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2007-01

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Lethbridge Undergraduate Research Journal

Lethbridge Undergraduate Research Journal
ISSN 1718-8482

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Citation:

Camille Belzil: Alzheimer's Dementia*. Lethbridge Undergraduate Research Journal.* 2007. Volume 1 Number 2.

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Abstract

Alzheimer's dementia is a complex disorder in both its symptoms and its mechanisms. While it is not a normal part of aging, its prevalence increases exponentially with age. As the 'baby-boomer' generation begins to enter the 65+ demographic in the West, we can expect to see an unprecedented number of cases of Alzheimer's in the near future. This paper discusses the methods of diagnosing and treating individuals with Alzheimer's with respect to their rights as individuals. Methods of easing the burden of caregivers through counseling and drug therapy are also covered. The etiology of Alzheimer's is discussed from a chiefly biomedical perspective, with notable attention to the genetic factors leading to higher risk of developing Alzheimer's. Lastly, social and ethical issues including

quality of care, euthanasia, and current societal values are considered.

Introduction

Alzheimer's dementia was first described by Emil Kraepelin as a behavioural syndrome in the elderly. Klunemann, Fronhofer, Wurster, Fischer, Ibach, and Klein (2002) describe the case of Johann F., a patient at Kraeplin's hospital, who was diagnosed with “presenile dementia” in the late 1800's. This patient was later admitted to the care of Dr. Alois Alzheimer in a Bavarian clinic, where the neuropathology of the disease was first described. Alzheimer's meticulous autopsies revealed miliary plaques in the brain of Johann F. and others with similar behavioural symptoms (Katzman & Bick, 2000). His work was the first to link the physical symptoms of the disease to what is now the most common form of dementia, and Kraepelin accordingly named the disorder after Dr. Alzheimer.

Alzheimer's is a primary dementia, meaning that the symptoms are a direct result of the disorder (Knox & Gekoski, 2003). The presence of this form of dementia is heralded initially by memory difficulties, beginning with poor memory for recent events. As the disorder progresses individuals with Alzheimer's begin to show language difficulties, sleep difficulties, agitation, helplessness, irritability and orientation difficulties. In the final stages of the disorder the individual is typically unable to properly communicate, becomes aggressive, performs repetitive actions, and is unable to care for themselves (Knox & Gekoski, 2003). This disorder greatly increases vulnerability to respiratory and cardiac disease as individuals near a vegetative state. Individuals suffering from Alzheimer's typically live only 10 years after the initial diagnosis. Over the later course of the disease these individuals require constant care: They sleep on disrupted cycles, and require supervision for their safety and those around them (Mace & Rabins, 1999). Alzheimer's is devastating not only for the sufferers, but also those around them and those who care for them.

‘Normal' and Dementia

In the study of abnormal psychology, dementia should be synonymous with abnormal. Nearly any aberration in cognitive function be it motor, executive, memory related or sensory qualifies as dementia (Knox & Gekoski, 2003). The word “dementia” itself refers to a state of being out of ones mind. This definition implies only that a ‘demented' individual has departed from a normal state of mind, though the word itself gives no hints as to what the proper state of mind should be. The vagueness of the term dementia leaves the expression open to interpretation. It can theoretically include anything cognitively abnormal, encompassing troublesome behaviour for which we have no better explanation.

This diagnostic loophole is crippling in that the diagnoses of dementias are based on using subjective perception of normal and applying that notion to others. In order to make a proper diagnosis of dementia, the individual (or body of individuals) making the diagnosis must collectively understand the difference between a normal state of mind and an abnormal one. This ambiguity is avoided in the practical sense. The diagnosis of all of the major dementias follows the etiology of diseases rather than the symptoms, allowing irrefutable diagnoses and sound approaches to treatments.

While the theoretical notion of dementia is vague, the dementias in DSM-IV are a group of mental illnesses with specific causes (Knox & Gekoski, 2003). This circumvents the need to understand what is normal and what is deviant. Since Alzheimer's is a disease of aging, it specifically calls into question what is normal and what is abnormal behaviour in an aging individual. What a younger individual may perceive as cognitive abnormality could just be the natural benign forgetfulness that so often accompanies old age. The persistent inclusion of the dementias (and specifically Alzheimer's dementia) in the DSM, though the majority are biological diseases, stands as evidence that people are able to subjectively distinguish between normal and abnormal behaviour. The symptoms first described by Emil Kraepelin have since been solidly linked to biological factors (Katzman & Bick, 2000). Though psychologists may never be able to define what is normal and abnormal, the case of Alzheimer's dementia shows that humans are able to subjectively perceive and differentiate between normal and abnormal despite the theoretical difficulties of defining normal behaviour.

