New Research of Alzheimer's Disease

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Introduction

Alzheimer's Disease has impacted so many lives and so many lives are lost at the hands of Alzheimer's Disease. The number of people that have been diagnosed with Alzheimer's Disease doubles every 5 years after the age of 65. The most taunting thing about the disease is the lack of a cure. The average number of years a patient with Alzheimer's Disease survives after being diagnoses is 8-10 years. This alone makes Alzheimer's Disease the fourth leading cause of death in industrialized societies.
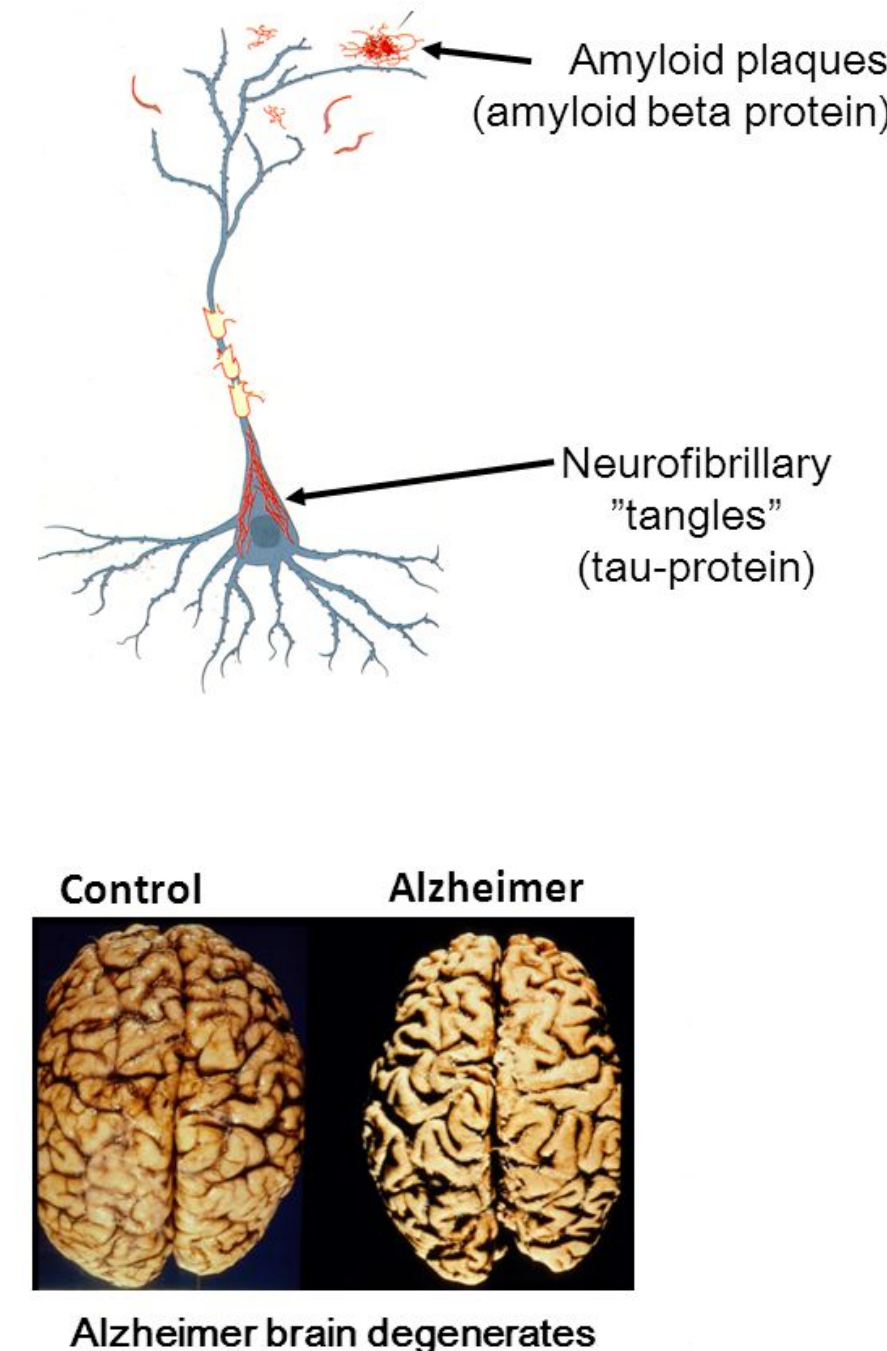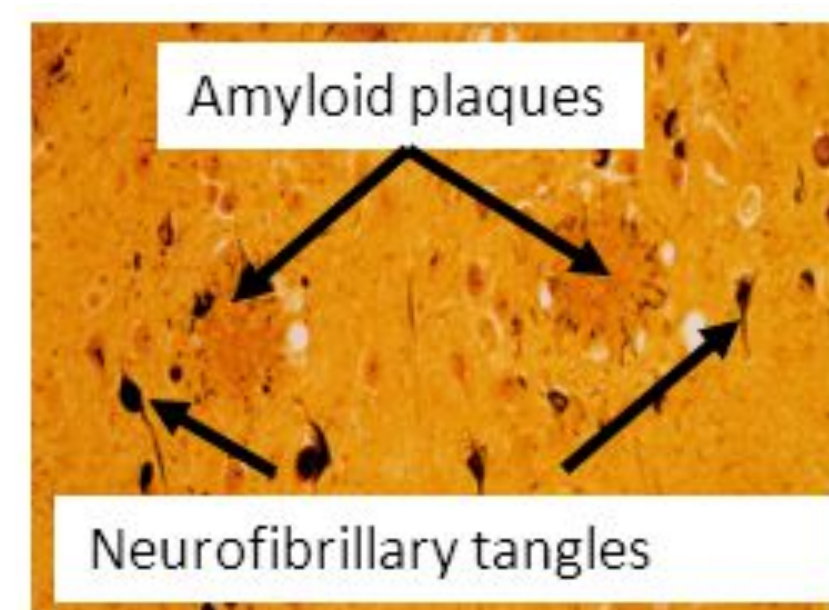
The financial burden families experience can be just as taunting as the disease itself. The estimated financial burden in the U.S. for the institutional care of AD patients totals to $100 billion per year; However, over the next 40 years it will cost insurance companies $20 trillion to care for AD patients.

