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Pathogenesis and treatment of Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is a degenerative disease which was first discovered in 1907, it has been a far-reaching disease difficult to cure. Hundreds of millions of people have been plaguing AD. The high incidence rate and high death rate of AD has brought tremendous burden to country and society. Human has made significant achievement in pathobiology so far. This article first makes a brief introduction about the history of AD, and the clinical presentation of AD patients. Besides that, some issues may be neglected. Hypotheses about the pathogenicity and new treatment policy of AD have been mentioned in this essay, providing effective remedy of AD, such as primary neuropathologic criteria, amyloid positron emission tomography imaging and targeted therapies. This thesis introduces AD by doing a literature review anlysis. The critical essay summarizes the main body of academic papers, evaluates academic articles in specific fields. But it may also face the problem of what to discuss in a literature review.

Keywords: Alzheimer's Disease, Pathology, Genetics, Public health, Literature review

1. Introduction

Alois Alzheimer recorded a case in 1907 concerning a 51-year-old woman who was going through mental health problems in addition to her memory rapidly failing. Four years later, she passed away. Due to its early start and the discovery of a novel pathological condition called the neurofibrillary tangle (NFT), this illness was distinguished from other degenerative and deadly neurological illnesses that were recognized at the time, such as senile dementia. The legitimacy of Alzheimer's disease (AD) as a new nosologic entity and the rationale behind famous psychiatrist Emil Kraepelin's promotion of an obviously novel sickness are still up for debate [1].

The prevalence and progression of Alzheimer's disease (AD), a diverse illness with a complicated pathobiology, are positively connected with the patient's age. It is linked to the buildup of tau and amyloid deposits in the brain. AD patients exhibit behavioral abnormalities along with cognitive and functional deficits that worsen over time. Research on the etiology and management of AD has advanced noticeably in recent years, but there has been no meaningful advancement in therapeutic treatment.

Many hypotheses about the pathogenicity of AD have been proposed. Despite this, the genuine pathogenicity of AD is still unclear, and the effective therapy has not been discovered yet.

A typical signal of AD patients is the abnormal deposit of amyloid-β (Aβ) peptides, which is a standard for the pathological diagnosis of AD. But it is neither the definitive cause of cognitive dysfunction in AD, nor the effective outcome measures for clinical trials.

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2. Clinical Presentation of AD Patients

The most significant symptom of AD is memorial impairment. Some patients may also manifest aphasia, executive dysfunction, apathy, or personality change [4].

The memory early in the past is rarely impacted, while recent memory usually fades into oblivion. Besides, memory about episode is affected, that about working and semantics is preserved. Executive dysfunction begins early in the disease course, and get worse with the development of the disease. A common but mild symptom shows primarily is language disturbance, patients usually have difficulty in finding word to express their meaning.

Although the neurologic examination of AD patients is normal, they may act anxiously, irritably, apathetically, and depressively. Some patients may also suffer from Parkingson's disease. In the later stage, pathologic reflexes like grasp, root and suck reflexes can emerge. They could cause plenty of complications, such as swallow difficulty, malnutrition, immobility, deep venous thrombosis, and infections. The most severe cause of these complications is death of patients.

3. Neuropathological changes in different stages of AD

Six steps of differentiation were possible due to the distinctive distribution pattern displayed by neurofibrillary tangles and neuropil threads. The transentorhinal layer Pre-α (transentorhinal stages I-II) was altered in a minor or severe way throughout the first two stages. The two types of limbic stages (III-IV) were distinguished by a noticeable predisposition of layer Pre-α in the correct entorhinal cortex and transentorhinal area. Furthermore, the sector of the first Ammon's horn was somewhat involved. Almost all isocortical association regions were destroyed, which was a defining characteristic of the two isocortical stages (stages V-VI) [2].

This progression suggests a spreading of pathological changes from the initial affected areas to more extensive regions of the brain. Furthermore, the recognition of these stages required qualitative evaluation of only a few key preparations. This suggests that the differentiation of these stages can be achieved through a focused qualitative assessment, which may have practical implications for the diagnosis and understanding of the progression of AD.

4. Hypotheses about pathogenesis of AD

The pathogenesis of Alzheimer's disease (AD) involves a complex interplay of genetic, epigenetic, and environmental factors. Key components of AD pathogenesis include the accumulation of amyloid-beta (Aβ) peptides, tau protein abnormalities, synaptic dysfunction, and neuroinflammation including the amyloid cascade hypothesis, which suggests that the accumulation of beta-amyloid peptides is the primary event triggering a cascade of neurotoxic processes. Another important aspect is the role of tau protein in the formation of neurofibrillary tangles, which disrupts the normal functioning of neurons.

In addition to these hallmark features, other factors such as neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired clearance of toxic proteins have been implicated in the pathogenesis of AD. Furthermore, genetic risk factors, such as the presence of the apolipoprotein E (APOE) ε4 allele, play a role in increasing susceptibility to the disease.

1. Accumulation of Aβ: A central feature of AD pathogenesis is the aggregation and accumulation of Aβ peptides in the brain. This accumulation may result from increased production of Aβ, decreased degradation by Aβ-degrading enzymes, or reduced clearance across the blood-brain barrier.

2. Tau Protein Abnormalities: Abnormalities in tau protein, leading to the formation of neurofibrillary tangles, are also characteristic of AD pathogenesis. These abnormalities contribute to neuronal dysfunction and degeneration.

