

Alzheimer disease pathophysiology diagnosis treatment and management biology essa...

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Introduction-Dementia is a syndrome initiated by neuronal damage due to a range of diseases including Alzheimer's disease, which is the most common form of dementia in modern times. Alzheimer's is a progressive neurodegenerative disorder implying significant memory loss (Alzheimer's Association, Thies and Bleiler 2011). Patients with this condition are unable to encode new memories or retain older ones (Selkoe 2001). Neuronal loss with distinct hippocampal atrophy is characteristic. It affects as many as 15 million on a global scale. On average 8 ½ years is the span between the start of disease and death (Francis et al, 1999)The most common cause of Alzheimer's is advanced age. Age can give rise to oxidative injury and mutations in mRNA (Munoz and Feldman 2000). However, a primary cause is the presence of certain mutated genes. These include the APP, β -amyloid precursor gene, PS1 and PS2 genes (presenilin genes). These mutated proteins maybe involved in increasing A β production and also damaging synaptic vesicle transport (Munoz and Feldman 2000). Also a common polymorphism in the APOE (apolipoprotein E) gene can cause Alzheimer's. This lipoprotein has been associated with repairing the synapse upon trauma. The ϵ 4 allele has been linked to increased Alzheimer's risk; an individual with this allele may develop disease 10 years before those with ϵ 2 and ϵ 3 alleles (Munoz and Feldman 2000, (Prusiner, 2001).). Other than genetics, environmental factors such as anti-inflammatory drugs may also cause Alzheimer's, in addition enzymes producing and hydrolysing acetylcholine may be down regulated (Munoz and Feldman 2000). Figure 1 summarises possible causes of neuronal loss (Munoz and Feldman 2000). Some signs and symptoms of Alzheimer's include paranoia and delusional

ideation. Others may also involve aggressiveness and phobias. Eventually it may progress to depression (Selkoe 2001). Figure 1: Causes of neuronal loss (Munoz and Feldman 2000). Pathophysiology The pathophysiology of Alzheimer's disease may initiate through genetic reasons or "sporadic" causes. With familial Alzheimer's A β 42 production (due to mutations in genes such as APP) is increased throughout life, while sporadic Alzheimer's may see an increase of A β 42 due to increasing age. After this A β 42 may collect in the association and limbic cortices. These A β 42 oligomers then can cause slight impairment in synaptic activity. Eventually these oligomers may deposit as diffuse plaques. All of this may result in inflammatory responses. Thereafter, ionic homeostasis may be down regulated resulting in oxidative injury and stress. Subsequently kinase and phosphatase activity is disrupted leading to tangles. All of this ultimately causes neuronal loss, synaptic damage and neurotransmitter shortages leading to dementia with presentation of significant cognitive impairment resulting in memory loss and cognitive disability (Selkoe 2002). Figure 2: Orange- amyloid plaques, pink- neurofibrillary tangles (Tavee and Sweeney 2010) A β 42 production may be aggravated by cleavages of the amyloid precursor protein via the action of β secretases at position 671 and γ secretases at position 711 or 713. This results in the production of A β 40-42 (Prusiner, 2001). Even prior to plaque formation A β 42 aggregates can cause damage in the CNS (Prusiner, 2001). Excessive NMDA receptor activation by glutamate may lead to excitotoxicity of the cell and may also activate the APP gene to increase A β 42. Glutamatergic neurotransmission can be significantly affected in Alzheimer's due to oxidative stress- this system has an important role in

cognition and memory (Butterfield 2003). Other research has Research also suggests that Bacteria such as the gram negative spirochetes can bear amyloidgenic protein that can induce an inflammatory reaction via cytokines, that can contribute to oxidative stress via free radical generation. It may also lead to apoptosis. (Miklossy J, 2008). Further research has suggested that mitochondria may have a role in oxidative stress. Accumulation of ROS (reactive oxygen species) in contrast to antioxidant deficiency can cause serious effects. Mitochondria are heavily responsible for ROS production. If the mitochondria are mutated, somatically or sporadically this can lead to increased ROS production (Yan et al, 2012). Also, it has been related in in vitro studies that the overexpression of APP (due to A β induction) can result in mitochondria fission- causing great disruption, including the increase of ROS. Eventually this disturbance can cause progressed synaptic loss (Yan et al, 2012). Figure 3: Effects of mitochondrial DNA damage (Yan et al, 2012).

