and associated compounds have a wide range of effects beyond inflammation. Some traditional NSAIDs are also anti-β-amyloidogenic, including ibuprofen and indomethacin, most likely acting via Y-secretase.[89] As yet, it is unclear whether NSAIDs exert their perceived preventative effects by modulating inflammatory response, influencing β-amyloid deposition, or through interaction between the two.

There is a need for further prospective prevention trials which could usefully focus on mild cognitive impairment.[90] Unfortunately, multiple challenges face such trials in Alzheimer's disease, as demonstrated in the ADAPT study,[91] which terminated early due to adverse effects. Concerns exist

regarding the safety and tolerability of NSAIDS used at a population level for prevention.[90]

End of life in Alzheimer's

There are surprisingly few autopsy studies that are focused on physical comorbidity in Alzheimer's disease.[92] Bronchopneumonia is the most frequently cited cause of death, typically accounting for almost half of all deaths.[92–95] This is frequently related to eating problems and probably reflects general frailty.[95] Compared to a matched, non-demented population, vascular-related deaths are more common in Alzheimer's disease, as is co-existent vascular disease,[92,96] while cancer is a much less common cause of death.[92,94] The high incidence of comorbidity at the end of life in Alzheimer's disease poses special medical and ethical dilemmas for clinicians.[97] The medical instinct to treat normally reversible pathology, such as bronchopneumonia, can arguably delay death and potentially prolong suffering in what most clinicians view as a terminal illness.[95] Furthermore, at this stage of their illness, affected individuals are unable to make informed decisions about their preferences. A better understanding of associated comorbidity and underlying pathophysiological mechanisms could help clinicians and patient welfare guardians make the most appropriate decisions in advanced Alzheimer's disease.

Conclusion

Physical comorbidities make important contributions to cognitive and functional decline in Alzheimer's disease. This has important implications for healthcare providers, as patients will often require access to services and expertise beyond that dealing with the behavioural and psychological manifestations of the condition. Patients are likely to benefit from improved team working between general practitioners, old-age psychiatrists, geriatricians and other specialists. Moreover, non-psychiatric associations of Alzheimer's disease may provide clues to pathological mechanisms of this important condition. In particular, the importance of vascular risk factors and arterial disease is increasingly recognized as important in the pathogenesis of the condition.

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