Cognitive decline in ageing

REVIEW ARTICLE

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ABSTRACT In recent years there have been major advances in the conceptualisation of dementia and cognitive decline in older age. Cognitive decline should be seen as a continuum, with the distinction between dementia and milder degrees of cognitive impairment being somewhat arbitrary and carrying no pathological justification. The co-existence of Alzheimer's disease and small-vessel ischaemic cerebrovascular disease in older people with cognitive impairment has also previously been under-recognised. These pathologies carry a long list of shared genetic and environmental risk factors, and the recognition of the fact that vascular disease and Alzheimer's pathology usually co-exist opens up additional possibilities for treatment and prevention of cognitive decline and dementia in older people. Subjects with a clinical diagnosis of vascular dementia will often have Alzheimer's pathology and may benefit from cognitive enhancers such as cholinesterase inhibitors. Conversely, subjects with clinical Alzheimer's disease may benefit from the active management of vascular risk factors. The traditional diagnostic labels of Alzheimer's disease and vascular dementia are unhelpful, as they fail to recognise the interaction between these pathologies. Prevention of cerebrovascular disease is likely to play an important role in attenuating cognitive decline in high-risk older patients.

Key words: Aging; Cognition; Dementia

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INTRODUCTION

Cognitive decline is one of the key threats to successful healthy ageing. The risks increase markedly with rising age, with a prevalence of dementia of approximately 30% in those aged over 90 years.[1] However, major cognitive impairment is not inevitable, even in advanced age. When Jeanne Calment of France, the world-record holder for longevity, died at the age of 122 years,[2] she was physically frail and had experienced significant sensory impairment in her later years but had not developed dementia. In contrast, the novelist Iris Murdoch had a progressive deterioration in cognitive function over the last 5 to 7 years of her life and died with dementia at the age of 79 years.[3] These famous personalities exemplify the extremes of change in cognitive function that can occur with ageing. However, it is increasingly recognised that cognitive decline in advanced age is a continuum, with no simple cut-off between physiological and pathological changes.

DEFINING COGNITIVE DECLINE

A variety of different terms or diagnostic labels are used to describe different stages along the spectrum of cognitive decline in older age, including dementia, mild cognitive impairment (MCI), and age-associated cognitive decline.[4] The boundaries between these different states are unclear and vary depending on the particular definitions applied. The application of different criteria to a single cohort of older patients can result in up to a 10-fold difference in the proportion labelled as having a dementia. The use of ICD-10 (International Classification of Diseases–10) diagnosed dementia in 3.0%, compared with 29.1% using DSM-III (Diagnostic and Statistical Manual

of Mental Disorders–III).[5] The different criteria for dementia use the same general constructs but vary in the combinations defining specific diagnoses. Therefore, when applying the diagnostic label of dementia to an individual patient, it is important to be explicit about which criteria are being used.

There are additional difficulties with dementia diagnosis. Accepted criteria require deterioration or impairment in social functioning[5] but this depends on the individual patient's degree of social engagement. For example, someone who was previously very socially active with complex responsibilities might note a deterioration in social function with modest cognitive decline, whereas a subject who has only very simple, undemanding social involvement might not have any deterioration in social function with much more significant cognitive deterioration.

A further complication is the pathophysiological overlap of dementia and milder degrees of cognitive decline, which is sometimes labelled 'cognitive impairment without dementia', or MCI,[6] which is very common in older people. The prevalence of DSM-III dementia in the over-65s has been estimated at 8%, while approximately 16% have MCI.[7] Those with MCI are at high risk of continuing cognitive decline and subsequent dementia.[6] It appears that the deterioration of cognition in older age marks the triggering of pathological processes associated with dementia.[8] Therefore, although the distinction between these states carries no pathophysiological justification, the terms do provide general summaries of the severity of cognitive decline.

PATHOLOGY AND INCIDENCE

Recent years have seen radical revisions of our understanding of the pathological processes that underlie cognitive decline and dementia in older people.[9] Two major postmortem studies, the Nun Study[10] in the US and the MRC CFAS study[11] in England, have shown that the interaction of Alzheimer's pathology and ischaemic cerebrovascular disease is particularly important in determining the severity of cognitive decline in old age.

The traditional understanding has been that Alzheimer's pathology is the sole cause of most cases of dementia in old age. However, Alzheimer's pathology has been shown to be present in a significant proportion of non-demented elderly, and these pathological changes are not necessarily sufficient to cause dementia.[11] Likewise, the presence of cerebrovascular disease on its own is generally not associated with major cognitive impairment.[10] However, the combination of Alzheimer's pathology and cerebrovascular disease has strong associations with cognitive decline and dementia.

The key form of cerebrovascular disease is small-vessel ischaemic damage, with a narrowing of the penetrating arterioles that supply the deep white matter, resulting in low-grade ischaemic damage with or without lacunar infarction. Postmortem studies have found that small-vessel ischaemic damage is present in over 75% of older people at death.[11] The associated patchy periventricular hypodensities seen on brain computed tomography are sometimes termed leukoaraiosis. T2-weighted magnetic resonance imaging (MRI) reveals white matter hyperintensities. The extent of this damage correlates with cognitive impairment and with gait abnormalities such as shortened step length.[12]

Covert cerebral infarction is also common in older people. The Rotterdam MRI study investigated over 1000 subjects aged 60 to 90 years.[13] They found that one quarter had at least one cerebral infarct, of which four out of five had no history of stroke: 'silent' brain infarction is 5 times as common as symptomatic infarction in older people. The presence of infarction on MRI was associated with a more than doubling of the risk of dementia.[14] Clinical stroke is also associated with an approximately 2-fold increased risk.[15] A large burden of unrecognised ischaemic cerebrovascular disease in older people is therefore evident. This includes progressive ischaemic damage to subcortical white matter and focal infarction, the extent of which correlates with risk of cognitive decline. The prevention of ischaemic cerebrovascular disease can therefore be expected to reduce the risk of cognitive decline and dementia in older people.

