Alzheimer's Disease Literature Review

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Abstract

Alzheimer Disease (AD) is a progressive neurodegenerative disorder that affects about 5.8 million people today, and is expected to grow to 13.8 million in 2050.[1] AD is a disorder that begins on the biochemical level with neurofibrillary tangles and β-amyloid plaques.[2] As the biochemical pathology accumulates throughout different regions of the brain, from the hippocampus to the cerebral cortex, it manifests in characteristic clinical symptoms.[2] These included forgetfulness, memory loss, behavior issues, and many other debilitating cognitive changes.[3] Alzheimer Disease leads to a low quality of life, as the clinical symptoms can be drastic, leading to many patients being bedridden. Although the affects of Alzheimer are life altering, there is currently no cure. AD is primarily treated with two medications, acetylcholinesterase inhibitors and memantine, which only slightly improve a subset of clinical symptoms.[4] Possible future treatments may target the root biochemical causes of AD.

Introduction

Alzheimer Disease is a neurodegenerative disorder that is the sixth leading cause of death in the United States.[1] The number of people affected is increasing greatly every year.[1] Alzheimer Disease is also the leading cause of disability and poor health, with quality of life deteriorating as the disease progresses.[1] As such, it is important we study Alzheimer Disease, because the number of cases is predicted to grow from 5.8 million people today, to 13.8 million people in 2050.[4]

Many people understand AD to be a disease of memory. Beyond forgetfulness, it also encompasses behavior, social skills, and thinking. Patients tend to forget small things such as where they put their keys, or the name of someone they know. Patients also tend to forget events that have happened or forget simple facts of which they had previously known. While some researchers have described it as a disease of natural aging, recent evidence has indicated that it is a slow, progressive pathology unique to those who suffer from it – not of all elderly individuals.

Until the last decade, most of our understanding of AD was that it was disease of beta amyloid pathology. One hypothesis is that β-amyloid plaques occur first in the brain, causing the hyperphosphorylated tau to form neurofibrillary tangles.[3] However, recent data suggests that tau may precede beta amyloid. A study suggests that the hyperphosphorlylation of tau precedes β-amyloid plaques, as brains were examined, evidence of hyperphosphorylated tau was present and β-amyloid plaques were not.[2]

As the biochemical pathology progresses, it spreads to different brain regions, affecting the brain's normal function. Some of the main brain regions that are affected by Alzheimer are the perirhinal and entorhinal cortices, the hippocampus, and the cerebral cortex.[2] These neural

circuits correspond to the characteristic impairments in memory, behavior, recollection, memory of facts, inability to distinguish time with events, and other sever and debilitating symptoms. [2] [3] [5] [6]

While there is no definitive cure for Alzheimer, two medications are typically prescribed to Alzheimer patients: acetylcholinesterase inhibitors and memantine.[4] Neither drug has a significant affect on Alzheimer alone but do have mild benefits on cognition. There has been more success using combination therapy and combining the two medications, resulting in benefits on behavior, global impression, daily activities, and also lower rates of withdrawal.[4] Future treatment options may target the tau and neurofibrillary tangles on the biochemical level, as they are believed to be the root of the disease.[2]

Biochemical Causes of Alzheimer Disease

Overview

The two biochemical causes of Alzheimer disease include tau and β-amyloid plaques: amongst researchers there is a debate as to which of these is the primary cause of Alzheimer. Both tau and β-amyloid plaques play a large role in progressing the disease and have detrimental effects on the brain. In Alzheimer disease, tau, a protein that holds microtubules together is hyperphosphorylated, breaking it apart from the microtubules and causing the microtubules to unravel. Amyloid precursor protein in AD is incorrectly cleaved, causing Aβ to clump together and form β-amyloid plaques that interrupt signaling in the brain.[7] These biochemical causes occur twenty to thirty years before clinical symptoms manifest.[8]

