Risk Factors and Clinical Treatments of Alzheimer’s Disease

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Abstract. Alzheimer Disease (AD) is a neurodegenerative disease and the most common form of dementia, which is characterized by progressive memory loss and cognitive decline. The pathologic symptoms of AD are amyloid beta (Aβ) accumulation and neurofibrillary tangles (NFTs) caused by protein tau. Age is the greatest risk factor for AD, and the opportunities of developing AD increase two-fold every 5 years after age 65. AD also has a raising tendency on healthcare costs as the population have longer life span than before. In 2017, about 5.3 million people over the age of 65 in the United States were diagnosed with AD and under the influence of AD caused dementia. Researchers has been predicted that over 100 million patients will suffer from AD by 2050. Consequently, there is an urgent need to improve the investigation and treatment of AD. This paper summaries risk factors of two types of AD, molecular networks and symptoms of AD, and also current and future treatments of AD.

1. Introduction

There are two types of AD, Familiar Alzheimer Disease (FAD) caused by presenilin (PSEN) mutations and amyloid precursor protein (APP) mutations, and Late-Onset Alzheimer Disease (LOAD) [1]. Age is the major risk for AD. Pathologically, Aβ accumulation in the AD brain is caused by APP and PSEN mutations in FAD, and apolipoprotein E4 (APOE4) in LOAD. APOE4 is the E4 allele of the APOE gene, which is responsible of lipid and cholesterol transportation [2]. Only about 1% of AD cases are FAD, which is associated with inherited genetic mutations; APP, PSEN1, and PSEN2. When people inherit these risk genetic factors from their family, they develop AD through Aβ accumulations before the age of 60. Compared with FAD, most AD cases are LOAD that occur after 60, and the presence of APOE4 increase the risk of AD. To be noticed that women are more vulnerable than men to AD [3]. In mild AD, patients appear functional dependence such as trouble managing finances. In moderate AD, patients develop more dependent on others. These patients may be not able to finish daily activities such as driving, bathing, and shopping. In serve AD, patients have total dependence on caretakers, and they also have motor as well as balance impairments. Clinical Dementia Rating is a powerful tool to evaluate degrees of dementia in AD, which is characterized by memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care impairments. Currently, medical treatments of AD contain acetylcholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine) and the N-methyl-D-aspartate (NMDA) receptor antagonist (Memantine) [3]. Acetylcholinesterase inhibitors are most effective to mild to moderate AD cases, but the adverse effects of this treatment is also obvious. Nausea, vomiting, diarrhea, cardiovascular and neurologic impairments commonly perform in patients who take acetylcholinesterase inhibitors. Acetylcholinesterase inhibitors slow down the memory loss process by reversibly binding and inactivating enzymes that reduce acetylcholine. Compared with acetylcholinesterase inhibitors, NMDA receptor antagonists works for mediating moderate to serve AD cases. NMDA receptor
antagonists inhibit excitatory amino acid neurotoxicity to recover parts of learning and memory abilities.

2. Risk Factors for FAD and the Amyloid Cascade Hypothesis for AD

Three major genetic risk factors (APP, PSEN1, and PSEN2) are related with FAD [1]. The amyloid cascade hypothesis explains the importance of Aβ peptide in the AD brain pathology, and it also plays a powerful role in academia research and pharmaceutical industry [4]. Insoluble Aβ accumulation and tau NFTs are identified by Aβ peptides and hyperphosphorylated tau proteins. The amyloid cascade hypothesis describes the AD pathology from genetic factors, which suggests that Aβ accumulation in the brain is the key hallmark that generates a cascade of events that initiates neurodegeneration and clinical dementia of AD. Aβ42 is the majority species of Aβ that forms insoluble Aβ plaques. Based on this hypothesis, three main therapeutic intervention methods are developed to reduce Aβ42 production, facilitate Aβ42 clearance, and prevent Aβ42 aggregation. Most deposited Aβ (about 4-10mg) are discovered in the grey matter of the cortex (about 42% of the weight of the brain). Besides APP, PSEN1 and PSEN2 genes can code homologous proteins to enhance Aβ production. The knockin (KI) and overexpression of APP, PSEN1, and PSEN2 in AD mice model directly cause the high level of soluble Aβ in the brain. Previous studies have demonstrated that the overexpression of APP in transgenic mouse models exhibited AD-like features [4]. Studies in 2D human neuron culture also demonstrated the primary neuron cytotoxic of Aβ42 [4].

