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Alzheimer's Disease

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Abstract

An overview of the background, etiology, pathophysiology, clinical features, diagnosis, treatment and prevention of Alzheimer's disease.

Keywords

amyloid, tau, Alzheimers, dementia

Disciplines

Nervous System Diseases | Neurology | Neuroscience and Neurobiology | Neurosciences

Comments

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I affirm that I have upheld the highest principles of honesty and integrity in my academic work and have not witnessed a violation of the Honor Code.

-Dylan Weber

Introduction

There are currently 35 million cases of Alzheimer's disease (AD) worldwide, making it the most prevalent neurodegenerative disease (Goedert & Spillantini, 2006; Liu et al., 2019). By 2050 it is expected to be at least 100 million cases worldwide (Yegambaram et al., 2015; Liu et al., 2019). The cost of AD is almost 500 billion per year (Weller & Budson, 2018). In the United States AD is a top cause of death with over a hundred thousand deaths annually (Yegambaram et al., 2015). Deaths are also increasing each year, with an increase of 89% in the years between 2000 and 2014 (Weller & Budson, 2018). The disease was studied starting in 1901 and then first summarized by Alois Alzheimer in Germany on November 3rd, 1906 (Goedert & Spillantini, 2006; Balin & Hudson, 2014; Herrup, 2010). Later on, Emil Kraepelin named the disease after Alois Alzheimer (Goedert & Spillantini, 2006). AD is a neurological disease that is caused by genetic and environmental factors (Goedert & Spillantini, 2006; Sindi et al., 2015).

Alzheimer's and dementia

AD and dementia are closely related and often discussed together. AD is a type of dementia and makes up 60-70% of dementia cases (Sindi et al., 2015). Dementia affects about 55 million people worldwide with a large proportion of cases being from AD (World Health Organization, 2022). Dementia is most commonly caused by AD (Weller & Budson, 2018), and signs and symptoms overlap between both.

Protein in the brain

The cause of AD is protein buildup in the brain causing dysfunction (Scheltens et al., 2016; Goedert & Spillantini, 2006; Yegambaram et al., 2015). The most involved and studied proteins are amyloid-β protein and tau protein. When these proteins build up in the brain,

neurological damage occurs, which affects brain function. Proteins can build up in the brain as a result of genetic mutations or environmental factors (Herrup, 2010).

Age

Increasing age can have a decreasing effect on brain health and is a risk factor for AD (Sindi et al., 2015; Herrup, 2010). The build up of protein and then damage to neurons takes time and usually has no effects seen until later in life, except in the case of early onset AD, which has a genetic origin (Balin & Hudson, 2014; Herrup, 2010; Solomon et al., 2014). One possible explanation for age's influence is the age-dependent hypothesis. The age-dependent hypothesis suggests aging leads to widespread synaptic dysfunction and cognitive decline, which is normal. However if an injury occurs, microglial activation and inflammatory processes can cause physiological changes in the brain. Then, with increased age, the change in physiology of the brain causes development of AD (Bellenguez et al., 2022).

Genetic

There is a known genetic link to the development of AD. A study by Bellenguez et al. found that people carrying an additional APOE-ε4 allele are at an increased risk of development (2022). APOE-ε4 allele has a typical role in fat metabolism. Additionally, ADAM17 could also play a role because of dysregulation in the nonamyloidogenic pathway. Lastly, GRN and TMEM106B play a role in brain health and have been shown to affect dementia. Having mild cognitive impairment, lipid imbalances, trouble with endocytosis, or impaired immunity have been linked to the development of AD as well (Bellenguez et al., 2022).

Amyloid protein

The APP gene on chromosome 21 plays an important role in Aβ peptide formation. The Aβ peptide bond has a function in the plaque formation from amyloid. PSEN1 and PSEN2 gene

mutations have also been related to AD. Mutations in the APP gene or PSEN gene lead to amyloid peptide buildup in the brain. The amyloid peptide buildup causes β-pleated sheet structures to form. Amyloid clusters form from β-pleated sheets which creates the amyloid plaque (Herrup, 2010). The formation of amyloid oligomers and dimers lead to visible plagues found in the brain (Scheltens et al., 2016). One possible explanation of plaque formation is sleep deprivation, however research has yet to provide conclusive evidence (Olsson et al., 2018).