Tau

Overview

As seen through multiple studies, it is believed that abnormally phosphorylated tau is the primary cause of Alzheimer Disease.[2] [9] [10] Researchers hypothesize that the abnormally phosphorylated tau is then followed by the buildup of β-amyloid plaques, further progressing the disease.[2] Braak et al., 2011 proposed the hypothesis that hyperphosphorylated tau occurs first, after examining 2,332 brains of individuals ranging from ages one to one hundred, using immunohistochemical techniques. The researchers observed brains that displayed abnormal tau proteins without any evidence of β-amyloid plaques, in younger patients; as they analyzed older patients, they began to note the addition of Beta-amyloid plaques, leading them to the conclusion that tau pathology precedes beta amyloid plaques.[2]

There may be some limitations to the Braak et al., 2011 study; such as there were significantly more male than female brains analyzed. Males and females could show and progress the disease

in different ways causing a bias in the results. For instance, AD is diagnosed more in woman at significantly higher rates than in men.[11] Oveisgharan et al., 2018 performed a study that showed women had higher AD pathology of both neurofibrillary tangles and β-amyloid plaques. Through this study, average age of death was slightly lower in women with AD.[11] Another limitation to Braak et al.'s paper is that all the brains studied were of deceased individuals, some of which displayed no symptoms at the time of death and may have not displayed any symptoms of AD had they lived to an older age.[2] It begs the question of whether early tau "pathology" is simply a normal process of aging, that is later amplified by the beta amyloid pathology of AD.

Normally, tau interacts with microtubules in order to keep them in place and prevent them from breaking apart.[7] The microtubules deliver molecules and nutrients throughout the cell. Microtubules are the "framework" of the cell, responsible for intracellular transport.[12] In Alzheimer disease, the tau that is holding microtubules together is hyperphosphorylated, causing it to break apart from the microtubules and form a tangle with other tau proteins. These neurofibrillary tangles cause the microtubules to break apart, making it harder for signals to be sent to other cells.[7]

Pretangles

In the somatodendritic compartment of neuronal cells, this hyperphosphorylated tau fills up, causing what is called a pretangle.[2] These pretangles gradually build up, causing neurofibrillary tangles. During the early stages of Alzheimer disease, these pretangles are responsible for the progression of the disease.[2] Understanding how pretangles arise and affect the brain during the disease process helps researchers explore treatment options for AD. These pretangles are "pre-pathological"- meaning, arising before disease pathology- and are typically seen in individuals ages 20-40.[2]

The progression of pretangles is typically characterized by three stages: Pretangle Stage A, B and C. Pretangle stage A refers to when changes are seen in the brainstem nuclei with projections to the cerebral cortex. Pretangle stage B is identified when somatodendritic compartments and noradrenergic projection cells are involved. Pretangle stage C is identified when subcortical lesions are more widely distributed.[2]

Neurofibrillary Tangles

The natural progression of pretangles in AD involves them clumping together further, to form larger and more severe neurofibrillary tangles. When identifying neurofibrillary tangles, six stages are used to classify the progression.[13] In all six stages, pretangle material in nerve cells is present. In stage I, the neurofibrillary tangles affect the transentorhinal region. During stage II, they progress to the entorhinal region and hippocampus. Stage III affects the basal neocortex and

areas of the temporal lobes. Stage IV affects the insular and basal cortex areas. Stage V progresses to the entire prefrontal cortex and high-order sensory association neocortex. Finally, stage VI affects premotor and primary motor areas and sensory first-order association neocortex.[2] The higher the stage, the greater the effect on the brain and greater clinical symptoms. It is almost certain that a patient has AD when the neurofibrillary tangles reach stages V and VI.[13]

β-amyloid plaques

Overview

Before Braak et al., 2011's groundbreaking experiment, the hypothesis that was widely accepted is that β-amyloid plaques were the primary cause of Alzheimer Disease.[3] Regardless of which pathological process occurs "first" in AD, the observed relationship between beta-amyloid plaques and neurofibrillary tangles is still poorly understood – they appear to increase with a similar pattern, in the same brain regions, but how they interact is still under-studied.