Many therapies have tried to help through different tactics yet none have seemed to solve the mysterious and merciless progression of the disease. This literature review focuses on different treatments being implemented to try to cure Alzheimer's Disease as well as some possible causes to the disease, with a section on biological characteristics to better help understand the causes.

Biological characteristics of AD

➢ **Amyloid or senile plaques: extracellular deposits**

➢ **intracellular neurofibrillary tangles (NFTs)**

Amyloid plaques (amyloid beta protein)

Neurofibrillary "tangles" (tau-protein)

Amyloid plaques

Neurofibrillary tangles

Control   Alzheimer

Alzheimer brain degenerates

➢ **Deterioration of neurons and synapses in the central nervous system**

➢ **Decreased levels of neurotransmitters: serotonin, noradrenaline, dopamine, glutamate, and acetylcholine (Carter, 2008).**

➢ **Minor inflammation is present in patients with high pathology of AD but do not present clinical signs of AD**

➢ **Inflammation can worsen the disease and cause neuronal damage and disrupt the blood brain barrier (Desai et al., 2008)**

➢ **oxidative damage can be found in Mild cognitive impairment patients (MCI)**
  - MCI is a condition between normal and Alzheimer's Disease
  - proves that oxidative damage may be the first occurrence in an Alzheimer's brain (Coppedè et al., 2008)

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Possible causes of AD

1. Overproduction of Aβ

- Aβ (beta-amyloid) plaques are a primary feature of those with AD and unique only to AD (Carter, 2008)

- APP cleavage product is amyloid peptides which form amyloid plaques (Coppedè, 2008)