Tau protein is specific toxic to neuron system by binding and stabilizing microtubules in axons [5]. Tau is a member of microtubule-associated protein (MAP) family, which is abundant in axons. When tau proteins are hyperphosphorylated, they accumulate in somato-dendritic compartments and disable normal neuron functions, especially in the frontotemporal brain. The accumulation of NFTs can disturb other proteins by executing their physiological function. Previous tau transgenic mice models observed central nervous system (CNS) damage in their brains and AD symptoms. The phosphorylation of tau negatively regulates its activity in promoting microtubule assembly. Compared with normal brains, AD brain contains 3- to 4-fold higher phosphorylation level of tau, which impairs the axonal transportation and harmed neurons in CNS. Additionally, the formation of tangles by tau can disintegrate the transport system in CNS. When this occurs, nutrients and neurotransmitters cannot be delivered to synaptic terminals, which leads to network dysfunction and over-pruning by glia [5].

Although supporters of the amyloid cascade hypothesis propose that abnormal Aβ accumulation is the start of AD symptoms, there is also growing evidence showing that Aβ and NTFs are synergistically triggering neuron/cell death [1]. Instead of Aβ and tau working independently, Aβ can help trigger the phosphorylation of tau protein, which changes tau from a normal state to a toxic state. The in vivo experiment of crossing transgenic tau P301L mutation mice with APP overexpression systems showed accelerated tangle formation in these hybrid mice than parental APP or tau P301L mice [1]. Other evidence suggests that tau pathology is not just an epiphenomenon of Aβ pathology in neurodegenerations, and tau can mediate the toxicity of Aβ in vivo. Tau gene KO in the APP transgenic mouse models showed that these mice exhibited better learning and memory abilities than control APP mutation transgenic mice.

3. Risk Factors for LOAD

As we mentioned before, LOAD accounts for nearly 99% in AD cases. Cognitive decline and dementia are the most serious symptoms of AD, and patients lost thinking abilities, memory abilities, and basic life skills [6]. A genetic risk factor, APOE, and modifiable risk factors are discussed in this section.

APOE mutation is the genetic risk factor for AD, which resolves transport and delivery of lipids, especially cholesterol, through APOE receptors [2]. Many cells in the brain can express APOE such as astrocytes, microglia, vascular smooth muscle cells, and choroid plexus. There are three majority isoforms of APOE (E2, E3, and E4). Although APOE3 (77%) is the most common type of APOE alleles, APOE4 is the strongest genetic risk factor for both FAD and LOAD. APOE4 is associated
with Aβ42 levels in cerebrospinal fluid (CSF) samples, and Aβ42 is responsible for insoluble Aβ plaques in AD brain [1]. In previous APP transgenic mice model experiments, APOE genes were closely related with insoluble Aβ deposition [2]. The knockout (KO) of APOE genes in APP transgenic mice dramatically reduced the amount of insoluble Aβ plaques. To be specific, APOE4 promotes Aβ aggregation by increasing the level of Aβ oligomers to accelerate Aβ self-aggregating propensity. As a result, Aβ aggregation and the formation of insoluble Aβ plaques in AD brain intensely influence synaptic functions and behaviors of AD patients [2].

Not like the genetic risk factor of LOAD, modifiable risk factors are associated with cognitive decline and dementia (usually caused by AD), which can be mediated by medical interventions or individual behaviors [6]. The Alzheimer’s Association summarize the modifiable risk factors as three respects; cardiovascular risk factors, lifestyle risk factors, and other risk factors. Cardiovascular risk factor includes diabetes, mid-life obesity, mid-life hypertension, and hyperlipidemia. Recent observational and longitudinal studies have shown a negative correlation between cognitive performance and diabetes, and the high blood sugar level can cause neuron cell dysfunctions [7]. Interestingly, there is also a consistent relationship between high blood pressure, high cholesterol levels and dementia. Furthermore, some cholesterol control medications, such as stain, may reduce the risk of AD dementia [7]. Lifestyle risk factors contain smoking, physical activity, diet, alcohol, cognitive training, and social engagement. Smoking and alcohol consumption may accelerate the degree of cognitive decline and dementia in AD patients. Mediterranean diet, which has little red meat and more whole grains, fruits, vegetables, fish, buts, and olive oil, may also reduce the risk of cognitive decline and dementia among aged people. Social engagement, such as volunteer work, club activity, and church, are potential protective factors that can reduce the influence of cognitive decline and dementia. Years of formal education, traumatic brain injury, depression, and sleep are other risk factors of AD related cognitive decline and dementia [7]. Most other risk factors are focused on the synaptic plasticity, and might perform a disruption on brain functions.