In the cell membrane there is a protein called the amyloid precursor protein (APP), which helps the neuron grow and repair itself. Although its exact function is unknown, APP is believed to be a factor in cell adhesion as well as supporting cell growth.[14] Over time, APP is broken down and recycled. Typically when being broken down, alpha-secretase (α-secretase) and gamma-secretase (γ-secretase) cleave the protein, leaving soluble portions of the protein that will dissolve. The problem occurs when beta-secretase (β-secretase) along with gamma-secretase cleave APP instead, leaving an insoluble fragment of the protein called amyloid beta. Amyloid beta molecules attach to one another outside of the neuron causing interruptions in the communication pathways. The clusters of amyloid beta are called β-amyloid plaques. When signaling pathways between the neurons are interrupted, functions such as memory are impaired. Not only do these plaques cause damage to signaling, they can start an immune response, which causes inflammation that may further damage surrounding neurons.[7]

β-amyloid Plaques in Alzheimer Disease

Brains of patients with diagnosed Alzheimer disease contain more β-amyloid plaques than a typical elderly brain. Alzheimer patients have an imbalance of production and clearance of Aβ. There is more evidence of β-amyloid plaques in Alzheimer brains because insoluble amyloid beta is being produced rather than the soluble form. Late onset Alzheimer disease is believed to be caused by reduced clearance of Aβ, while early onset is primarily due to over-production of Aβ.[3] As patients grow older, more evidence of β-amyloid plaques is found.[2]

Braak Stages

Braak stages are used to track neurofibrillary degeneration. The progression of β-amyloid plaques throughout different brain regions can be distinguished using Braak stages A, B, and C. In Braak stage A, β-amyloid plaques are found in the basal neocortex and perirhinal and entorhinal cortexes. In Braak stage B, β-amyloid plaques spreads to the neocortex and hippocampus. Finally, in Braak stage C, β-amyloid plaques are found in all areas of the cortex.[3] As the stages progress, the pathological symptoms worsen.

Neuroanatomy and Symptoms of Alzheimer Disease: Imaging Studies and Clinical Symptoms

Overview:

Alzheimer Disease begins on the biochemical level with β-amyloid plaques and neurofibrillary tangles.[2] Due to the buildup and advancement of the plaques and tangles, a standard pattern of brain regions is affected, causing clinical symptoms.[3] Some of the main regions of the brain affected by Alzheimer Disease are the entorhinal and perirhinal cortexes, the hippocampus, and finally the cerebral cortex.[2] These stages mirror the progression of the neurofibrillary tangle stages.

Areas of the Brain Affected by Alzheimer and Resulting Clinical Symptoms

Entorhinal and Perirhinal Cortices

The basal neocortex – which includes the perirhinal, entorhinal and transentorhinal regions – is the brain structure first primarily affected by AD.[2] This is consistent with the biochemical findings in Braak et al., 2011; as both Braak Stage A and neurofibrillary tangle stage I identify these regions as initially altered by AD disease pathology. Beta-amyloid plaques are first deposited in the perirhinal and entorhinal cortexes, and neurofibrillary tangles are first found in the transentorhinal region.[2]

The perirhinal and entorhinal cortexes are responsible for episodic memory of both recent and distant events.[5] The perirhinal cortex is associated with visual recognition memory, that consists of recollection and familiarity.[6] The entorhinal cortex is important for memory and associating between events. When these cortices are damaged by AD, the normal function begins to decline. One of the first symptoms of AD is forgetting recent events and typical memories, such as names, due to the disease compromising the portions of the brain responsible for memory.[3]

Hippocampus

As Alzheimer Disease progresses, it not only compromises the perirhinal and entorhinal regions, it also affects the hippocampus. The perirhinal and entorhinal cortices, along with the hippocampus, are located in the medial temporal lobe.[2] These three regions are close to one another as there is a network between them involving memory and other brain functions.[8] Braak stage B, along with neurofibrillary tangle stage II identify the hippocampus.[2] The biochemical aspect of Alzheimer Disease progresses to the hippocampus after affecting the nearby entorhinal and perirhinal regions. The clinical symptoms already shown are typically slight memory loss and forgetfulness.[3]

The hippocampus is the region of the brain that is in charge of memory of events at a specific time. During AD, the hippocampus along with its function is compromised. AD destroys synapses in the brain causing the hippocampus to lose volume, affecting its function.[3] The hippocampus is also responsible for episodic memory, and when Alzheimer progresses to the hippocampus, the deficits to episodic memory greatly increase.[5] In a patient, when AD reaches the hippocampus, a common symptom could be forgetting where he or she placed their keys.