- the earliest neurological symptom of AD is Aβ plaques and precede NFTs on an average of 20 to 30 years (Carter, 2008)
  - o NFTs are helical filaments that result from hyperphosphorylation of tau proteins
  - o hyperphosphorylation is caused by cell dysregulation
  - o NFTs severely harm neurotransmitter transport and axonal integrity
  - o studies on familial AD patients show that there is a mutation of APP but not on tau proteins, so NFT formation is a direct result of Aβ peptides on tau proteins (Hadavi et al., 2016)

- Aβ is toxic to cultured neurons

- There is still some uncertainty regarding whether it is extracellular or intracellular Aβ aggregates that cause AD (Carter, 2008)

2. Complement activation (Coppedè et al., 2008)

- Group of plasma proteins that destroy invading pathogens
- 4 functions of complements proteins:
  - o recognizes target cells
  - o opsonization: the marking of cells for phagocytosis
  - o inflammatory stimulation
  - o kills the cell membrane through insertion of membrane attack complex
- Functions of complement proteins are carried out by 2 major cascades (both are activated in AD patients): classical and alternative pathways.
- Tau protein (causes NFTs and Aβ) is a major activator of the classical complement pathway.
- Studies on gene & protein expression demonstrate that complement proteins are up-regulated in areas of the brain the degenerate & experience inflammatory changes in AD.

3. Oxidative Damage

- Could be one of the earliest occurrences even before Aβ and NFT formation

4. Elevated levels of metals in the brain (Coppedè et al., 2008)

- No direct link definitively proven.
- Aluminum, Zinc, Copper, Iron, and Mercury in the brain may be linked to the development and/or progression of the brain

5. Dysregulation of the cholinergic system (Hadavi et al., 2016)

- The cholinergic system is related to cognitive repair.

Treatments

1. Neurotransmitter based theory (Carter, 2008)

- Prescribing drugs that inhibit the production of acetylcholinesterase (AChE) and raise the levels of acetylcholine

- Glutamate receptors are drugs used to block the overstimulation of the receptor by glutamate

- AChE inhibitors can slow the progression of the disease and provide symptomatic benefits

- Problems with this theory is that it only provides relief for a temporary duration

Treatments Continued

2. Inhibiting Aβ Production

- Cholesterol lowering drugs have been shown to inhibit β-secretase and stimulate α-secretase
- Vaccines: CAD106 (Sterner et al., 2016).
- Targets antibody production of Aβ
- 67% of patients developed antibodies to Aβ with 50 μg
- 82% of patients developed antibodies to Aβ with 150 μg
- Still in clinical trials

3. Inhibiting complement activation and Infiltration for therapy use

- Complement activation can be reduced by up-regulating endogenous inhibiters
- Engineering cells to express high levels of complement inhibitors
  - o May reduce inflammatory consequences
  - o Reduced inflammation may lead to reduced brain lesion formation
- Producing agents that can help block complement activation
- Making the blood brain barrier permeability
- May reduce potential problems with antibody treatment

4. Stimulate an autoimmune response against the peptide of Aβ (Carter, 2008)

- Method proven in transgenic mice expressing human Aβ
- Mice were immunized with fibrillar Aβ1-42 and did not have as much amyloid formation and had some clearance of pre-formed amyloid plaques
- Fibrillar Aβ1-42 is not being tested anymore since human testing showed that patients developed aseptic meningoencephalitis
- Immunized mice performed better on cognitive tasks showing increased cognitive results from lowered Aβ levels

5. Biomaterials (Hadavi et al., 2016)

- Biomaterials are defined as material that is used to help treat parts of the body
- Biomaterial can deliver drugs, cells, and proteins
- They can help regenerate lost tissue in the brain and bring new cells that may have died at the hands of tau proteins.

Current State of Treatments

As of today none of these treatments have been able to slow down the progression of AD. The stimulation of an autoimmune response against the peptide of Aβ successfully reduced amyloid plaques in mice; however, when tested on humans the studied was shut down because so many subjects died from aseptic meningoencephalitis.

Some treatment is able to cure somatic symptoms of the disease yet none have been able to completely cure Alzheimer's Disease. Some treatments are still in clinical studies (for example the efficacy of the use of biomaterials and CAD106 is still being tested), so hopefully they will be able to find a treatment that will slow down the progression and cure the disease.

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