NEW DIRECTIONS IN TREATMENT

The frequent coexistence of Alzheimer's disease and ischaemic cerebrovascular disease can be explained by the long list of shared genetic and

environmental risk factors, including apolipoprotein e4 polymorphism,[16] hypertension,[17] hypercholesterolaemia,[18] elevated plasma homocysteine,[19] diabetes mellitus,[20] metabolic syndrome, cigarette smoking,[21] systemic inflammation,[22] obesity, low physical activity, and low educational and socioeconomic status.[9] The recognition that vascular disease and Alzheimer's pathology usually coexist opens up additional possibilities for treatment and prevention of cognitive decline and dementia in older people. Cognitive enhancers were initially developed for patients with clinically diagnosed Alzheimer's dementia who were thought most likely to have deficits in acetylcholine that might be partly reversed with cholinesterase inhibition. However, randomised controlled trials have shown that subjects with a clinical diagnosis of vascular dementia or mixed vascular/Alzheimer's dementia can also benefit.[23] This wide spectrum of benefit is likely to be due to the pathological overlap and common coexistence of Alzheimer's pathology with cerebrovascular disease.

PREVENTION AND INVESTIGATION

Drugs that reduce the risk of ischaemic vascular disease might be expected to attenuate cognitive decline with ageing, and delay or reduce the risk of dementia. Currently the evidence is patchy; however, there are strong links between elevated blood pressure and cognitive decline or dementia, including clinically diagnosed Alzheimer's disease.

Hypertension and cholesterol reduction

The systolic hypertension in Europe (Syst-Eur) study[24] showed a 50% reduction in the incidence of dementia (including clinically diagnosed Alzheimer's disease and vascular dementia) with a calcium channel blocker. The PROGRESS trial[25] found that prevention of recurrent stroke with a thiazide diuretic plus an angiotensin-converting enzyme inhibitor was associated with reduced risk of cognitive decline and dementia.

The effect of statins is less clear. These drugs could exert beneficial effects through several different mechanisms, including cholesterol lowering and a reduced risk of stroke, and by reducing inflammation, which could both attenuate the progression of Alzheimer's pathology and reduce the risk of cerebrovascular damage. Observational studies have found that older people who are prescribed statins are less likely to develop dementia than those who are not given these drugs. However, these results have not been confirmed in randomised controlled trials. The Heart Protection Study[26] found that 5 years of simvastatin had no effect on the prevalence of major cognitive impairment at the end of the study. In the PROSPER study, pravastatin had no effect over 3.2 years on general cognitive function (Mini-Mental State Examination score), speed of information processing (Letter-digit Coding Test or Stroop-Colour-Word-Test), or verbal memory (Picture-Word Learning Test).[27,28] These studies recruited subjects who were predominantly cognitively intact, and the results cannot be extrapolated to MCI or early dementia. Clinically significant longer-term beneficial effects also cannot be excluded by these studies.

Other potential preventative agents

Although limited, a small randomised controlled trial found cognitive benefits of aspirin in subjects with cerebrovascular disease and dementia.[29] More substantial but negative data have been generated for non-steroidal anti-inflammatory drugs. One year's treatment with naproxen or rofecoxib (a cyclo-oxygenase-2 inhibitor) had no effect on the progression of mild-to-moderate Alzheimer's disease.[30] The randomised controlled trial data for the effect of oestrogens on cognition in older women has proved even more disappointing, indicating an increased risk of cognitive decline with active treatment.[31] Other drugs of potential interest include peroxisome proliferator-activated receptor gamma (PPARG) agonists, cholesterol acyltransferase inhibitors, thienopyridines, folic acid, vitamin B12, anti-oxidant vitamins, and alternative antiplatelets such as clopidrogrel.[9]

Interventional possibilities

There are a number of important issues to be considered in the development of future interventional studies. High-quality randomised controlled trials will be necessary, as results from observational datasets often are subject to bias, and the results in patients from one end of the spectrum of cognitive decline may not be re-

produced at the other. The general classification of study participants as cognitively healthy, MCI, or dementia may therefore be helpful. Further selection of subjects with additional risk factors for cognitive decline may also improve exploratory intervention studies, for example including patients with elevated homocysteine levels in future trials of folic acid.

Future investigation

Investigators must decide whether they are primarily addressing cognitive decline or incidence of dementia; it is not clear which approach is most cost-effective. Detailed cognitive assessment is likely to be required to detect early effects but is expensive to perform. There are tools that allow the cheap detection of incidence of dementia (eg telephone follow-up); however, this approach will require very large studies over a prolonged period, even in relatively high-risk groups, such as those with MCI. Current funding mechanisms do not allow investigators to perform studies of adequate duration. This can be partly addressed by using large cohorts; however, studies of 5 to 10 years duration are likely to be required.

CONCLUSION

'Healthy ageing', MCI, and dementia are a continuum with common risk factors for cognitive decline across this spectrum. For most patients, clinically significant cognitive decline results from a complex interplay between Alzheimer's pathology and cerebrovascular disease. Traditional diagnostic labels of monopathology Alzheimer's disease and vascular dementia are unhelpful as they fail to recognise this synergy. This new concept suggests a number of new plausible strategies to prevent or delay cognitive decline and dementia: prevention of cerebrovascular disease is likely to play an important role in attenuating cognitive decline in high-risk older patients. Promising results have been found for blood-pressure lowering, and there are realistic hopes that evidence will emerge for further effective strategies to reduce the risks of cognitive decline and dementia in older people.

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