ALZHEIMER'S DISEASE

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June 2013

Although Alzheimer's disease (AD) was first characterised more than 100 years ago, there is still no effective treatment for the disorder. Today, it is the most common form of dementia, accounting for about 55% of all cases, thus imposing enormous social and economic burden on society. It is estimated that 278,707 Australians are currently living with dementia and the number is projected to increase to almost one million by 2050 (Access Economics, Australia). Ten years ago, dementia was the 6th leading cause of death in Australia but today it is the third leading cause of death (Australian Bureau of Statistics). Therefore any disease-modifying treatment could potentially reduce the cost to society.

The age of onset for AD is commonly after the age of 65 but people with a genetic form of the disease (less than 10% of cases) will show signs and symptoms much earlier. Clinically, people with AD show a deterioration of the ability to form new memories. In particular, memory for facts, events and the meaning of words gradually diminish, although memory of the most distant past may persist longer. They show deficits in logical thinking and planning as well as being disoriented in space and time. Problems with language appear and gradually patients demonstrate changes in personality. All these changes may be assessed by neuropsychological examinations.

Definitive diagnosis of AD is frequently confirmed at autopsy, although potential new tests are being developed, including the use of brain imaging (MRI, PET) and monitoring of abnormal brain protein levels in blood, urine and/or cerebrospinal fluid. The brains of AD patients show a general loss of brain volume, with the hippocampus and frontal lobes most severely affected. On a cellular level, AD is characterised by three major neuropathological hallmarks: the extracellular deposition of beta-amyloid (Aβ) plaques, the formation of plaque-associated dystrophic neurites and the presence of neurofibrillary tangles (1, 2). Aβ peptide is derived from the amyloid precursor protein (APP) and is a normal component of the body. However in AD, Aβ undergoes a conformational change and becomes neurotoxic, ultimately aggregating into insoluble fibrils and sheets typical of plaques. An unresolved issue is why Aβ became insoluble and formed plaques. The neurofibrillary tangles are bands of abnormal filamentous material that accumulates in the neuron cell bodies and dendrites. The tangles are primarily composed of the microtubule-associated protein called tau that shows abnormal phosphorylation and are associated with alterations in microtubule, thereby interfering with normal transport functions. These neuropathological changes reflect initially abnormal cell function, and ultimately cause cell death. Although the presence of amyloid plaques and neurofibrillary tangles is a characteristic of AD, it does not always concur with the degree of clinical impairment. More recent studies have suggested that neuronal and synaptic loss may be a more reliable predictor of functional impairment.

A current direction of drug treatment for AD is focused on the role of the neurotransmitter acetylcholine as early research showed that cells that make this neurotransmitter, such as those located in the base of the forebrain, are vulnerable to degeneration. Hence the strategy involves administration of drugs that are acetylcholinesterase inhibitors which act to prevent the breakdown of acetylcholine. These drugs do not arrest the course of the disease but are able to produce a modest slowing of cognitive decline.

In recent years, substantial data derived from genetics, animal modeling and biochemical research support the notion that Aβ, the major component of amyloid plaques play a central role in AD pathophysiology (3). In the normal adult, homeostasis of Aβ peptides in the interstitial fluid is delicately balanced between the process of generation from APP and the rate of clearance from the

brain via transport across the blood-brain barrier (4). In AD, this homeostasis is disrupted. Thus a common target in research is reduction of Aβ production or increased rate of clearance. Efforts to limit Aβ production have focused on developing compounds that inhibit the proteolytic enzymes β- and γ-secretase (5). However despite considerable research on this front, few chemical compounds have reached the clinical trial phase. Hence it is paramount to develop new strategies that are relevant both in prevention and in treatment following onset of disease. In this regard, a better understanding of mechanisms regulating AD pathogenesis is necessary as a preventative and protective measure against the disease.

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