Cerebral Cortex

Alzheimer, being a progressive disease, eventually takes over the entire cerebral cortex. As stated by Braak et al. 2011, in Braak stage C as well as neurofibrillary tangle stages III through VI, the entire cerebral cortex is compromised. Early on in AD the clinical symptoms are not as severe and can mimic symptoms of old age.[2] When the disease reaches the cortex, the symptoms become debilitating.

The cerebral cortex is the surface of the cerebrum that processes most of the information in the brain.[15] In Alzheimer Disease there is significant synaptic loss in the cerebral cortex greatly impacting normal function[3]. When the cerebral cortex is affected, attention and memory are affected along with sensory association areas.[2]

The cerebral cortex is comprised of four lobes: the frontal lobe, parietal lobe, temporal lobe, and occipital lobe.[16] The frontal lobe is responsible for speech and language, along with personality. Also according to Jawabri & Sharma, 2020, the function of the parietal lobe is learning, language, special awareness, and the ability to discern between objects based on size, color, or shape. The temporal lobe's function is semantic memory, recollection, familiarity, and episodic memory. Lastly, the job of the occipital lobe is visual processing and interpretation.[16]

The temporal lobe is most significantly impacted by AD.[8] According to Wolk & Dickerson, 2018, semantic memory is one of the last symptoms of Alzheimer Disease, which is logical as the temporal lobe, which is responsible for semantic memory along with other functions is one of the last brain regions affected. Semantic memory is the memory of facts such as vocabulary and concepts.[5] According to Braak et al., 2011's study, brains that were examined that were in neurofibrillary tangle stages III, IV, V, and VI, had more lesions in the temporal lobe. Patients at this stage in the disease typically forget what words mean, are unable to recall an event, confuse the time frame of the event, cannot remember something that they have previously seen, and are unable to distinguish between objects.[16]

Schroeter et al., 2009, conducted a meta-analysis of AD using 1351 patients. A meta-analysis is a study which combines results from multiple other studies in order to make larger statistical conclusions. According to the meta-analysis, when AD brains were studied using MRI, there was atrophy detected in the perirhinal, entorhinal, hippocampal, and temporal regions.[8] This study aligns with what other researchers have concluded, that Alzheimer Disease greatly affects these regions. Schroeter et al., 2009 also concludes that neurofibrillary tangles begin in the perirhinal and entorhinal cortices, progress to the hippocampus, and then finally to the cerebral cortex. This study confirms what previous studies have also concluded about the brain regions affected on the biochemical level over time. Imaging studies like this may allow researchers to pinpoint a certain biomarker of AD, and eventually use it to target with treatment options.[8]

Treatment Options for Alzheimer Disease

Overview

There is no concrete cure to Alzheimer Disease at this time, but there are two medications that may have some effect on slowing or lessening the symptoms. The two medications that may be prescribed to AD patients are acetylcholinesterase inhibitors and memantine.[4]

Acetylcholinesterase Inhibitors

One of the two medications that a doctor may prescribe to an AD patient is an acetylcholinesterase inhibitor. Joe & Ringman 2019 states that acetylcholinesterase inhibitors benefit mild cognitive impairment with its effect being consistent throughout all stages of dementia. Acetylcholinesterase is an enzyme that is responsible for synaptic recycling of acetylcholine in gray matter.[4] Acetylcholinesterase inhibitors inhibit acetylcholinesterase, which helps increase the length of time that acetylcholine can work.[4] Acetylcholine is a neurotransmitter that modulates several cognitive processes, including memory function. It is heavily present in the hippocampus.[17]