Tau protein

Tau protein also plays an important role in AD along with amyloid protein. Tau protein occurs in the brain as neurofibrillary tangles. This occurs when tau protein becomes phosphorylated. The combination of amyloid plaques and neurofibrillary tangles cause synaptic loss and cell death, causing damage to the brain and dysfunction (Scheltens et al., 2016).

Clinical features and diagnosis

The largest clinical feature of AD is cognitive decline (Gauthreaux et al., 2022; Chung et al., 2015). This can take the form of trouble with memory, thinking, or concentration. Aging is typically associated with a decline in mental capacities, but cognitive decline in AD is a worsening of mental state that is much more severe than normal aging (Murman, 2015). Showing signs of memory trouble, a withdrawal from social activities, poor judgment, misplacement of items, difficulty thinking or difficulty doing familiar tasks all suggest AD (Chung et al., 2015). These signs along with other common factors such as age, provide enough evidence for additional testing to be necessary (Weller & Budson, 2018).

Diagnostic criteria was initially put in place by the National Institute of Aging-Alzheimer's Association in 1984 (Weller & Budson, 2018). It was revised in 2011 as technology changed to allow for more non-invasive testing. One of the best ways to test for AD

is a specialized PET scan. In this type of test a PET scan is conducted using one of three currently approved radiolabeled tracer agents: florbetaben, flutemetamol, or florbetapir. This test has been found to have 96% sensitivity and 100% specificity (Weller & Budson, 2018). The largest down side of the test is the cost; additionally most insurance companies do not cover it yet. Another procedure with accuracy 85%-90% is lumbar puncture procedure which analyzes fluid to determine CSF Aβ42 and hyperphosphorylated tau peptide to determine if a patient has AD. This procedure is less expensive, however it is more invasive and less accurate. Some newer methods that are under development are blood serum protein tests and serum microRNA tests (Weller & Budson, 2018).

Aducanumab

Aducanumad is a drug for treatment of AD that has recently received FDA approval and is the only drug on the market that treats the cause of disease (Schneider, 2020). Aducanumad treats AD by targeting the buildup and cause of amyloid protein in the brain (Schneider, 2020; Budd Haeberlein et al., 2022). Aducanumad is a monoclonal antibody that when in the body, selectively binds amyloid β and resolves amyloid protein plaque in the brain. Studies have shown that this drug can cause significant reduction in plague causing AD (Schneider, 2020; Budd Haeberlein et al., 2022). Despite this there is also evidence to suggest the drug wouldn't be beneficial. The approval of the drug is controversial, yet the drug manufacturer, Biogen, has made it available to patients (Schneider, 2020).

Galantamine, rivastigmine, and donepezil (cholinesterase inhibitors)

Other drugs for AD look to treat symptoms of the disease rather than the disease itself. It is believed that cholinergic neurons are lost with AD and then the loss of these neurons causes cognitive dysfunction (Vaz & Silvestre, 2020; Standridge, 2004). Galantamine, rivastigmine, and

donepezil look to solve this problem, by restoring cognitive function. The listed drugs are all cholinesterase inhibitors. In particular they stop acetylcholine hydrolysis, which increases cholinergic neurotransmission (Vaz & Silvestre, 2020; Gauthier & Molinuevo, 2012). All three of these drugs have no significant difference in efficacy (Vaz & Silvestre, 2020).

Prevention

Drinkwater et al. suggests 40% of cases could be prevented by lifestyle modifications (2021). The largest preventative measure to AD and dementia is physical activity, keeping an active brain and social activity (Sindi et al., 2015). Social engagement has been found to decrease the likelihood of developing AD. A cohort study done in 2018 from the Journal of Epidemiology and Community Health found individuals in the highest group for social engagement had a 46% less chance of developing AD/ dementia than the lowest social engagement group (Drinkwater et al., 2021). Physical activity has been well demonstrated to prevent development of AD, however the exact mechanism on how/why has not been established. It is possible that remaining physically active allows for more blood flow to the brain which helps to preserve cognitive function (Beckett et al., 2015). Smoking, hypertension, obesity, and physical inability are linked to an increased risk of developing AD. Avoiding these risk factors could reduce the risk of development by 8-15% (Sindi et al., 2015; Toda & Okamura, 2016; Solomon et al., 2014).These modifiable risk factors should be preventable through proper care of the body and medication if necessary.

