Dementia at old age: a clinical end-point of atherosclerotic disease

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The main causes of dementia at old age are Alzheimer’s disease and vascular dementia. The clinical presentations of late-onset Alzheimer’s disease and vascular dementia can barely be differentiated. This clinical observation is supported by pathological findings. Late-onset dementia should be considered a multifactorial disease, in which both vascular factors and amyloid dispositions contribute to cognitive decline.

Introduction

Dementia is among the most disabling diseases of old age. Its prevalence is estimated to be at least 15–20% in those aged 80 years or older (Fig. 1)¹, although lack of consensus on diagnostic criteria makes this estimate uncertain². Commonly used criteria, such as the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders, can differ by a factor of 10 in the number of persons classified as having dementia².

Because of our ageing population, dementia will become a major burden for health care budgets during the next few decades. In the U.S.A. the total direct and indirect costs of dementia were estimated to amount to over US$100 billion per year³,⁴. The therapeutic arsenal for prevention and treatment of dementia is currently very limited. With new insights into the causes of this multifactorial disease, however, both old and new drugs may become available for use in this indication within the next few years.

Developments in the diagnosis of dementia

During the early part of the 20th century cerebral atherosclerosis was considered to be the main cause of dementia. In 1894 Otto Binswanger⁵ described extensive ischaemic lesions in the white matter of patients with mental and physical deterioration that was not caused by syphilitic general paralysis. Some years later this condition was termed ‘Binswanger’s disease’ by Alois Alzheimer, who had reviewed the necropsy material referred to by Binswanger (for review⁶). In 1907 Alzheimer’s classic paper on neuritic plaques⁷ was published. Until the 1950s, Alzheimer’s disease (AD) was regarded as a rare disorder, affecting only younger persons (pre-senile dementia). AD is currently believed to be the most common form of dementia both in younger and in older patients, and vascular dementia (VAD) is considered the second commonest form.

Alzheimer’s disease

The hallmarks of the Alzheimer brain are beta-amyloid plaques and neurofibrillary tangles (Fig. 2). The amyloid hypothesis states that amyloid plaque formation is the core feature of AD⁸-¹¹. Plaques and tangles can only be found at autopsy or by brain biopsy, and therefore a definite diagnosis of AD cannot be made during life in the vast majority of patients. Diagnostic criteria focus on probable or possible AD¹².

AD is a degenerative disorder, which is insidious in onset with gradual decline of cognitive functions. Memory impairment is present in the very early stage of the disease, and patients have difficulty retaining information for more than a few minutes. As the disease progresses access to older memories becomes impaired also. Other cognitive
losses include aphasia, apraxia, disorientation, visuospatial dysfunction, and impaired judgement and executive functioning. Functional impairments, such as difficulties with medication, finances or using a telephone, and getting lost in unfamiliar surroundings, are often the first signs for the patient or family that something is wrong. Social skills remain intact for a long time. Irritability, anxiety and depression in the early stages, and delusions, hallucinations, wandering and aggression later in the disease course impose a burden on caregivers and may lead to nursing home placement.

Two types of AD may be distinguished: the early-onset, familial type, with autosomal-dominant inheritance related to mutations in the presenilin genes on chromosome 1 or 14; and the sporadic, late-onset type. The latter occurs in those older than 70 years and has no known pattern of inheritance. The vast majority of patients with AD have the late-onset type, and recent molecular/biological breakthroughs in our understanding of the aetiology of pre-senile dementias do not necessarily apply to the common senile dementias.

Vascular dementia

In 1974, the term ‘multi-infarct dementia’ was introduced by Hachinski and coworkers to describe the mechanism that they believed to cause VAD. Since then, vascular mechanisms other than brain destruction by multiple infarcts have been linked to dementia. It has been demonstrated that even a small, single infarct can have the same functional impact as multiple infarcts when it is strategically located. Furthermore, it is understood that white matter changes also result from cerebral vascular disease. These changes, which were increasingly recognized following the introduction of computed tomography and, in particular, magnetic resonance imaging, are very common in old age and are associated with cognitive decline. In particular, associations have been found between periventricular white matter lesions and cognitive dysfunction. Histologically, these lesions are best described as incomplete infarcts that result from insufficient perfusion due to small-vessel disease.

