Is Alzheimer's Disease Another Brain on Fire? (Big News Big Debate)

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Is Alzheimer's disease another brain on fire? Big news. Big debate.
Depression is never simple. More than a prescription, it's plan for quitting.

ABSTRACT

Dementia is a term used to describe symptoms that affect memory, performance of daily activities and communication skills. Alzheimer's disease (AD) is the most common type of dementia. AD worsens with time and affects memory, language and thought. Younger people can develop dementia or AD, and the risk increases as the age advances. Still, none of the conditions is a normal part of aging. As the disease progresses, deficits in memory, visuospatial orientation, judgment, personality and language are seen. Typically, over a course of 5-10 years, the affected individuals become profoundly disabled, mute and immobile. Patients rarely become symptomatic before 50 years of age; the incidence of the disease increases with age, and the prevalence roughly doubles every 5 years, starting from a level of 1% for the 60- to 64-year old cohort. Progressive increase in the incidence with increasing age has given rise to major medical, social and economic concerns in countries with aging populations. About 5-10% of cases are familial forms of AD; these have provided important insight into the pathogenesis of the more common sporadic form of the disease. While pathologic examinations of brain tissue remain necessary for the definitive diagnosis of AD, the combination of clinical assessment and modern radiologic methods allows accurate diagnosis in 80-90% of cases as confirmed at autopsy.

Keywords: Alzheimer's disease, senile dementia, genome-wide association studies, immunoblotting, guanylate cyclase activity, 8-hydroxyguanosine

Alzheimer's disease (AD) is a complex, neurodegenerative disease that presents with impaired cognitive function in elderly individuals. AD imposes immense suffering on patients and their families. Younger people can develop dementia or AD, and the risk increases as the age advances. Exposure to cortisol over several days at doses and plasma concentrations associated with physical and psychological stress in humans can reversibly decrease specific elements of memory performance in otherwise healthy individuals, similar to pharmacological glucocorticoids treatment. Vitamin E and vitamin C supplements, when used in combination, seem to be associated with a decreased prevalence and incidence of AD.

Over the years, memory loss and other cognitive deficits in the elderly have been considered to be occurring as a result of the aging process and are called "senile dementia," whose prevalence and incidence increases with age.

The fact that certain mitochondrial defects seen in AD patients are not brain-limited, as shown by lower enzymatic activity, such as cytochrome oxidase, in mitochondria from peripheral cells (platelets and fibroblasts), provide a firm support to the concept of AD being a systemic disease.

Resveratrol, and its derivative pterostilbene, can potentially cross the blood-brain barrier and impact brain activity. The most common form of dementia, occurring in more than half of affected individuals, is AD.

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AD is a progressive neurodegenerative disorder characterized by severe impairments of memory, language and behavior. Elevations in total-tau (T-tau), phosphorylated tau (P-tau) (S396), interleukin-6 (IL-6) and hydroxyl radical ($^{\bullet}OH$) in the cerebrospinal fluid (CSF) have a significant correlation with cognitive impairment in patients with Parkinson's disease (PD). The findings thus highlight the potential biomarkers relating pathological proteins, neuroinflammatory factors and free radicals in PD patients with cognitive impairment.

It has been suggested that neuronal damage in chronic neurodegeneration leads to a damaging pro-inflammatory microglial response. Peripheral and central inflammations play a key role in the pathogenesis of AD.

Genome-wide association studies (GWAS) have identified several risk AD candidate genes for inflammatory pathways, which support the critical role of inflammation in early AD etiology. A meta-analysis showed that there is increased systemic inflammation in patients with PD, which is closely related to dementia with Lewy bodies (DLB). Brain tissue in patients with AD is exposed to oxidative stress or OS (e.g., protein oxidation, lipid oxidation, DNA oxidation and glycoxidation) during the course of the disease.

