

ALZHEIMER'S DISEASE
Alzheimer's disease (AD)
Dr Helen Macpherson (PhD)
Swinburne University
June 2013

Content

In the elderly, Alzheimer's disease (AD) is the most common form of dementia and is characterized by the DSM-IV as a marked decline from previous functioning in short term memory, and a severe disruption to language, planning or visual processing (American Psychiatric Association, 2000). Those with AD also experience disturbances to global cognitive function and the ability to care for themselves. Individuals who have experienced a decline in cognition which is greater than expected for their age and education level, but is not severe enough to meet the criteria for dementia are classified as in the stage of Mild Cognitive Impairment (MCI) (De Mendonca, Guerreiro, Ribeiro, Mendes, & Garcia, 2004). Activities of daily living are maintained in those with MCI, whereas they are impaired in AD (Petersen, 2004). In many cases MCI represents a preclinical stage of AD, particularly in those with the amnesic form of MCI (Mitchell & Shiri-Feshki, 2009).

The major risk factor for AD is age (Carr, Goate, Phil, & Morris, 1997). Other predictors of AD include vascular risk such as hypercholesterolaemia, hypertension, atherosclerosis, coronary heart disease, elevated homocysteine levels (Duron & Hanon, 2008; Lange-Asschenfeldt & Kojda, 2008; Selhub, 2006), oxidative stress (Polidori, 2004), obesity (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003) and diabetes (Ott et al., 1999).

The neuropathological process of AD has been well documented. Enlargement of ventricles and hippocampal atrophy occurs due to substantial loss of brain tissue, nerve cells, synapse and dendrites, caused by the presence of neurofibrillary tangles and beta amyloid plaques (A β) (Kidd, 2008; Petrella, Coleman, & Doraiswamy, 2003; Rusinek et al., 1991). Pathologically, these AD-characterising features are caused by the deposition of abnormal proteins. Neutritic or senile plaques are extracellular deposits of A β surrounded by dystrophic neurites, reactive astrocytes, and microglia, whereas tangles are intracellular aggregates formed by a hyperphosphorylated form of the microtubule-associated protein tau (Blennow, de Leon, & Zetterberg, 2006). According to the amyloid cascade hypothesis, the pathogenic mechanism of AD is an imbalance between the production and clearance of A β in the brain, leading to neuronal degeneration and dementia (Hardy & Higgins, 1992). Damage initially occurs to the large cortical neurons subserving cognition in the temporal lobe structures and pyramidal cells found in the cortical memory pathways, then later in the remaining neocortex and association areas (Braak & Braak, 1991; Norfray & Provenzale, 2004). Mechanisms such as neurovascular dysfunction, inflammatory processes, oxidative stress, and mitochondrial dysfunction are thought to elicit this neuropathology (Blennow et al., 2006).

Additionally, there is evidence that vascular impairments play a role in the cognitive decline seen in AD (de la Torre, 2002), although the extent of this relationship is still largely unknown. Dysfunction of the cerebrovascular system is often observed early in the onset of AD. Impaired structure and functioning is seen in virtually all cell types of the neurovascular unit (cerebral blood vessels and associated cells including neurons, glia, astrocytes, pericytes, smooth muscle cells and endothelial cells) (Iadecola, 2010). Impaired functioning of the neurovascular unit can lead to alterations in blood flow regulation and perfusion, disruptions of the blood-brain-barrier, depletion of the vascular reserves and impaired neuro-regeneration mechanisms, such as neurogenesis and angiogenesis (Pimentel-Coelho & Rivest, 2012). These alterations may have a substantial impact on the gradual degeneration of cognition seen in AD. The characteristic accumulation of A β in blood vessels in AD is associated with cerebrovascular deficiencies such as hypercontractility and reduced blood supply to the brain. The structural and functional integrity of the brain is dependent on a constant and well-

regulated blood supply, and disturbances of the cerebral blood flow can lead to brain dysfunction, cognitive decline and death.