Diagnosis Neuroimaging is a major field in the diagnosis of Alzheimer's disease. Alzheimer's disease should be diagnosed after excluding other possible types of dementia. Neuroimaging for Alzheimer's present atrophy centered mainly at the medial temporal lobe, other dementias may present wider atrophy (O'Brien 2005). This field can be further divided into two types: structural and functional imaging (O'Brien 2005). Structural imaging includes techniques such as the CT scan and MRI scan. They aim to visualise the structure of the brain and to determine any anatomical blemishes within the brain morphology (O'Brien 2005). A patient with Alzheimer's disease may exhibit medial temporal lobe atrophy on a CT scan, although this technique sometimes does not reveal any atrophy within Alzheimer's

patients (O'Brien 2005). The MRI scan provides higher resolution imaging which can differentiate between the grey and white matter of the brain, possibly showing minute changes within the vasculature of the white matter and showing distinct hippocampal atrophy (within the medial temporal lobe) in most patients, even during the initial stages of disease (O'Brien 2005).

Figure 4 shows hippocampal atrophy in an Alzheimer's patient as a pose to the control. Figure 4: A coronal MRI scan showing hippocampal atrophy in patient A (Alzheimer's disease) in contrast to patient B (control) (O'Brien 2005) Figure 2: MRI scan (coronal view) showing clear evidence of

hippocampal atrophy in a case of a) Alzheimer's disease compared to b) a control subject. Functional imaging aims to reveal information about the physiology of the brain. A physiological symptom of Alzheimer's is hyperperfusion (excessive blood perfusion) (O'Brien 2005). This can be visible through a functional imaging technique known as a Perfusion SPECT.

Figure 5 shows an example of this. SPECT can be investigated for use to further detect other neurochemical factors by the use of radioactively labelled ligands- one such ligand of interest is for the nicotinic receptor, which is implicated very early in Alzheimer's (O'Brien 2005). Figure 5: A Perfusion SPECT scan displaying biparietal and bitemporal hyperperfusion in patient A (Alzheimer's disease) in contrast to patient B (control) (O'Brien 2005) Figure 3: Perfusion SPECT scan showing evidence of biparietal and

bitemporal hyperperfusion in a) an Alzheimer's disease case compared to b) a control subject. Other than neuroimaging, certain cognition tests may also be used to diagnose Alzheimer's. These include for example, asking a patient to draw a clock and the MMSE test which tests various parts of cognition

such as memory and orientation giving a score of 0-30 that indicates the level of cognitive impairment (the higher the score, the more impairment) (Sheehan 2012). Other tests include the Barthel index and the Montreal Cognitive Assessment (Sheehan 2012). Other diagnostic possibilities are being investigated in research. Various studies have proposed that high levels of cerebral spinal fluid versus low A β 42 levels is specific for Alzheimer's, this can provide a possible biomarker that can be used to diagnose Alzheimer's and differentiate it from other dementias (Agarwal and Tripathi 2011). Also, the APOE gene is currently being researched for possible diagnostic use via APOE genotyping (Sun et al. 2012). Treatment of Alzheimer's disease

Drug therapies: Currently there is no cure for Alzheimer's, all therapies provided aim to reduce cognitive impairment. Both drug therapies and non-drug therapies can be used to achieve this. A major category of drugs used for Alzheimer's therapy are cholinesterase inhibitors. These aim to avert the reduced cholinergic transmission in the synaptic clefts (Herrmann et al. 2011). These inhibitors stimulate the production of the neurotransmitter acetylcholine by inhibiting the action of acetylcholinesterase, an enzyme involved in hydrolysing acetylcholine This implies improved cognition (Herrmann et al. 2011). Other mechanisms by which cholinesterase inhibitors work include expressing nicotinic receptors and also by expressing different isoforms of acetylcholine- other mechanisms have also been related (Herrmann et al. 2011). The current cholinesterase inhibitors include donepezil, rivastigmine and galantimine. Donepezil works as a reversible inhibitor binding to acetylcholinesterase, causing inhibition of acetylcholine degradation as the drug (donepezil) is hydrolysed instead;

