ALZHEIMER'S DISEASE
Alzheimer's Disease
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Alzheimer's Disease (AD) is a neurodegenerative disease which clinically presents with key symptoms including a progressive decline in memory, impairments in speech, language, spatial orientation, and dysfunction in the sensori-motor systems and is the most common cause of dementia(Martins, Hone et al. 2006)(Martins, Hone et al. 2006; Ames 2010). The symptoms of AD may occur as early as the age of 40 years, but is most commonly seen after the age of 60 years. AD is also characterised neuropathologically by the deposition of misfolded proteins, particularly aggregated b-amyloid peptide in the form of plaques and intracellular neurofibrillary tangles (Bertram, Lill et al. 2010). These changes are often accompanied by microvascular damage, including vascular amyloid deposits and inflammation of the affected brain regions. Loss of neurons and synapses in the neocortex, hippocampus and other subcortical regions of the brain and also common features of AD (Puglielli, Tanzi et al. 2003). The memory loss and neurodegenerative damage of AD are essentially irreversible.

Due to the fact that dementias are relatively common, have relatively long duration, and lead to marked impairment in social and occupational functioning, their burden level is high (Brookmeyer, Evans et al. 2011). It was estimated that $156 billion is spent annually to care for patients with dementia worldwide(Wimo, Jonsson et al. 2006). In Australia, the costs associated with aged care spending are estimated to be around 1% of GDP (Access Economics, 2009). By the 2060s, spending on AD is set to outstrip that of any other health condition. It is projected to be $83 billion (in 2006-07 dollars), and will represent around 11% of the entire and residential aged care sector spending (Access Economics 2009). A five-year delay in the onset of the disease is projected to reduce expenditure by 50%, projected to save $8.9 billion per year in 2032 and $41.4 billion by 2062. It is expected that a successful treatment for AD would cut-down global costs by 30-40%, however unfortunately no curative drugs have so far been developed for AD. Until a treatment is found, research into prevention and delay of onset of AD is necessary. The etiology of AD has been strongly attributed to genetic makeup, however it has been debated that environmental factors (such as diet and viruses) are just as important in onset of AD (Grant, Campbell et al. 2002).

Genetics

Genetically, AD is usually divided into two forms: (1) familial cases with inheritance of predominantly early-onset (<60 years, early-onset familial AD (EOFAD)), and (2) more sporadic cases of AD with less apparent familial inheritance and usually of later onsetage (LOAD; +60 years; Bertram, Lil et al. 2010)EOFAD is caused by autosomal dominant inheritance of mutations in the amyloid precursor protein (APP) in 50% of families, whereas the defective gene(s) in the remainder have yet to be identified(Rubinsztein 1997).

The majority of AD cases are LOAD cases, and are not thought to be due to genetic mutations. Many studies have confirmed that an increased frequency of the APOE-4 allele in AD and the association of the APOE-4 allele with LOAD(Cacabelos 2000). Apolipoprotein E is a protein constituent of both triglyceride-rich lipoproteins (TRL) as well as high density lipoproteins (HDL), which plays an important role in liver uptake of TRL remnants (Lahoz, Schaefer et al. 2001). It is the most abundant apolipoprotein in the cerebrospinal fluid, and it has been associated with growing neurons as well as neuron repair (Mahley 1988). It has three common alleles; E2, E3 and E4. The association betweenincreased risk for AD and APOE-4 continues to be by a margin the lead association finding even in modern-day genetic studies of late on-set of AD. In contrast to APOE-4, a protective effect of APOE-2 for late on-set of AD has also been proposed. The rarer APOE-2 allele appears to exert protective effects (or ''healthier aging'') when inherited with the APOE-3 allele as

compared to homozygous APOE-3 allele carriers, a finding that has been consistently replicated (Bertram, Lill et al. 2010). Along with AD risk, the APOE gene has also been linked to numerous other neuropsychiatric disorders as well as a number of cardio and cerebrovascular diseases (Peck, Smeeth et al. 2008). Studies have shown that the presence of the E4 allele is associated with elevation in Low-Density Lipoproteins (LDL) cholesterol, while E2 is associated with decreased levels in LDL cholesterol (Davignon, Gregg & Sing, 1988). Furthermore, a meta-analysis by Dallongeville, Lussier-Cacan et al. (1992) showed that participants with the E2 and E4 alleles had higher triglyceride levels than subjects with the E3 allele. Finally, a study by Lahoz, Schaefer et al. (2001)conducted on subjects from the Framingham Heart Study, found that the presence of the E4 allele resulted in a significantly increased odds for cardiovascular disease in men (odds ratio of about 61% with adjustments for age and 63% with adjustments for both age and other risk factors). In women, the odds ratio was at 48%, but did not reach statistical significance due to the smaller number of cardiovascular events (Lahoz, Schaefer et al. 2001). Since APOE genotyping is most evidently linked to both cardiovascular risk and cognition, the avenue of vascular effects on cognition is open to exploration. Furthermore environmental factors have been purported to be just as important as genes in the on-set of AD.

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