Oxygen radicals have a role in several biochemical activities of cells such as signal transduction, gene transcription and regulation of soluble guanylate cyclase activity. Nitric oxide ($NO^{\bullet}$) is a key signaling molecule known to regulate the relaxation and proliferation of vascular smooth muscle cells, leukocytes adhesion, platelets aggregation, angiogenesis, thrombosis, vascular tone and hemodynamic.

Deep sequencing data yield convincing evidence that the spectrum of somatic point mutations in mitochondrial DNA (mtDNA) in aging tissues lacks G>T transversion mutations. There is a significant increase of an oxidized nucleoside derived from RNA, 8-hydroxyguanosine (8-OHG), and an oxidized amino acid, nitrotyrosine, in vulnerable neurons among patients with AD. OS is associated with normal aging and several neurodegenerative diseases, including AD.

HISTORY

It was not until 1901 that German psychiatrist Alois Alzheimer identified the first case of what became known as AD, named after him, in a 50-year-old woman, Auguste D. He followed her case, until she died in 1906 when he first reported publicly on it. During the next 5 years, 11 similar cases were reported in the medical literature, some using the term *Alzheimer's disease*. Emil Kraepelin first described the disease as a distinctive disease after suppressing some of the clinical (delusions and hallucinations) and pathological features (arteriosclerotic changes) mentioned in the original report of Auguste D. Alzheimer's disease, also named presenile dementia by Kraepelin, was included as a subtype of senile dementia in the 8th edition of *Textbook of Psychiatry*, published in 1910. The terminology was changed after 1977, when a conference on AD came to the conclusion that the clinical and pathological manifestations of presenile and senile dementia were almost identical. The authors also mentioned that this did not rule out the possibility that they had different causes. This eventually led to the diagnosis of AD independent of age. The term "senile dementia of the Alzheimer type (SDAT)" was used to describe the condition in those aged above 65, with classical AD being used to describe those who were younger. AD usually affects people between ages 60-65, as in Ms. Auguste D's case, who was 55 years old when she died. She had a form what is now known as early-onset AD.

SIGNIFICANT GAP IN RESEARCH

Use of vitamin E and vitamin C supplements in combination is linked with decreased prevalence and incidence of AD. Antioxidant supplements should be further studied as agents for the primary prevention of AD. Antioxidant vitamins, specifically the combination of vitamin E and C supplements, may prevent AD. A formal proof of such an effect can only be obtained from randomized prevention trials. A valid demonstration of their efficacy would have significant public health implication. The link between abnormal mitochondrial gene expression and oxidative damage in the development and progression of AD is not clear. Using immunoblotting, digitonin fractionation, immunofluorescence and electron microscopy techniques, the link between mitochondria and Aβ in Tg2576 mice and N2a cells expressing mutant human amyloid precursor proteins (APP) and wild-type (WT) human APP was investigated and an association was found between mutant APP derivatives (Aβ monomers and oligomers) and mitochondria in cerebral cortex slices from Tg2576 mice and N2a cells expressing mutant APP.

WHERE DOES THE RESEARCH GO NEXT?

Oxidative damage may impair cell structure and function, being cause and effect of a mitochondrial

reduced activity. The damage is not restricted to the brain alone but can also be seen in peripheral cells and tissues. Scientists are treating AD as a systemic disease and are paying more attention to the correlation between the brain and other organs. NO is a signaling molecule that regulates the relaxation and proliferation of vascular smooth muscle cells, leukocyte adhesion, platelets aggregation, angiogenesis, thrombosis, vascular tone and hemodynamic. Current neurobiology research suggests that unregulated metal metabolism plays a catastrophic role in catalyzing *in vivo* chemical reactions leading to OS and neuronal cell death as final cause. Metals are key cofactors in carrying out several *in vivo* catalytic enzymatic reactions in cellular metabolism and cell signaling. Mutations in Mt DNA or metal overload in aged brain gives way to OS and free radical-mediated pathological changes in neurons. Neuronal proteins and structural components are altered due to OS in different neurological disorders leading to neuroinflammation and loss of cognitive function in AD, PD, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). OS has been defined as the key pathological cause of neurodegeneration, and antioxidants are proposed as therapeutic options to fight-free radical generation and maintenance. Evidence suggests that brain tissue in patients with AD is exposed to OS (e.g., protein oxidation, lipid oxidation, DNA oxidation and glycoxidation) during the course of the disease.