4. Diagnosis and Neuroimaging of AD

Neuroimaging technologies such as functional magnetic resonance imaging (fMRI) and electroencephalography analysis (EEG) can provide various spatial and temporal data to analysis the cognitive process in brain [8]. When neuroscientist compare brain activities and working status in more experimental conditions, fMRI and EEG are two conventional and non-invasive techniques to analyze the activity in a specific brain region associated with the activity in another region defined as functional connectivity [8]. fMRI and EEG can image intrinsic functional connectivity, and identify the structural changes in AD brain [9]. To be specific, previous studies of fMRI proposed that the AD brain performs decreased functional connectivity in a precuneus and posterior cingulate cortex versus healthy control. However, an increased functional connectivity in frontal default regions was observed in AD brain. This increased functional connectivity can be explained by a possible compensatory mechanism caused by the synaptic function loss in posterior brain regions. This observation implies that the hyper-connectivity of a brain region may be triggered by the hypo-connectivity of another brain region [9].

Besides fMRI and EEG, the brief memory and executive test (BMET) is a sensitive cognitive screening tool to detect the vascular cognitive impairment (VCI) and AD [10]. Compared with conventional fMRI and EEG, BMET provide the early identification and relative accurate diagnosis of AD patients with VCI. A pilot study suggested that the BMET provided 91% sensitivity and 85% specify of AD patients with small vascular diseases (SVD). However, the flaws of BMET are obvious. BMET performs a powerful ability to differentiate VCI patients from AD, but not a useful discriminator. Furthermore, the population of AD patients with VCI is relative small, and current data collection cannot stratify the AD and SVD patients. BMET is an alternative diagnosis tool in AD clinical investigations and specific clinical settings.
5. Gender difference in AD
Among all AD patients, two-thirds are women. Surprisingly, not many studies mentioned the gender difference in AD. About 81.7% of women and 24% of men over age 90 are diagnosed with AD [11]. A MRI study has indicated that women experienced a lower risk of developing mild cognitive impairment (MCI) given a higher level of hippocampal volume compared to men. Increased hippocampal volume reduces the progression of AD, and women with reduced hippocampal volumes are more vulnerable to AD [11].

   The hippocampal volume is associated with the performance on verbal memory assessment in females under age 70. On the contrary, men are not affected by the relationship of hippocampal volume and AD. Furthermore, males with increased white matter hyperintensities (WMH) also have an increased risk of MCI, but there is no evidence suggests increased WMH in female with AD. Although many researchers believe that the APOE4 gene increases the risk of MCI or AD among females and males, the relationship between APOE and hippocampal volumes is not obvious. There might be a difference between female AD patients and male AD patients because of their various responses of later life stressors. For example, a bereavement experiment showed that females experienced a raising level of cortisol in no bereavement group while males only experienced raising level of cortisol in the bereavement group [11]. When females and males experience same psychological stresses or cumulative childhood adversities, females might have higher responses among protein levels, which might stimulate synaptic impairments.

6. Inflammation in AD
Instead of supporting amyloid cascade hypothesis, some other researchers propose an immune system-mediated action in AD pathogenesis [12]. The inflammatory response is driven by the brain’s intrinsic myeloid cells. The amyloid cascade hypothesis points out that neuroinflammation is the result of amyloid accumulations at the late stages of AD. However, recent preclinical and clinical data indicate that neuroinflammation is not only caused by amyloid accumulation but also immune system activation.

   CNS-resident myeloid cells remodel brain synapses and support CNS plasticity, and these myeloid cells are also sensitive to danger signals, such as protein aggregates or amyloid accumulations. When myeloid cells detect the abnormal action of amyloid plaques, these cells would clear amyloid plaques through receptor-mediated phagocytosis and degradation. Impairment of myeloid cells can accelerate amyloid aggregation by reducing degrading abilities. Furthermore, various structures of amyloid beta; monomers, oligomers, protofibrils, and fibrils; may trigger the inflammation activity and cytokine production in CNS-resident myeloid cells. Currently, most therapies of AD have focused on Aβ or tau hallmarks. Reducing the inflammation response in AD brains provides another suggestion in AD treatments. Potential immune targets for AD (TREM2, CD33, CR1, RXR, NLRP3, CD36, CD14, IL-12, IL-6, TNF-TNFR, CX3CR1, P2X7R, SCARA1, and TGFβ1) can be utilized to develop AD treatments to inhibit Aβ phagocytosis or induce Aβ clearance rate in the brain [12]. Combining current Aβ/tau therapy with modulating inflammation therapy can considerably delay the progression of AD.