Theories of Alzheimer's

While no single cause has been elucidated as of yet, the theories and evidence of Alzheimer's pathology fall under the umbrella of biomedical theory. The risk factors for developing the disease based on epidemiological data involve chiefly physiological factors and diet (Knox & Gekoski, 2003). Genetic correlation with probability of developing disease and time of onset also support a biomedical model. Also, Raber, Huang and Ashford (2004) have shown that Alzheimer's dementia has largely invariable pathology, largely independent of ethnicity or cultural differences. The prevalence of Alzheimer's grows significantly with age, again indicating that there are physiological risk factors that compound in elderly patients. The biomedical model is perhaps supported most by changes in the actual morphology of the brain (Knox & Gekoski, 2003). Cortical shrinkage and ventricular expansion in Alzheimer's dementia have not been linked with any specific cause or effect of the disease, but indicate that Alzheimer's has biomedical associations (Knox & Gekoski, 2003; Carmichael et al., 2006).

The correlation between education level and development of Alzheimer's dementia shown by Wilkosz, Miyahara, Lopez, DeKosky and Sweet (2006) suggests that the onset of the disorder may be more complicated than simply

genetics. This relationship has been contested by some however, and it remains controversial. If there is indeed a correlation, it could be that the biomedical model of Alzheimer's dementia is influenced by cognitive experience. Conversely, it could be interpreted as the cognitive decline being less noticeable in individuals with substantial educations. Alzheimer's dementia is almost definitely a disorder that can be explained by biomedical theory, but perhaps not to the exclusion of other theories. The relationship between cognitive experience and aging needs to be explored more thoroughly before any conclusions can be drawn.

Diagnosis of Alzheimer's

Dementia of the Alzheimer's type is catalogued in the DSM-IV as an axis I disorder (Knox & Gekoski, 2003). The key factor for diagnosing Alzheimer's and to a large degree other dementias is memory impairment. The individual must also exhibit dysfunction in one of four areas: Language (aphasia), motor function (apraxia), object recognition (agnosia), or planning, organizing, sequencing and abstracting (executive function) (American Psychiatric Association, 1994). For a positive diagnosis to be made, other types of dementias must first be ruled out. These include a variety of biological disorders with known causes, such as Parkinson's, Huntington's, HIV infection, cardiovascular disease, subdural haematoma, hydrocephalus, Creutzfeldt-Jakob's disease, folic acid deficiency, chronic alcoholism, malnutrition, hypothyroidism, brain tumours or recent brain trauma. These factors can be relatively easily ruled out with brain imaging, genotyping and history tracing. This is an important step in the diagnosis of Alzheimer's, as these disorders cause dementias that are symptomatically similar. Another important aspect to a positive diagnosis of Alzheimer's is that there must be a cognitive decline (American Psychological Association, 1994). Events such as strokes or brain trauma cause cognitive impairment, but not the continual decline seen with neurodegenerative disorders. Symptoms of Alzheimer's dementia must also be persistent, and not over the course of passing delirium. If the dementia is better associated with another psychiatric disorder such as schizophrenia or major depressive disorder, again the diagnosis is made in favour of these disorders.

Once a diagnosis of Alzheimer's dementia is made, it is categorized based on time of onset. Onset after the age of 65 is classified as late onset, and diagnosis before the age of 65 is considered early onset. Alzheimer's affects individuals typically only after the age of 65, but can affect individuals as early as the age of 40 (Canadian Alzheimer's Society, 2005). The only way to definitively diagnose an individual with Alzheimer's, again to the exclusion of other forms of dementia, is by post-mortem tissue analysis. The brains of individuals with Alzheimer's show high levels of cell death, buildup of β-amyloid protein plaques, and neurofibrillary tangles (Knox & Gekoski, 2003). These ‘plaques and tangles' are characteristic of and invariably indicate Alzheimer's pathology, and post-mortem diagnosis can be made based on their presence. Raber, Huang and Ashford (2003) have shown that neural degeneration is not

isolated but centres heavily on the hippocampus, a structure pivotal to the formation of new memories. Therefore hippocampal degeneration is another key marker to the presence of Alzheimer's dementia.

