Alzheimer's Disease:

A Look Into the Enemy of the Elderly

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Abstract

Alzheimer's Disease (AD) is the single most common cognitive disorder among the aged. Nowadays, it is becoming more prevalent due to global increases in life expectancy and thus a larger population over 65 years old. This overall aging has an economic and social impact; caring for patients with Alzheimer's costs the United States over 40 billion dollars annually (Ionedes, 1992), and in developing countries ¾ of citizens will be over 60 by 2025, footing a bill these nations cannot handle (Marques, Oliveira, Outeiro, & Pereira, 2012). Therefore, it is important for individuals to be aware of AD and its affects on the body. An excess of the amyloid-beta peptide and TAU protein targets neurons and their synapses in the human brain, causing an eventual and total loss of the functions of language, memory, motor and recognition. Those with the disease are ill fated towards death, which is a calamity in the lives of millions of families. There is no conclusive cure or pathology, and debates of definition and clinical testing surrounding these categories, essential to understanding Alzheimer's Disease, continue. Genes, epigenetics, and the environment all play confounding roles in the etiology. RNA-Sequencing helps scientists analyze pictures of changing tissue, but medical care is restricted to therapy and psychotropic drugs still in their prematurity. Alzheimer's Disease is an unsolved problem, but its answers are more demanded now than they ever have been.

An old adage states individuals improve with age, growing both wiser and more perceptive. Although age may benefit some, it is the very thing that is killing others. As the single known risk factor for Alzheimer's Disease (AD), growing older increases susceptibility to cognitive problems rather than keeping them at bay. Over 90 percent of cases of AD occur after age 65, but elderly and medical professionals alike remain confounded by the disease's biological markers (Marques et al., 2012). Its etiology is determined to be multifactorial, yet the medical community has not universally accepted any pathological theories (American Psychiatric Association, 2000). Researchers continue to look for ways to combat AD in the early stages, and have progressed through studies of postmortem RNA-Sequencing and transcriptomic (RNA snapshot) studies (Sutherland, Janitz, & Kril, 2011). Although scientists can: observe genetic and environmental modifications in Alzheimer's-affected DNA, form a comprehensive list of symptoms, and confidently diagnose AD, they have not been able to establish a definitive pathogenesis for the disorder, which still makes preventative treatment only a goal for the future.

Background Information/Prevalence

AD affects the central nervous system, beginning with the hippocampus and the entorhinal cortex (Marques et al., 2012). Dementia is the central characteristic, producing a loss of cognitive functions (memory, language, and executive). AD is distinguished from other forms of lunacy by the period of life in which it mainly occurs, the latter half (age 65 and older), known as late-onset (Sporadic AD). In fact, its prevalence surges as an individual grows old; 11 percent of males and 14 percent of females at age 85 escalate to 36 percent of males and 41 percent of females at age 95 (American Psychiatric Association, 2000). Because age is the central cause, AD is more prevalent now than it ever has been, due to the overall maturation of the human population (partially tied to the post-World War II baby boom). Sixty percent of all dementia is

of the Alzheimer's type, making it the most common neurodegenerative disease linked to the elderly (Sutherland et al., 2011). Early-onset AD does exist under age 65, but these cases are much less common, as they stem mainly from either Down Syndrome related complications or inherited mutations in genes (Family AD), accounting for only three percent of diagnoses. Other possible risk factors are past problems with hypertension, diabetes, and obesity, which all exacerbate the effects of aging (Marques et al., 2012). Genes are also associated with susceptibility, and although no exact biological causes have been confirmed, they may cause certain features to exist in an AD-affected brain that lead to neurodegeneration.

Etiology- Environment vs. Genes

Genetics account for a small percentage of Alzheimer's cases, but epigenetics and the environment are believed to be primarily involved in its etiology. In a small number of diagnoses, often in early-onset, autosomal dominant AD, a patient inherits a mutated gene from a parent who possesses it along with one normal gene on a pair of autosomal chromosomes. This inheritance is 50-50 and, as previously stated, rare. Epigenetics, falling between nature and nurture, may also have a role in causing AD. This route involves DNA/gene modulation caused by environmental factors as opposed to inheritance. The aging process, a patient's lifestyle, or general life events are speculated to contribute to AD epigenetic onset (Marques et al., 2012). For example, exposure to lead during brain development, as shown in rodent studies, can mutate the gene that regulates the amyloid-beta peptide, producing many of the hallmarks of Alzheimer's such as senile plaques and neurofibrillary tangles. Hence, epigenetics and the environment are closely linked. Another study involving animals demonstrated this connection: mice that had epigenetic mutations in two genes affiliated with AD raised in an "enriched environment" displayed "less AD pathology" than those raised in a "standard environment." This

reduced pathology was indicated by smaller amounts of the amyloid-beta peptide in the "enriched environment" mice, which would translate into reduced manifestations of AD in the brain (Marques et al., 2012, p. 378). Scientists and doctors have theorized that the environment and epigenetics cover most AD occurrences more than genetics. They both deal with increased levels of amyloid-beta, which among other factors is responsible for the neurological structures that generate disease-related symptoms.