Recent emerging evidence of the role of cerebrovascular function in the pathogenesis of Alzheimer's disease has highlighted the need for more research to be conducted in this area (Glodzik, Randall, Rusinek, & de Leon, 2013). Therapeutic options to improve cerebral blood flow in AD patients could potentially have a substantial effect on slowing and/or delaying the onset of cognitive deterioration.

References

- American Psychiatric Association. (2000). *Diagnostic criteria from DSM-IV-TR*. Washington, D.C.: The Association.
- Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *Lancet*, *368*(9533), 387-403.
- Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, *82*(4), 239-259.
- Carr, D. B., Goate, A., Phil, D., & Morris, J. C. (1997). Current concepts in the pathogenesis of Alzheimer's disease. *American Journal of Medicine*, *103*(3A).
- de la Torre, J. C. (2002). Alzheimer Disease as a Vascular Disorder: Nosological Evidence. *Stroke*, *33*(4), 1152-1162. doi: 10.1161/01.str.0000014421.15948.67
- De Mendonca, A., Guerreiro, M., Ribeiro, F., Mendes, T., & Garcia, C. (2004). Mild cognitive impairment: Focus on diagnosis. *Journal of Molecular Neuroscience*, *23*(1-2), 143-147.
- Duron, E., & Hanon, O. (2008). Vascular risk factors, cognitive decline, and dementia. *Vascular Health and Risk Management*, *4*(2), 363-381.
- Glodzik, L., Randall, C., Rusinek, H., & de Leon, M. J. (2013). Cerebrovascular Reactivity to Carbon Dioxide in Alzheimer's Disease. *Journal of Alzheimer's Disease*, *35*(3), 427-440. doi: 10.3233/jad-122011
- Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., & Skoog, I. (2003). An 18-year follow-up of overweight and risk of Alzheimer disease. *Archives of Internal Medicine*, *163*(13), 1524-1528.
- Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: The amyloid cascade hypothesis. *Science*, *256*(5054), 184-185.
- Iadecola, C. (2010). The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathologica*, *120*(3), 287-296.
- Kidd, P. M. (2008). Alzheimer's disease, amnesic mild cognitive impairment, and age-associated memory impairment: Current understanding and progress toward integrative prevention. *Alternative Medicine Review*, *13*(2), 85-115.
- Lange-Asschenfeldt, C., & Kojda, G. (2008). Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: From vessels to neurons. *Experimental Gerontology*, *43*(6), 499-504.
- Mitchell, A. J., & Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia - Meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica*, *119*(4), 252-265.
- Norfray, J. F., & Provenzale, J. M. (2004). Alzheimer's disease: Neuropathological findings and recent advances in imaging. *American Journal of Roentgenology*, *182*, 2-13.
- Ott, A., Stolk, R. P., Van Harskamp, F., Pols, H. A. P., Hofman, A., & Breteler, M. M. B. (1999). Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*, *53*(9), 1937-1942.
- Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183-194.
- Petrella, J. R., Coleman, R. E., & Doraiswamy, P. M. (2003). Neuroimaging and early diagnosis of Alzheimer disease: A look to the future. *Radiology*, *226*(2), 315-336.

- Pimentel-Coelho, P. M., & Rivest, S. (2012). The early contribution of cerebrovascular factors to the pathogenesis of Alzheimer's disease. *European Journal of Neuroscience*, *35*(12), 1917-1937.
- Polidori, M. C. (2004). Oxidative stress and risk factors for Alzheimer's disease: Clues to prevention and therapy. *Journal of Alzheimer's Disease*, *6*(2), 185-191.
- Rusinek, H., De Leon, M. J., George, A. E., Stylopoulos, L. A., Chandra, R., Smith, G., . . . Kowalski, H. (1991). Alzheimer disease: Measuring loss of cerebral gray matter with MR imaging. *Radiology*, *178*(1), 109-114.
- Selhub, J. (2006). The many facets of hyperhomocysteinemia: Studies from the Framingham cohorts. *Journal of Nutrition*, *136*(6).