There are three different acetylcholinesterase inhibitors: donepezil, rivastigmine, and galantamine. Donepezil is pure acetylcholinesterase, available in pill form, that helps improve daily activities and only has a mild effect on cognition.[4] Rivastigmine is combined acetylcholinesterase and butyrylcholinesterase inhibitor available in twice daily oral form, and once daily transdermal form. Rivastigmine has a mild benefit on cognition, but no benefit on behavior.[4] Galantamine in an inhibitor of acetylcholinesterase that is available in immediate and extended release oral forms, that only has a slight benefit on cognition.[4] The gastrointestinal side effects of these medications that occur in 5-33% of patients include anorexia, nausea, vomiting, and diarrhea. Other common side effects are dizziness, fatigue, insomnia, bradycardia, and muscle cramps.[4] Joe & Ringman, 2019 concludes that there are no significant disease modifying effects of acetylcholinesterase inhibitors.

Memantine

The other medication that a doctor may prescribe to a patient with AD is Memantine. Memantine is a low affinity N-methyl-D-aspartate (NMDA) receptor antagonist, available in immediate and extended release pills.[4] Glutamate is the major excitatory neurotransmitter in the human central nervous system that works with two types of receptors. One type is an ionotropic cation-selective ligand-gated channel (iGluR). NMDA receptors are a class of iGluRs. The NMDA receptor is important for normal development of the brain.[18] In AD, the theory is that excess excitatory transmission is neurotoxic – that is, causes neuron death, leading to worsening symptoms of AD.[4] NMDA receptor antagonists – those that oppose the activity of NMDA – may lessen the toxicity of glutamate transmission in those suffering from AD.[4]

According to Joe & Ringman, 2019, the benefits of this medication include better global impression -- which refers to how much a patient has improved since taking the medication -- cognition, and daily activities. It is also well tolerated. Also according to Joe & Ringman, 2019, the downsides of the medication are that it caused more aggression in those who were previously agitated, it had less benefits than acetylcholinesterase inhibitors, and there is also a higher rate of withdrawal. The side effects of Memantine include dizziness, nausea, and confusion.[4]

Combination Therapy

Although the medications on their own do not have a significant effect on Alzheimer Disease, combining the two may have a greater effect. When combined, there is no further benefit on cognition, but there are benefits on behavior, as well as lower rates of withdrawal, and benefits on daily activities and global impression.[4] Although there is no definitive cure for the disease, these medications are a step in the right direction in finding a cure.

Future Treatment Targets

Given what is known about the biochemical pathology of Alzheimer disease, future treatments should target tau and neurofibrillary tangles. It is believed that the hyperphosphroylation of tau and neurofibrillary tangles are the primary cause of AD[2], which may be a possible target for future treatments. Targeting the disease at the source possibly would have a greater effect than existing treatments, which only addresses the symptoms.

Conclusion

Alzheimer Disease is a crippling disease that is the number one leading cause of dementia. Beginning on the biochemical level, tau is abnormally phosphorylated, causing neurofibrillary tangles, leading to the formation of β-amyloid plaques.[2] These changes on the biochemical level cause interruptions in signaling as well as other issues and spread to numerous regions of the brain.[2] The biochemical pathology spreads from the perirhinal and entorhinal cortices to the hippocampus and to the cerebral cortex. Years after the biochemical pathology presents, clinical symptoms are then presented in different ways such as inability to remember, failure to remember facts, objects, places, and things that were once familiar, behavioral changes, confusing time frames of events, and not being able to distinguish between objects.[2 3 5] Although Alzheimer is a debilitating disease that affects countless individuals, there is no concrete cure. There are two medications, acetylcholinesterase inhibitors and memantine, that have no significant affect alone besides a mild benefit on cognition. The two medications combined have a greater affect such as an improvement on behavior, global impression, and daily activities all with a lower rate of withdrawal.[4] Possible future treatment targets may target the source of the problems on the biochemical level: the abnormally phosphorylated tau and β-amyloid plaques.

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