Diagnosis/Symptoms

Whether it is due to genetics or a combination of epigenetics and the environment, neurodegeneration by AD is commonly marked by neuritic plaques and neurofibrillary tangles (NFT). Both fixtures cause a loss of neurons, in severe cases up to 90 percent in certain brain areas such as the hippocampus and temporal/frontal neocortices. NFTs are associated with an abundance of the tau protein, and plaques arise from high amounts of the amyloid-beta peptide, which are toxic to neurons (Sutherland et al., 2011). Synapses are also hindered by NFTs and plaques, which prevent neurological impulses (Marques et al., 2012). Depletion of synapses and neurons ultimately transition into the outward signs of AD that characterize the disease for the general population. Symptoms appear gradually, intensifying with time. They begin with short-term memory loss, followed by aphasia (language disturbance). Apraxia, (existing motor function but impaired ability to complete motor tasks) and agnosia (existing sensory function but impaired ability to recognize and identify objects) emerge together. Further motor problems also appear as the illness progresses, causing the patient to be bedridden (American Psychiatric Association, 2000). The necessity of supervision becomes constant to an extent that they are often checked-in to a nursing home or hospice. From the point of diagnosis to death, doctors predict a passage of eight to ten years. The criteria for diagnosis of AD involves the

manifestation of one or more of these symptoms, along with memory handicap in which the individual disremembers new or previously learned information. Additionally, effects must be gradual and cause obvious decline in such a way to impair a patient socially and occupationally. Dementia of the AD type cannot be related to use of a substance, another central nervous system disorder, or a systematic condition that carries dementia as a symptom (such as HIV) (American Psychiatric Association, 2000). Scientists can thoroughly study components of AD that are observable and associate them with the disease, but the lack of finite knowledge about its etiology still inhibits advancements towards successful treatments.

Treatment

Despite the obstacles scientists have encountered relating to the origins of AD, they are making advancements in the development of treatment using transcriptomic studies of DNA. The most efficient process of transcription is RNA-Sequencing, in which a snapshot can be taken of the cell activity in a tissue at any moment (Sutherland et al., 2011). In recent years, labs have found ways to observe large amounts of tissue at once with high levels of accuracy. When comparing snapshots, researchers can detect the DNA modulation that produces AD and target which genes the disease directly affects. Transcriptomic analysis is now being conducted at early stages of AD, before neuron loss is severe, in order to use the differential gene expressions presented in conjunction with creation of preventative treatment (Sutherland et al., 2011). The amyloid-beta peptide (noted to be toxic to neurons) has been shown to accumulate in cognitively sound individuals before they experience dementia of the AD type, and "maximum deposition occurs in the disease's early stages" (Cummings, 2008, p.394). Studies involving mice demonstrate that preventing amyloid-beta deposits is successful in delaying the progression, and

in some cases the establishment, of AD (Cummings, 2008). Such procedures for humans are still being tested.

Along with preventative amyloid therapies, which target underlying disease processes, behavioral therapies are beneficial in improving a patient's quality of life. One studied method is Reality Orientation Therapy (ROT), associated with improvements in cognition. It is administered in hospitals to patients already taking psychotropic medication. In one hospital observed, sessions of 45 minutes were implemented everyday to individuals of varying impairments. They were given support and stimulation through physical, group, and psychotherapy occasionally accompanied by computerized cognitive training, which focuses on attention, concentration, verbal and spatial abilities, and motor speed (Raggi et al., 2007). Results were analyzed using the Neuropsychiatric Inventory (NPI); patients showed notable decreases in apathy, agitation, delusions, and hallucinations (Raggi et al., 2007). Positive symptom decline was made possible by social and environmental stimulation, essential aspects of behavioral care that integrate an Alzheimer's sufferer back into their community. These can range from various forms of therapy for the patient along with people close to them, to employment or volunteer work. It is important to keep them active not only to lift their self-esteem, but also to delay their deterioration (Ionedes, 1992). ROT and forms of stimulation impede AD, putting off intensive care, and amyloid remedies bear preventative benefits (Ionedes, 1992). However, while AD lacks a set etiology it also lacks a cure. Additionally, the disease is surrounded by controversy relating to its definition and treatment.

Current Controversies

Developing appropriate and successful care for AD requires a number of steps that raise necessary questions. Medication must possess a mechanism of action, physically modifying AD.

Once this medication is developed, it must be tested in clinical trials. Issues have emerged regarding both the definitions of disease modification and the disease itself, the morals of testing patients in clinical trials, and drug labeling. Pharmaceutical companies argue over which areas of AD they should focus on crafting medicine for, because its diagnostic criteria are still debated. However, commonly used benchmarks have been released by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; AD is characterized by deficits in memory and one other cognitive area (perception, language, etc.), and often stems out of Mild Cognitive Impairment, a more mild deficit of perception (Cummings, 2008). A consensus is also absent concerning disease modification. It is suggested that it must both address the underlying neurobiological processes of AD that causes degeneration, and delay illness evolution. Consequently, it is then disputed if disease modification really alters the process of cell death, or simply changes the course of the overall disease (Cummings, 2008). This confusion makes pharmacological labeling difficult, because the area a medicine is intended to aid must be clearly indicated on its label.

When a drug needs to be tested in patients with advanced AD, ethical tensions arise over the value of the tests. It must be considered whether a patient's survival takes precedence over their quality of life. Although existence may be prolonged, a person could be so impaired (final stages of AD affect movement and slow internal systems) that living longer is not beneficial (Cummings, 2008). The fact that matters of ethics in clinical trials, along with these other controversies, continue to be deliberated, stunts further research about AD.

AD is a complex disorder that remains baffling to the medical world, but new findings are published that move scientists closer to solving the mystery of its pathogenesis. Processes such as RNA-Sequencing supply a look into gene and epigenetic modulation, connecting the dots

between brain development, amyloid and TAU levels, and physical manifestations of the disease. Despite this progress, the lack of information about a cause and a cure grows more worrisome as AD becomes more prevalent. Its many symptoms of cognitive decline can be assuaged with psychotropic medication and therapy, but an unfortunate prognosis leaves much to be desired in the area of prevention. An aging population confronts doctors with a range of AD cases they will be able to diagnose and research, hopefully leading to treatment that focuses on altering the disease itself.

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