The classic clinical presentation of VAD is a stepwise impairment of cognitive functions, with a temporal association with stroke. This classic type of VAD, however, affects only a small minority of patients. In contrast, many demented patients with gradual cognitive decline without serious motor symptoms (reminiscent of an Alzheimer’s type of dementia) do have severe white matter lesions on magnetic resonance imaging, with or without lacunar infarcts. Therefore, vascular factors are likely to contribute to dementia not only through infarcts but also through incomplete infarcts that result from insufficient perfusion caused by small-vessel disease. Currently, eight different types of VAD have been distinguished.

The role of atherosclerosis in late-onset dementia

The pivotal role of cerebrovascular disease in the pathogenesis of VAD is beyond doubt. In 1970, in their classification of dementia, Tomlinson et al. stated that the mechanism that underlies the various types of VAD is atherosclerosis in the vast majority. That the risk factors for VAD are the same as those for cerebral vascular disease, including smoking, hypertension, older age, diabetes mellitus, atrial fibrillation, coronary heart disease and
peripheral vascular disease, is not unexpected and confirms the role of atherosclerosis in this disease\cite{17,25}. However, accumulating evidence indicate that late-onset AD is also associated with atherosclerotic disease\cite{25–28}. Patients diagnosed during life as having probable AD, with plaques and tangles at autopsy, had brain infarcts in up to 25% of cases\cite{26}. In the Nun study\cite{28}, 102 nuns underwent neuropsychological examinations at regular intervals. Autopsy revealed that 60% of those with only plaques and tangles had been diagnosed as having probable AD during life, whereas this diagnosis was attributed to 90% of those who had not only plaques and tangles but also infarcts. It has been shown that cardiovascular disease and risk factors for cerebrovascular disease (i.e. smoking, hypertension, diabetes and atrial fibrillation) are risk factors for AD, suggesting an interaction of atherosclerosis with AD\cite{23,25,29}.

These findings indicate that there is considerable overlap between VAD and late-onset AD, challenging the conventional diagnostic criteria for types of dementia at old age.

Dementia at old age is a multifactorial disease

The clinical presentation of VAD and late-onset AD can barely be differentiated. The current diagnostic criteria for AD have a sensitivity of only about 50%, reflecting the many features that VAD and other types of dementia share with AD\cite{12}. This clinical observation is supported by recent pathological findings in late-onset dementia from the Medical Research Council Cognitive Function and Ageing Study\cite{27}. In that autopsy study it was shown that most patients with dementia had a mixed form of AD and VAD. Of the demented persons, 64% showed neuritic plaques and 81% had signs of vascular disease, whereas these features were found in 33% and 76% of the non-demented individuals, respectively. There were no clear thresholds of these features that predicted dementia status\cite{27}. In a study reported by Esiri et al.\cite{30}, it was shown that cerebral vascular disease significantly worsens cognitive performance in the early stages of AD. Taken together, these data strongly suggests that late-onset dementia is a multifactorial disease, in which both vascular factors and amyloid dispositions contribute to cognitive decline in old age. The individual contributions of these factors to cognitive decline cannot yet be determined on the basis of disease characteristics or by using brain imaging techniques. The view that dementia at old age is equivalent to AD should therefore be abandoned.

Dementia is an end-point for cardiovascular intervention

The finding from the Systolic Hypertension in Europe (SYST-EUR) trial\cite{31} that antihypertensive treatment reduces the risk for dementia, especially of the Alzheimer’s type, strongly supports the concept that atherosclerosis plays a pivotal role in the development of dementia at older ages. More recently, evidence has been obtained from two cross-sectional studies\cite{32,33} that cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk for dementia by 70%. The mechanism that may underlie this possible beneficial effect of the statins is subject to speculation\cite{34}. Nevertheless, it seems beyond any doubt that the presence of atherosclerosis or, more specifically, cerebrovascular disease contributes to the development of cognitive decline and dementia at old age. New clinical trials should be designed to examine the impact of cardiovascular risk reduction on cognitive function and dementia in elderly persons as end-points of atherosclerotic disease. An example of this new generation of clinical trials is the ongoing Prospective Study with Pravastatin in the Elderly at Risk (PROSPER), which is investigating the effect of pravastatin 40 mg . day \(^{-1}\) on cognitive function in men and women aged 70–82 years\cite{35}.

Conclusion

Late-onset dementia is a multifactorial disease in which vascular factors contribute to cognitive decline. Therefore, dementia at old age should be considered an end-point of atherosclerotic disease, and new clinical trials should be
designed to examine the impact of cardiovascular risk reduction on dementia.

References