Cause

As with any complex disorder with such a wide array of symptoms, there is no single causal factor in Alzheimer's dementia. It is best treated as a sum of factors, most of which fall under the categories of genetic predisposition and environmental conditions. The broadest category of risk is genetic, specifically carried on the apolipoprotein E (apoE) gene (Canadian Alzheimer's Society, 2005). Research summarized by Raber, Huang and Ashford (2006) shows that the four variants (ε1- ε4) are associated with different risks of developing Alzheimer's dementia. The ε4 variant in particular carries the highest risk of developing Alzheimer's as well as greater risk of early onset. While only 2% of the US population is homozygous for the ε4 allele (ε4/4), they account for 16% of Alzheimer's cases. Heterozygotes for this allele (ε3/4) account for 42% of Alzheimer's cases, and individuals homozygous for the ε3 allele (ε3/3) account for 35% of the remaining cases. Interestingly, the ε2 allele has been associated with a degree of protection from developing Alzheimer's disease (Raber et al., 2006). The disproportionately high percentage of cases in individuals homozygous or heterozygous with the ε4 allele has prompted research into the function of the apoE protein, and how structural variants coded for by different alleles affect Alzheimer's pathology.

The role of the apoE protein in the body is typically to bind and transport serum cholesterol for processing (Bales et al., 1999). The different apoE variants all serve this function with varying efficacy. Raber, Huang and Ashford (2004) postulate that the ε4 variant is ineffective at serving this function, leading to higher serum levels of cholesterol. This predisposes ε4 carriers to cardiovascular disease due to higher levels of cholesterol deposition in the blood stream (atherosclerosis). The mechanism by which the ε4 allele is thought to lead to Alzheimer's is not as clear cut. In studies with transgenic mice expressing the Alzheimer's genotype, the presence of apoE is sufficient to induce the deposition of amyloid-β plaques in the brain (Bales et al., 1999). The variant apoE proteins coded for by ε1- ε4 again vary in efficacy of amyloid-β binding, with ε4 binding the most at homeostatic pH (Strittmatter et al., 1993). The mechanism by which amyloid-β proteins are subsequently deposited into plaques is unknown, but has devastating consequences.

Firstly, the deposition of amyloid-β plaques induces internalization of N-methyl-D-aspartate (NMDA) receptors in the cortex (Snyder et al., 2005). The NMDA glutamate receptors are pivotal for the process of long-term potentiation: NMDA receptor internalization could account for the learning and memory deficits characteristic of Alzheimer's dementia. Secondly Strohmeyer, Kovelowski, Mastroeni, Leonard, Grover and Rogers (2005) have shown that the presence of amyloid plaques induces an immune response by the microglia

in the brain. Subsequent release of inflammatory cytokines such as interleukin-6 and tumour necrosis factor-α causes a delocalized inflammation, which invariably leads to neuronal damage (Strohmeyer et al., 2005). This phenomenon is ostensibly responsible for the emaciated cortex and enlarged ventricles of individuals with Alzheimer's. The delocalization of this effect would also account for the variety of cognitive deficits seen in Alzheimer's dementia. Raber, Huang and Ashford (2004) also link the development of neurofibrillary tangles with different apoE isoforms, but not to the same degree as amyloid-β plaques. The ε4 allele is again associated with elevated formation of tangles characteristic of Alzheimer's pathology though the mechanism and clinical significance are still unclear (Raber et al., 2004).

Epidemiological surveys have given important clues as to environmental factors that influence the development of Alzheimer's dementia. The most notorious of these theories is level of exposure to metal ions. For example, epidemiological studies report that individuals living in areas with aluminum content in the water are more susceptible to developing Alzheimer's (Knox & Gekoski, 2003). Interestingly, this theory is somewhat supported by the 'plaques and tangles' model: amyloid-β plaque deposition is increased in relation to exposure to other metal ions such as copper and zinc, as shown by Raber, Huang and Ashford (2004). Exposure to high levels of aluminum has also been associated with increased formation of neurofibrillary tangles (Knox and Gekoski, 2003).

