

Alzheimer's disease—The Inexorable Epidemic

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Alzheimer's disease (AD) is the most common form of dementia which refers collectively to syndromes of progressive deterioration of memory along with other cognitive domains such as language, praxis and executive function. More than 70 million people worldwide have dementia currently and AD accounts for over 50% of all dementia cases. AD combined with cerebrovascular disease accounts for another 10% to 20% of cases particularly in Asia.

The principal risk factor for AD is age. After 65 years of age the incidence of the disease doubles every 5 years. After the age of 85 one in three individuals will have dementia. Alzheimer's Disease International estimates the prevalence of AD in Singapore to be 22 000 in 2005, and is anticipated to rise to 52 600 in 2020 and 187 000 by 2050.¹ This is commensurate with the rapidly aging population and in the context of modest population growth. Only the advent of major disease-modifying therapeutics directed at early disease can avert such a dismal future.

Can we recognise the disease early? To a certain extent we can. An early form of the disease is called mild cognitive impairment (MCI). MCI can be detected by sophisticated neuropsychological testing. It can also be detected using a simple questionnaire that we developed and given to family members and/or caregivers. The instrument asks a series of questions regarding progressive change in performance. Interestingly the same type of questionnaire given to the subject is not informative and tends to pick up the worried well.²

Beyond early recognition, we are often asked if something can be done to alter the disease course. The current mainstay of treatment is cholinesterase inhibitors. These drugs improve neurotransmission by reducing the breakdown of acetylcholine and provide mild symptomatic relief in Alzheimer's disease, but they lose efficacy over time as the disease progresses. A more recent addition to the armamentarium is Memantine which is a partial N-methyl-D-aspartate (NMDA) agonist. Its effect is also modest.

In discussing therapeutic interventions, here we briefly revisit the pathophysiology of AD. A key feature of the disease is β -amyloid peptide ($A\beta$) plaques and prominent neurofibrillary tangles in the hippocampus and medial temporal lobe structures. β -amyloid peptides are the

breakdown products by proteolysis of the amyloid precursor protein. Three enzymes in this pathway include beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1), a β -secretase, and γ -secretase. Accumulation of amyloid is believed to be the main culprit in the pathophysiology of AD. This has proven useful in the development of PET imaging ligands as a method of detecting and assessing the progress of AD. However the sensitivity and specificity of the technique is limited. So far the progress is insufficient to fully warrant large scale use as a diagnostic technique.³ Hence diagnosis currently remains a detailed clinical assessment, neuropsychological testing and appropriate neuroimaging.

Attempts have been made to remove and or reduce $A\beta$ as a method of treating AD. Clinical trials of γ -secretase inhibitors,⁴ vaccination with $A\beta$, and monoclonal antibodies against $A\beta$ epitopes are currently ongoing and results are eagerly awaited. The antibodies bind $A\beta$, induce phagocytosis and enhance clearance of $A\beta$. These studies will be the definitive tests for the amyloid hypothesis. Early indications were not as positive as expected. Vaccination in a phase 2a trial resulted in encephalitis in some subjects. Moreover, follow-up of immunised patients showed no benefit despite plaque reduction. Another phase 2 trial of passive immunisation resulted in cerebral oedema in some patients. Phase 3 trials of monoclonal antibodies against $A\beta$ are currently under way.⁵

Another target is the neurofibrillary tangle and tau protein. The major component of the neurofibrillary tangle is an abnormally hyper-phosphorylated aggregated form of tau. Although many mutations of tau occur in frontotemporal dementia with Parkinsonism, they are not seen in Alzheimer's disease. This raises the issue of the importance of tau. Nevertheless, there are trials of methylene blue which reduces tau aggregation which are in progress. These trials are likely to address the importance of tau in the pathogenesis of Alzheimer's disease.

Is AD inherited? The heritability of AD is estimated to be around 58%.⁶ Suffice to say, inheritance is most likely polygenic and multifactorial. Several genome-wide association studies comprising thousands of subjects have consistently shown that APOE e4 allele is associated with AD. APOE is the primary cholesterol transporter in the

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brain. Homozygous APO e4 is associated with an 8-fold risk of developing AD. Other genes have been identified in some studies but not in others, suggesting much lesser roles. Many endeavours involving the 'omics', e.g. genomics, transcriptomics, proteomics and metabolomics are proceeding this time and may provide new insights into the disease pathophysiology.

Given this state of affairs and while we wait with bated breath for 'wonder' drugs, the question that comes up is whether we can do anything to prevent dementia now. There are few randomised controlled studies that have shown any benefit, e.g. in a double-blind controlled study spanning 6 years and involving 3000 subjects, use of Ginkgo Biloba did not result in less cognitive decline in older adults than placebo.⁷ However one epidemiological study that is of particular interest is by Hall et al.⁸ Their study showed that early life education and participation in cognitive improvement strategies factors appear to enhance cognitive reserve and delay memory decline in the early stages of dementia. They followed 488 cognitively intact community residing individuals with clinical and cognitive assessments every 12 to 18 months. They then assessed the effect of self-reported participation in cognitively stimulating leisure activities on the onset of memory decline as measured by the Buschke Selective Reminding Test in individuals who developed incident dementia. What they found was quite striking - each additional day of enhanced cognitive activity at baseline delayed the onset by 0.18 years. Level of education did not change the effect of cognitive activities. This study along with other similar reports suggests that there may be some truth that exercising our brain, just as much as exercising our body, may be of benefit. Clearly it will do no harm.

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