7. Cholinesterase Inhibitor Therapy
The cholinergic hypothesis suggests that cholinergic systems in AD process influences loss of acetylcholine neurons and loss of enzymatic function for acetylcholine synthesis, and these two changes directly cause AD symptoms such as memory loss and cognitive degeneration [13]. The cholinesterase inhibitor therapy is designed to enhance cholinergic transmission by preventing acetylcholine activities [14]. The cholinesterase related drugs such as donepezil, rivastigmine, and galantamine are suggested to be the first-line treatment for AD. Reviews of these drugs mentioned its ability in recovery of cognitive functions and recovery of activities of daily living in mild and moderate AD patients. However, the drug tolerability of cholinesterase inhibitors are considered by researchers. After 3 months of treatment, patients have to increase the dose to get the same efficacy. Other adverse effects such as syncope, bradycardia, and pacemaker insertion also influence the
decision of patients. Further improvements of cholinesterase inhibitor treatment should be done to reduce the drug tolerability and adverse effects.

8. Copper-ion Chelation Therapy
As we mentioned before, AD is characterized by Aβ plaque accumulation and NFTs. The inhibition of Aβ assembly is one of the primary therapeutic strategies for treating AD. Metal ions are involved in the pathogenesis of AD by increasing the assembly and neurotoxicity of Aβ species [14]. Copper ions can accelerate the formation of Aβ accumulation by influencing the formation of neurotoxic reactive oxygen species (ROS). Researchers developed a copper-ion chelation therapy by combining copper ions with metal complexation and ligand interaction to bind with Aβ plaques for Cu²⁺ elimination and Aβ assembly inhibition abilities. The designed conjugate can bind with Cu²⁺ from Aβ plaques and become dimers, and this therapy showed an impressive ability in inhibition of Cu²⁺ and Aβ aggregation in vitro. Compared with presently marked drugs, the copper-ion chelation therapy provides new insights into altering AD progression [14]. This therapy also provides a creative design by changing copper from a risk factor into useful compounds to prevent Aβ aggregation. However, the drawback of the copper-ion chelation therapy is also obvious. This therapy has been practiced in vitro, and side effects of this therapy is still unknown. Compared in vitro tests, in vivo tests can provide a better examination about cell viability and cellular toxicity based on various cell interactions.

9. Resveratrol and Other Grape-derived Polyphenols in AD Treatments
There is increasing evidence that uptake dietary polyphenols, such as resveratrol, might beneficially influence AD processes by preventing dementia and other neurodegenerative disorders [15]. Several studies suggest that grape-derived polyphenols improve neuroplasticity mechanisms, reduce inflammatory mechanisms, and prevent Aβ as well as tau neuropathology mechanisms. However, the bioavailability of resveratrol is uncertain. Resveratrol only has less than 1% oral bioavailability, and few evidences can suggest the in vivo resveratrol bioavailability in animal models. People still do not know the bioavailability and metabolites of resveratrol in human brain. For now, there are 85 clinical trials investigating the mechanism of resveratrol in cognitive performances [15]. Compared with conventional AD therapies, resveratrol might provide an alternative scenario to treat AD.

10. Conclusion
AD is a devastating disease that influences millions of people, especially the elders. AD patients not only facing dementia and cognitive dysfunctions, but also other neurodegenerative disorders. Two important hallmarks of AD are Aβ plaques and tau NFTs. The majority researchers support the Aβ cascade hypothesis; Aβ accumulation is the trigger to tau NFTs and other neurodegenerative symptoms in neuron cells. However, there are also data suggest that tau and Aβ synergistically work together to block or influence normal neuron cell functions. Compared with LOAD, FAD is strongly genetic associated. APP, PSEN1, and PSEN2 are three major risk genes of FAD, and APOE is the genetic risk factor of LOAD. fMRI, EEG, and BMET can be used to diagnose AD patients, and clinical facts also indicate a gender difference in AD patients. The current treatments for AD are acetylcholinesterase inhibitors and the NMDA receptor antagonists. Drug tolerability of these traditional treatments makes researchers to find out novel AD treatments. There are potential AD treatments such as copper-ion chelation and resveratrol, but more in vivo tests are needed to prove the efficiency and performance of these new treatments. Over 100 million patients be influenced by AD by 2050, and more novel and stable treatments are needed.

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