Patient Review: Still Alice Movie

The movie is about Professor Alice Howland. In the movie she taught at Columbia University. The movie outlines her progression and development of Alzheimer's disease (AD) with a focus on the emotional impact of the disease.

Alice is an expert in the field of linguistics and is an excellent public speaker. The first sign of AD was during a presentation to her peers at UCLA. She completely forgot what she was trying to say mid presentation. She seems embarrassed and surprised because it usually doesn't happen to her. Later that day she decides to go for a run and gets lost despite being very familiar with the area. This experience is scary for her because it makes her begin to doubt herself. There were also small instances of her forgetting things, but they seem minor. Also she is just getting older so it doesn't appear to be out of the ordinary. With the current events going on she decided to go talk to her doctor and her doctor told her it could be menopause. The doctor then asks her numerous questions. To start he tells her to remember an address and after some questions he asks her the address which she can't remember. He asks more questions then orders an MRI. From this point forward things progressively get worse. After tests come back they conclude she has AD that is progressing quickly.

The movie allowed me to see and understand the disease from three key perspectives not covered in research: family/ social life, professional life, and personal life. One event in the movie really emphasizes how AD affects one's family and social life. Alice usually makes Thanksgiving dinner for her family. Since her family doesn't know about her diagnosis yet, she still makes Thanksgiving dinner as normal. As she is making dinner, her family arrives and greets her. Her kids are very excited to eat her food and make comments on it as they arrive.

However, Alice is having a very hard time remembering how to cook and her recipes. She has to write down everything in order to remember it, such as “remove turkey from the oven”. The worst of it is she can’t remember any of her personal recipes so she has to look up recipes for everything, losing her personal touch. This is saddening because although it doesn’t really make a difference, she isn’t able to do a small thing for her family by making her own recipe for them. Another example of how AD affects her family life is Alice and her daughter have an argument over Alice unknowingly invading her daughter’s privacy. Then later that day, Alice wants to apologize but all she can remember is that they fought but not what they fought about. Lastly, her daughter is in a show performing and after the show she asks her how long the cast was in town for. She has to be reminded that the lady performing is her daughter.AD interferes with the relationships she is able to have with her family because it removes her ability to make meaningful connections, share memories, or even remember who they are.

In her professional life, Alice sees many struggles as well. As expected, it affects her ability to teach. At the end of her last semester she receives poor evaluations from students and has to meet with the head of the department about it. She then explains her condition and tells him how much her career means to her and that she wants to keep teaching as long as possible. Ultimately, it is decided she can’t continue teaching, thus taking away a major source of pride and achievement in her life. This part made me realize the value in tasks we might not always enjoy or want to do. For example, learning and teaching is a privilege not a chore. I learned it is important to appreciate these simple things because not everyone has them, and it isn’t a guarantee that you will have them forever.

In her personal life, she is crumbling. After being diagnosed, she understood what would happen as the disease progressed. So everyday she knew she would struggle more and more. She

could no longer go out on her own or be left alone. All of the negatives from AD leave someone with a lot of anger, sadness, and depression. Alice records a video which gives her instructions for when she can no longer answer a set of simple questions. As time progresses she completely forgets about the questions, but when left alone one day, she accidentally finds the video. The video is a message instructing her to kill herself by overdosing on medication. At the time Alice made the video, she figured that when the disease progressed to the point she couldn't remember her kids names, she should end her life. When she is in the process of overdosing, someone comes in and she stops. However it is clear what she is attempting to do. After this her husband is so pained by seeing his wife go from being the "smartest person he ever knew" to her current state, he decides he needs to leave. The youngest daughter is then tasked with taking care of Alice until she passes. By this point, Alice can't function independently and needs constant supervision. The attempt of suicide puts into perspective how miserable it must be for Alice to live with AD.

AD is devastating not because of physical pain, but from emotional pain. The disease takes so much from a person. You can go from a well educated respected professor, with a loving husband, successful kids, and your health to someone who can't go to the bathroom by themselves. However this doesn't mean you can't love and be loved. Alice still had the love from her family. Our memories and experiences may be a large portion of who we are but they aren't the entirety of who we are. Alice tries to hold on to this as she shares a loving moment with her daughter at the end of the movie.

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