WAYNE STATE UNIVERSITY SCHOOL OF MEDICINE

CENTER FOR MOLECULAR MEDICINE AND GENETICS

WHY 'AMYLOID CASCADE' IS A MISGUIDED HYPOTHESIS OF ALZHEIMER'S DEMENTIA ETIOLOGY

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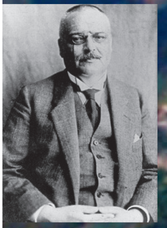

Aloysius "Alois" Alzheimer (1864–1915)

Alzheimer's dementia (AD) refers to disorders of the mind characterized by a progressive and irreversible memory loss, mental decline, remarkable personality changes and loss of self. Advanced or old age is the only important risk factor for developing AD. Other risks include head trauma, stroke, cerebrovascular and cardiovascular events, neuropsychiatric conditions, obesity, diabetes, and APOE4 gene. Some rare forms of AD are inherited and caused by dominant mutations in APP, PS1 or PS2 genes.

In the US, one in eight over 65, and one in two over 85 years of age has AD. In 2013, AD research was funded with $850 million, while $1 billion a day was spent to look after 5.5 million people living with AD, at homes and nursing homes. In 2010-2050, it will cost $20 trillion to provide health care for many more people with AD.

All clinical trials targeting Aβ peptides and amyloids for AD treatment have failed. Did the trials fail because of what was done was too little or too late, or did the trials fail simply because our ideas about AD etiology are wrong?

The 'amyloid cascade' hypothesis says that AD begins with the assembly and accumulation of Aβ peptides into oligomeric and fibrillar extracellular amyloids in the brain, causing reactive inflammation and immune responses, synaptic failure and neuronal cell death. The 'amyloid cascade' hypothesis has dominated AD research and clinical trials for 25 years.

'AMYLOID CASCADE' HYPOTHESIS IS TOO GOOD TO BE TRUE

By definition, AD is diagnosed with amyloids in the brain, detected at post-mortem autopsy or by PET brain imaging of demented individuals.

APP, PS1 or PS2 gene mutations that cause AD also increase Aβ peptides production and amyloid formation. These and other data on APP and Aβ peptides strongly support the 'amyloid cascade' hypothesis of AD etiology, so why do we think the hypothesis is wrong?

The hypothesis is wrong because the data are about correlation, and correlation never makes the difference between the cause and effect, that is, what if AD is the cause of 'amyloid cascade' in the brain?

The hypothesis is wrong because it is known that brain amyloids and the natural history of memory and mind problems cannot be causally linked. Careful autopsy studies have revealed an undisputed fact: 30% of individuals, cognitively normal in life, were found at autopsy to have a typical brain pathologic profile of AD, including amyloids.

The hypothesis is wrong because every clinical trial for AD treatment targeting Aβ peptides and amyloids has failed. None of the Aβ lowering drugs showed any efficacy, only made the patients feel worse.

TRIALS AND ERRORS

ClinicalTrials.gov (July 1, 2014) records have 1435 trials in AD treatment and research. The most recent five high-profile trials were all terminated early because of adverse drug reactions.

Semagacestat. When in August 2010, Eli Lilly canceled two trials, it had enrolled 2,600 patients in 31 countries for more than two years. The drug, semagacestat, a γ-secretase inhibitor designed to reduce Aβ peptides production and amyloid formation in the brain, did not help the AD patients in any way, only made them worse in their everyday living. Alarmingly, patients on semagacestat also had a higher incidence of skin cancers.

Avagacestat, developed by Bristol-Myers Squibb, another inhibitor of Aβ peptides production, with less side effects, was well tolerated at daily oral doses of 25 and 50 mg, yet did not improve any clinical outcome measures.

AN1792 (aggregated human Aβ42 peptide), developed by Janssen and Pfizer, was used in the first active immunotherapy trial for AD. The trial was terminated early because 6% (18/300) of the patients developed serious health problems including autoimmune meningoencephalitis and death.

Bapineuzumab, a humanized mouse monoclonal antibody against Aβ peptides, developed by Johnson & Johnson and Pfizer, failed in two trials to improve either cognition or daily living of patients with mild to moderate forms of AD. The major adverse findings were vasogenic edema.

Solanezumab, another humanized monoclonal mouse antibody against Aβ peptides, developed by Eli Lilly, also showed no efficacy. The major adverse findings were vasogenic edema and brain microhemorrhages.

PREVENTION IS THE ONLY CURE

The Dominantly Inherited Alzheimer Network (DIAN) is an international collaboration to research inherited forms of AD caused by APP, PS1 or PS2 gene mutations.

Medellin, in the hilly Antioquia region in the northwest Colombia, is home to 5,000 people from 25 families. One third of the family members have a PS1 gene mutation E280A making these people the most extended Alzheimer family in the world.

Medellin people are the first DIAN study subjects of Alzheimer's Prevention Initiative (NCT01998841). In this $100 million trial, 100 asymptomatic family members with the PS1 gene mutation will get the drug **Crenezumab**, an antibody against Aβ peptides, developed by Genentech. Another 100 family members with the PS1 gene mutation do not get the antibody, and 100 family members with unknown PS1 gene status do not get the antibody. The trial is expected to last till 2020.

PERSPECTIVES

Why every trial for AD treatment and therapy has failed? Time after time, and after all the money invested and wasted, we have not helped a single AD patient. This gives AD research a bad name.

There are no Alzheimer survivors. How long do the people living with AD have to wait? We have to do something else than study APP metabolism and Aβ peptides, and we must do it now because time is running out.

How do we study and model something like AD that takes a lifetime to present the first signs and symptoms of memory and mind problems?

With no cure or treatment for AD, clinical trials aiming to delay the onset and slow the progression of AD in DIAN people are justified, obvious and long overdo. DIAN people provide an unprecedented opportunity to study and understand mind and what the brain does in health and disease.

FURTHER READING

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