evidence suggests that donepezil also prevents apoptosis and reduces A β production (Herrmann et al. 2011). In a study by Rosenblatt et al of Alzheimer's patients in assisted living facilities, donepezil treatment showed improvement in MMSE scores. Most of those who received the 10mg also had a side effect such as nausea. However there was general improvement through donepezil treatment as can be seen in figure 6 (Rosenblatt et al. 2010). Figure 6: Efficacy of donepezil as demonstrated through improved MMSE scores (Rosenblatt et al. 2010)Rivastigmine may have a longer effect, with the potential of inactivating acetylcholinesterase for as long as upto a day. This drug has also been associated with the inhibition of butyrylcholinesterase, another enzyme thought to be linked to Alzheimer's. Rivastigmine can be administered as a daily transdermal patch (Herrmann et al. 2011). The third cholinesterase inhibitor of significance is galantamine. Galantamine inhibits acetylcholinesterase reversibly and also may modify the shape of the nicotinic acetylcholine receptor to enhance cholinergic transmission (Herrmann et al. 2011). A study by Santoro et al on cholinesterase inhibitors in Italy suggested that after 12 weeks, there was worsening of MMSE scores and also ADAS-Cog scores (Santoro et al. 2010)Figure 7: Efficacy of cholinesterase inhibitors as demonstrated in a study of Italian patients (Santoro et al, 2010)Apart from cholinesterase inhibitors, another drug that may be used is Memantine, a N-methyl-d-aspartate receptor (NMDA) inhibitor. This drug is particularly for more severe cases of disease. NMDA is a type of an ionotropic receptor for the neurotransmitter glutamate. It has been associated with cognition and hence has been implicated within Alzheimer's disease. Upon the binding of

glutamate to the receptor, the opening of a channel that allows calcium ions to enter the cell initiates. Due to a certain trauma, excessive levels of glutamate may remain, meaning the influx of calcium ions. If this continues it can lead to excitotoxicity of the cell and consequently apoptosis.

Memantine may help reduce this excitotoxicity by antagonistically blocking the NMDA receptor channel (in a non-competitive manner, meaning it needs glutamate to stimulate the channel. This eventually aims to regulate the influx of calcium cells. A Daily dosage of upto 20mg maybe prescribed. (Kelly M Makino and Anton P Porsteinsson 2011)Future drugs are currently investigating the possibility of these mechanisms in treating Alzheimer's: limiting the generation of A β and A γ secretases, averting cerebral plaques forming, preventing A β aggregates and provoking an immune response to clear A β . The neuro-inflammatory and mitochondrial dysfunction pathways are also being studied (Herrmann et al. 2011). One potential group of drugs is currently focusing on CDK inhibition. Toxicity via A β can be averted by CDK inhibition, though this can only achieve partial neuronal rescue as shown in this study. Other molecules may need to be co targeted in order for CDK inhibition to fully work (Xu et al. 2013). http://www.sciencedirect.com/cache/MiamilImageURL/1-s2.0-S1873506112001183-gr4_lrg.jpg/0?wchp=dGLbVBA-zSkzSFigure 8: Relative cell viability with various CDK inhibitors in hiPS cell derived neurons (from stem cells) (Xu et al. 2013)Non Drug Therapies: In order to achieve reduced cognitive impairment, other methods may also be utilised. Medical foods are one area of interest. For example, foods such as AC -1202, which is provided as a powder to be consumed mixed with water, can cause positive effects due to nutrients such

as glycerine and caprylic acid, nutrients which have been associated with cognitive enhancement. Multi-nutrient drinks like Souvenaid bearing omega - 3 fatty acids and vitamin C have been linked with cognitive enhancement. Despite side effects, studies have been positive, showing some enhancement in cognition, further studies are currently being conducted to analyse the possibility of medical foods in treatment (Shah 2011). Another nutrient which has been associated with cognitive enhancement is caffeine, which can increase alertness and improve mood. It is an antagonist that inhibits adenosine receptors (Dresler et al. 2013). As well as this, physical exercise has also been related to cognitive enhancement (Dresler et al. 2013). Other methods include tDCS (transcranial direct stimulation) - a non-invasive procedure placing electrodes on the scalp for neuronal stimulation via the sending of a current through the brain- this procedure however is as specific. An invasive therapy includes deep brain stimulation. This involves the surgical application of electrodes. Brain stimulation therapies aim to provoke neuronal stimulation hence instigate cognitive enhancement. Furthermore, deep brains stimulation allows access to particular regions of the brain to instigate specific responses- this is a novel possibility implicated in various neurodegenerative disorders such as Alzheimer's disease (Dresler et al. 2013). Figure 9: Deep Brain Stimulation (Laxton and Lozano, 2012)Case studyA 69 year old women presents with symptoms of worsening forgetfulness (typical of dementia). An uncle of hers also has dementia. Initially, her MMSE score is normal. Two months later the symptoms progressed to irritability; in her latest MMSE examination she failed to draw a clock properly. Upon this, Alzheimer's disease is diagnosed. Her MMSE score

gradually decreases over the next two years, with added forgetfulness and anxieties. By this point she has become more dependant, even finding it difficult to select her own clothes. Figure 10 shows clock drawing patterns of patients at different MMSE scores (Gauthier 1998). Figure 10: Clock drawings at different MMSE scores (Gauthier 1998)

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