MAJOR ADVANCES AND DISCOVERIES

There is increasing attention towards identifying biomarkers for diseases in which OS is involved. Various invasive and semi-invasive means of assessing oxidative biomarkers are available; these include measurements in CSF, synovial fluid, bronchoalveolar lavage (BAL) fluid, urine and tissue biopsies. Recent studies focus on noninvasive techniques to evaluate OS, for instance, inflammatory lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. The assessment of biomarkers of OS in exhaled breath condensate represents a promising area of future research in inflammatory lung diseases. Resveratrol is well-tolerated; however, gastrointestinal discomfort and diarrhea have been observed at high doses. Neuroprotective efficacy of resveratrol has been demonstrated in animal models of vascular dementia.

CURRENT DEBATE

Low levels of zinc in the body were believed to contribute to the development of Alzheimer's. However, when scientists at the University of Melbourne in Australia tested the zinc theory, they encountered unexpected results. While some researchers found excessive aluminum in the brain tissues of Alzheimer's sufferers, others stated that the aluminum came from chemical agents, the researchers used to analyze the brain tissue. Population studies have shown that people were more likely to have Alzheimer's if they had been drinking from public water treated with aluminum sulfates to make the water clearer. Animal studies have shown an aluminum-Alzheimer's link. When aluminum was injected into the brains of rabbits and cats, changes in their behavior and their brain mimicked changes in Alzheimer's victims.

Dialysis fluid is made from water containing large amounts of aluminum. This may give rise to a condition called dialysis dementia. An experimental drug that draws aluminum out of the body seems to slow down the progression of AD. Aspirin therapy may prevent AD. While taking an aspirin every day can ward off stroke and heart disease, now there may be another unexpected benefit.

Some Alzheimer's experts believe that aspirin, ibuprofen, naproxen and another nonsteroidal anti-inflammatory drugs (NSAIDs), commonly recommended for arthritis, can prevent AD. A study was conducted with 50 pairs of elderly twins. Only one of each set of twins had used NSAIDs. That twin was less likely to develop AD or developed it years later than the other twin. However, one must talk to the doctor before starting an aspirin a day. NSAIDs can cause ulcers and bleeding in stomach.

Therefore, an individual's risk of heart disease, stroke and Alzheimer's must be weighed against the risk of stomach problems and bleeding. AD is the most common cause of dementia in older adults, with an increasing incidence as a function of age. The disease usually becomes clinically apparent as insidious impairment of higher cognitive functions.

Over a period of 5-10 years, the patient becomes extremely disabled, mute and immobile. Patients rarely become symptomatic before the age of 50. The incidence of the disease increases with age, and the prevalence increases nearly twofold every 5 years, starting from a level of 1% for the 60- to 64-year old cohort. The progressive increase in the incidence with increasing age has given rise to major medical, social and economic concerns in countries with aging populations. About 5-10% of cases are familial forms of AD. These have provided important insight into the

IJCP SUTRA 251: To revive a cardiac arrest victim, compress the center of the chest of the victim within 10 minutes of death (earlier the better) at least for the next 10 minutes (longer the better), with a speed of at least 10×10=100 per minute.

pathogenesis of the more common sporadic form of the disease. Pathologic examinations of brain tissue are necessary for the definitive diagnosis of AD. However, the combination of clinical assessment and modern radiologic methods enables accurate diagnosis in 80-90% of cases as confirmed at autopsy.

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