Infection with certain pathogens has also been associated with the development of Alzheimer's, especially herpes simplex virus type 1 (oro-facial herpes, HSV-1) and tuberculosis (Knox and Gekoski, 2003). While both infections are normally contained in the body, under certain circumstances they can become delocalized and infect brain tissue. The resulting encephalitis causes substantial damage, similar to that of the microglial inflammatory response to amyloid-β plaques. Since severe encephalitis invariably leads to a degree of dementia, it is uncertain whether HSV-1 and tuberculosis infections induce or aggravate Alzheimer's, or are symptomatically the same. Interestingly, *Helicobacter pylori*, the gastrointestinal parasite implicated in causing the majority of peptic ulcers, has also been correlated with development of Alzheimer's (Kountouras et al., 2005). The mechanism is unknown and there have been no reported cases of *H. pylori* encephalitis. The gradual degradation of the immune system is a natural part of aging, and the elderly often succumb to opportunistic infection or the reactivation of chronic infections such as HSV-1, tuberculosis and possibly *H. pylori*. With a deficient immune system, these infections can delocalize to the brain and cause encephalitis and dementia. There is little research done on the interaction between the aging immune system and the aging brain beyond these epidemiological studies, and potentially a great deal more to be learned in this area.

Treatment

Presently, all treatment of Alzheimer's (medical or therapeutical) is targeted at decreasing expression of negative symptoms and cognitive decline. There is no known way to reverse the damage or inhibit the formation of plaques and tangles. Individuals with Alzheimer's often suffer from depression as well, necessitating various treatments for that and other comorbid conditions (Mace & Rabins, 1999; Knox & Gekoski, 2003).

The first major group of drug treatments is the cognitive enhancers. Of these, acetylcholinesterase (AChE) inhibitors were the first category of drugs developed to treat individuals with Alzheimer's. Examples of these drugs include donepezil, galantamine, and the now outdated tacrine (Canadian Alzheimer's Society, 2005). By blocking its natural metabolism, these drugs allow more acetylcholine to remain in the synapses for longer and stimulate cholinergic receptors more potently. This is an interesting method of approaching treatment: While individuals with Alzheimer's do indeed have decreased cholinergic function, Kumar, Durai and Jobe (1998) show that they also have lower functioning of several of the major cortical neurotransmitters (e.g. serotonin, norepinephrine and certain neuropeptides). It is not yet proven that acetylcholine is even involved in the pathology of Alzheimer's; lowered cholinergic function could be equally well explained by the massive neuronal death in the cortex. AChE inhibitor use therefore seems unjustified in treating Alzheimer's. However stimulation of the cholinergic system, specifically the nicotinic acetylcholine receptors, improves functional memory (Giocomo & Hasselmo, 2005). In fact the stimulation of this system by smoking tobacco has been shown to be an epidemiological protective factor against the development of Alzheimer's (Knox & Gekoski). This relationship seems to vindicate the use of AChE inhibitors, if only to delay the cognitive decline associated with Alzheimer's dementia. AChE inhibitors can have undesirable side effects, such as anxiety, gastrointestinal problems, drowsiness, and in some cases liver toxicity (Canadian Alzheimer's Society, 2005).

A novel method of treatment involves NMDA antagonism. Strohmeyer, Kovelowski, Mastroeni, Leonard, Grover and Rogers (2005) show that in inflammatory reactions in the brain, neurons undergo glutamate-induced excitotoxic cell death . The death of these neurons causes further inflammation, creating a cascade effect and compounding damage similar to a stroke model. Excitotoxic cell death is caused by excessive calcium ion influx through the NMDA glutamate receptor (Strohmeyer et al., 2005). Floden, Li and Combs (2005) conjecture that the influx of calcium is toxic to the cell, activating both apoptotic and necrotic pathways. The hope of NMDA blockers, specifically the new drug memantine, is to prevent this from occuring. Memantine is thought to bind the NMDA receptor, blocking the voltage gated ion channel with a higher affinity than the native magnesium ion (Floden et al., 2005). The high affinity of the drug for the channel itself decreases influx by physically blocking calcium ions from entering the cell. This drug, conversely, has relatively benign side effects ranging from headaches to drowsiness (Canadian Alzheimer's Society, 2005). It can be safely used in conjunction with AChE inhibitors for maximum

effect.

