Alzheimer's Disease:
A brief overview of Alzhiemer's disease

Dr Adele Woodhouse (BSc, Hons, PhD)
Wicking Dementia Research and Education Centre, University of Tasmania
23/06/2013

Alzheimer's disease (AD) is the most common form of dementia. The pathological hallmarks of AD include β-amyloid (Aβ) plaques, dystrophic neurites and neurofibrillary tangles (NFTs). All of these pathological hallmarks involve abnormal insoluble protein aggregates that have the capacity to disturb normal cellular functioning (Woodhouse et al., 2006). However, there is disagreement within the AD literature as to whether it is Aβ plaques, soluble Aβ or NFTs that are the primary causative agent of AD. AD-associated pathology appears first in the limbic and basal frotal, temporal and occipital cortices and subsequently spread to the remaining areas of the cerebral cortex (Braak and Braak, 1991). This burden of pathology increases as AD progresses, eventually resulting in substantial brain atrophy, which is at least partially due to overt neuronal degeneration and death.

Alzheimer's disease is diagnosed with neurophsycological testing, of which there are several types (Karttunen et al., 2011; Harrison 2013). The first symptoms observed are generally mild-cognitive impairments including language difficulties, attention deficits and memory impairments especially with respect to the formation of new memories (Price et al., 1993; Arnaiz and Almkvist, 2003). However, recent studies suggest that the mild-cognitive deficits in early or preclinical AD may be more widespread in nature (Salmon, 2012) and associated with behavioural symptoms (Karttunen et al., 2011). Furthermore, not all people that present with mild-cognitive impairments will progress to a diagnosis of AD (Arnaiz and Almkvist, 2003; Robert et al., 2006; Klekociuk and Summers; 2012). Ongoing research at the Wicking Dementia Research and Education Centre are currently investigating whether we can better predict which patients with mild-cognitive impairment will progress to a diagnosis of AD. As the disease progresses cognitive impairments increase; language skills deteriorate (including oral skills, reading and writing), deficits in executive function develop (planning/judgement), although long-term memory (the oldest memories) remains intact until the end-stages of disease (Carlesime and Oscar-Berman, 1992; Price et al., 1993). Eventually in the late stages of AD long-term memories will also be lost, motor skills are impaired, communication becomes difficult and other behavioural symptoms occur, most commonly agitation, anxiety and irritability (Price et al., 1993; Mega et al., 1996; Karttunen et al., 2011). AD patients will become less independent as the disease progresses over time requiring increasing care, with the late stages commonly spent bedridden.

There are presently no effective treatments to slow down the progression or to decrease the symptoms of AD (Parnetti et al., 1997). Currently, the therapies most commonly available for AD patients are cholinesterase inhibitors, which enhance cholinergic neurotransmission (Brion, 1996; Brodaty et al., 2001) and N-methyl-D-aspartate (NMDA) glutamate receptor antagonists (Livingston and Katona, 2004). However, the currently available cholinesterase inhibitors and NMDA antagonist therapeutics for AD only decrease the clinical symptoms of AD in subset of patients, and this reprieve is usually only temporary, as these therapeutics do not affect disease progression (Parnetti et al., 1997). Thus, there is dire need for therapeutic interventions that either slow or stop the progression of AD.

Assuming that Aβ plaques are the primary etiological agent of AD, two possible approaches to treating AD exist: to prevent Aβ accumulation and plaque formation or to protect neurons against the damaging effects of Aβ (Vickers et al., 2000). There are a range of strategies being investigated for the development of new AD therapeutics that include but aren't limited to: anti-inflammatory drugs, dietary supplements and antioxidants, cytoskeletal stabilising drugs, drugs that modify the production of Aβ from its precursor protein, Aβ aggregation inhibitors, increasing Aβ clearance from the brain, drugs that alter the connections between nerve cells and drugs that alter the activity of nerve cells. As the number of promising therapeutics in animal model of AD that have translated into successful clinical trials are very few, there is an increasing focus on developing combination therapies that incorporate multiple drugs acting via different approaches for the treatment of AD (http://www.alzforum.org/new/detail.asp?id=3517),