Losing one's memory can have devastating effects on an individual, and frequently results in depression and in some cases psychosis (Jeste & Finkel, 2000; Mace & Rabins, 1999). Drug therapy for individuals with Alzheimer's dementia and comorbid conditions accordingly includes a course of antidepressants or antipsychotics. The complications arising from peripheral conditions also make behavioural therapy a useful treatment (Knox & Gekoski, 2003). While behavioural therapy cannot in any way cure or influence the biological condition, they facilitate care of individuals with Alzheimer's. Counseling for caregivers is also available to help them cope with the demanding task of caring for these individuals. These also help inform caregivers on how to promote the quality of life and safety of individuals with Alzheimer's (Knox & Gekoski, 2003). This helps caregivers to cope with behavioural symptoms in a natural manner, taking some of the emphasis off of medications.

Social/Ethical Issues

Canada and the Western world in general are currently in the wake of a massive population boom. The ‘baby boomer' generation is composed of individuals who will soon be classified as senior citizens. Following current demographic trends, in 5 years individuals over the age of 65 will represent 14.1% of the Canadian population, the highest percentage in history (Knox & Gekoski, 2003). While Alzheimer's is not in any way a normal part of aging, its prevalence increases exponentially with age. The number of individuals with Alzheimer's will likely increase at a rate proportional to the increase in elderly individuals. To compound an already troublesome situation, life expectancies continue to rise following advances in medicare. In summary, the prevalence of Alzheimer's will increase significantly in the next few decades, as will the need for long-term care for those suffering from it. The burden of providing this care will fall on the under-represented economically productive demographic. This population shift brings up the moral dilemma of how to treat such a large number of people. Providing good quality of care for individuals with Alzheimer's is becoming increasingly unfeasible due to the rising demand for long-term care facilities. The low birth rate of the baby-boomers means that there are fewer young relatives to care for their elderly parents, which can be a psychologically demanding task. Conversely, the cheapest and most viable option, care homes, typically entails poorer quality of life for individuals with mental disorders. Western society needs to reevaluate moral treatment of the elderly in order to ensure proper care.

Currently, our society holds in the highest regard the qualities of productivity and rationality (Post, 1995). An individual suffering from Alzheimer's is almost without exception unable to work, and has lost (or is fast losing) ‘rationality'. By current standards, individuals with Alzheimer's contribute nothing worthwhile to society. Similarly, in their campaigns to euthanize the mentally ill the Nazis

described the existence of the mentally ill as “lebenumwertes Leben” - Life unworthy of life (Post, 1995). This crude parallel demonstrates how though in Canada we do not euthanize the mentally ill, we hold the very same values that would justify doing so. Furthermore, it calls into question what we really mean by ‘rational' or ‘productive'. The problem of subjective perception once again arises: We base our values on what we ourselves would do and the qualities that we value in ourselves. This is a typical but unfair way of judging others: The decision making demographic typically does not suffer from neurodegenerative diseases of aging such as Alzheimer's. Assuring proper care for individuals with Alzheimer's will first necessitate a reevaluation of what it means to be a valued member of society.

A suggestion to circumvent the issue of quality of life is to legalize euthanasia. Allowing humane death could give individuals with Alzheimer's the choice to escape from a chronic and terminal illness. Euthanasia in the case of Alzheimer's is a particularly troublesome issue. Firstly, requests for euthanasia in these individuals are rare (Post, 1995). This is likely due to cognitive degradation, misunderstanding and confusion as to their situation. Allowing caregivers to opt for euthanization of a relative with Alzheimer's dementia on his or her behalf is another possibility, but raises weighty moral issues. This predicament again calls into question societal values of productivity and rationality, and whether we have the right to impose our values on individuals who may not share our point of view. The question of euthanasia also requires that we are able to quantify suffering in another individual in order to make the best decision on their behalf, which is theoretically impossible. Most obviously, allowing euthanasia presumes that we as a society have the moral authority to end life. These problems currently have no answer. Caring properly for the growing number of individuals with Alzheimer's will no doubt call into question our ethics as a society.

There are an alarming number of individuals who will develop Alzheimer's dementia in the next few decades. Within 10 years, an individual can cease being a contributing member of society and become a substantial burden on relatives and caregivers. As the elderly population grows, so does the need to understand the mechanisms of this disease. Novel treatments and diagnostic measures are increasingly geared at making it a more manageable disease for caregivers as well as those suffering from it. Researchers have made large advances in elucidating the exact cause of Alzheimer's and continue to make promising discoveries, but there is little hope of a cure. Alzheimer's dementia is a looming problem that needs to be fully explored by science and research, but always keeping in mind that those who suffer from it are human beings and are valuable to society.

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Lethbridge Undergraduate Research Journal
ISSN 1718-8482