A better understanding of the etiology of AD including the link between Aβ deposition and the neuronal pathology and abnormal neuronal function in AD will lead to more effective treatment of the disease. This highlights the importance for continuing research into the disease mechanisms. It should also be noted that successful application of therapeutics in clinical settings would need to occur early in the disease process before substantial neuronal degeneration and death has occurred. The accurate diagnosis of preclinical AD cases prior to the clinical diagnosis of AD utilising a combined biomarker/imaging approach may soon be possible (Borroni et al., 2007; de Leon et al., 2007; Bateman et al., 2012) and represent another important area of ongoing research.

If you would like to learn more about dementia and Alzhiemer's disease, including risk factors, symptoms, diagnosis, medical management, disease progression, living with dementia, brain anatomy, pathology and future research pathways, you can access the Wicking Dementia and Research Education Centre's free Massive Open Online Course (MOOC) at http://www.utas.edu.au/wicking/wca/mooc.

References

Arnáiz E, & Almkvist O (2003) Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. Acta Neurol Scand Suppl 179: 34–41.

Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC;Dominantly Inherited Alzheimer Network (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease N Engl J Med 30: 795-804.

Borroni B, Premi E, Di Luca M, Padovani A (2007) Combined biomarkers for early Alzheimer disease diagnosis. Curr Med Chem 14:1171-1178.

Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239-259.

Brion JP (1996) The neurobiology of Alzheimer's disease. Acta Clinica Belgica 51:80-90.

Brodaty H, Ames D, Boundy KL, Hecker J, Snowdon J, Storey E, Yates MW (2001) Pharmacological treatment of cognitive deficits in Alzheimer's disease. Med J Aust 175:324-327.

Carlesimo GA, Oscar-Berman M (1992) Memory deficits in Alzheimer's patients: a comprehensive review. Neuropsychol Rev 3: 119-169.

De Leon MJ, Mosconi L, Blennow K, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Tsui W, Saint Louis LA, Sobanska L, Brys M, Li Y, Rich K, Rinne J, Rusinek H (2007) Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. Ann N Y Acad Sci 1097:114-145.

Harrison J (2013) Cognitive approaches to early Alzheimer's disease diagnosis. Med Clin North Am 97:425-38.

Karttunen K, Karppi P, Hiltunen A, Vanhanen M, Välimäki T, Martikainen J, Valtonen H, Sivenius J, Soininen H, Hartikainen S, Suhonen J, Pirttilä T; ALSOVA study group (2011) Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. Int J Geriatr Psychiatry. 5: 473-82.

Klekociuk S Z, Summers M (2012) Longitudinal profiling of mild cognitive impairment subtypes. Alzheimer’s & Dementia 8, Suppl 1: 555.

Livingston G, Katona C (2004) The place of memantine in the treatment of Alzheimer's disease: a number needed to treat analysis. Int J Geriatr Psychiatry 19:919-925.

Mega MS, Cummings JL, Fiorello T, Gornbein J (1996). The spectrum of behavioral changes in Alzheimer's disease. Neurology 46:130-135.

Parnetti L, Senin U, Mecocci P (1997) Cognitive enhancement therapy for Alzheimer's disease: The way forward. Drugs 53:752-768.

Price BH, Gurvit H, Weintraub S, Geula C, Leimkuhler E, Mesulam M (1993) Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease. Arch Neurol 50:931-937.

Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M, Legrain S, Dubois B (2006) Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: a one-year follow-up study. Clin Neurol Neurosurg 108:733–736.

Salmon DP (2012) Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. Curr Top Behav Neurosci. Epub.

Vickers JC, Dickson TC, Adlard PA, Saunders HL, King CE, McCormack G (2000) The cause of neuronal degeneration in Alzheimer's disease. Prog Neurobiol 60:139-165.

Woodhouse A, West AK, Chuckowree JA, Vickers JC, Dickson TC (2005) Does β-amyloid plaque formation cause structural injury to neuronal processes? Neurotoxicity Research 7:5-15.