3. Synaptic Dysfunction: Dysfunction and loss of synapses, as well as aberrant neural network activity, are key substrates of cognitive decline in AD. These abnormalities are thought to be caused by copathogenic interactions among diverse factors and pathways.

4. Neuroinflammation: Neuroinflammatory processes, including microglial activation and the release of pro-inflammatory molecules, play a role in the pathogenesis of AD, contributing to neuronal damage and cognitive impairment.

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Three genes—amyloid precursor protein (APP), presenilin (PS)-1, and PS-2—have been linked to early-onset Alzheimer's disease (AD) in those under 60 years of age, according to genetic research. The processing of APP, a protein involved in the synthesis of amyloid-beta peptides, is impacted by these mutations. The production of various amyloid-beta peptides and their relative ratios are altered as a result of the alterations.

Transgenic animal models of AD have been developed to study the molecular and cellular mechanisms of AD pathogenesis in vivo. These models have been used to investigate the effects of Aβ and tau pathology on neuronal function and survival, as well as to test potential therapeutic interventions.

5. Treatment

5.1. Primary Neuropathologic Criteria

The primary neuropathologic criteria for AD diagnosis includes the presence of extracellular β-amyloid deposition as neurotic plaques and intracellular accumulation of hyperphosphorylated tau as neurofibrillary tangles. These pathological hallmarks are fundamental to the diagnosis of AD.

The newly revised criteria for the diagnosis of AD dementia now incorporate the use of biomarkers as supportive evidence for the underlying pathology. Personalized medicine is a rapidly evolving field that aims to tailor medical treatments to individual patients based on their unique genetic, environmental, and lifestyle factors. It is playing an increasingly important role in transforming pharmaceutical development and clinical trials.

In addition to clinical symptoms and cognitive assessments, biomarkers such as cerebrospinal fluid (CSF) levels of amyloid and tau proteins, and amyloid positron emission tomography (PET) imaging are considered as valuable indicators of the pathological changes associated with AD. Personalized medicine approaches are helping to identify biomarkers that can be used to diagnose AD earlier and more accurately, track disease progression, and predict treatment response. These biomarkers include genetic markers, imaging markers, and fluid biomarkers.

5.2. Amyloid Positron Emission Tomography Imaging

Advancement of pathology has been made possible through techniques in the field of AD. For instance, amyloid positron emission tomography (PET) imaging. It is an ability to visualize amyloid pathology in the living human brain, which allows for the detection of amyloid deposition in the brain. By visualizing amyloid pathology in living individuals, researchers and clinicians can gain a better understanding of the underlying pathology of AD. This improved understanding can lead to more accurate diagnosis, staging, and monitoring of the disease, as well as potentially informing the development of targeted therapeutic interventions. Overall, the visualization of amyloid pathology in the living human brain has the potential to significantly impact our approach to AD diagnosis and treatment.

Biomarkers like PET allow for the detection of pathological changes associated with AD in the early stages, even before the emergence of clinical symptoms. They also contribute to more accurate and specific diagnosis of AD, aiding in distinguishing it from other neurodegenerative disorders with similar clinical presentations, potentially leading to more effective treatments.

5.3. Targeted Therapies

For AD, targeted therapies may focus on molecules such as amyloid-beta (Aβ) peptides and tau proteins, which are known to play a central role in the development of the characteristic neuropathological features of the disease. These therapies may include drugs that aim to reduce the production of Aβ, enhance the clearance of Aβ from the brain, prevent the aggregation of Aβ into toxic forms, or interfere with the abnormal phosphorylation of tau protein.

Targeted therapies aim to achieve greater efficacy with fewer side effects compared to traditional, non-specific treatments.

Clinical trial design refers to the planning and organization of studies conducted to evaluate the safety and efficacy of medical interventions, such as drugs, medical devices, or behavioral therapies, in human

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subjects. Clearly defining the primary and secondary objectives of the clinical trial, such as assessing the efficacy of a new treatment in slowing disease progression, improving cognitive function, or reducing the burden of symptoms.

First of all, establishing criteria for the inclusion and exclusion of participants based on factors such as age, disease stage, genetic background, and other relevant medical conditions to ensure the trial's results are applicable to the intended patient population.

Secondly, implementing randomization to assign participants to different treatment groups and blinding to ensure that neither the participants nor the researchers are aware of who is receiving the experimental treatment, reducing bias in the study results.

Besides that, identifying specific measures, such as cognitive assessments, biomarker levels, or functional abilities, to evaluate the impact of the intervention on the disease and the well-being of the participants. Planning the statistical methods that will be used to analyze the data collected during the trial to determine the treatment's efficacy and safety. Ensuring that the trial is conducted in accordance with ethical principles, including obtaining informed consent from participants and minimizing potential risks.

Well-designed clinical trials are essential for generating reliable evidence regarding the safety and efficacy of potential treatments for AD, and they play a critical role in advancing our ability to develop effective interventions for this complex and devastating disease.

5.4. Future Disease-modifying Therapies

There are several possible opportunities for developing future disease-modifying therapies for AD.

1. Applying anti-amyloid treatment strategies to the preclinical disease, ideally as early as possible, with drugs shown to hit their target effectively.
2. Pursuing non-amyloid-based therapies, such as tau- and ApoE-directed therapeutics, which remain at an early stage of development but hold great potential.
3. Developing therapies that modulate the neuroimmune or microglial response in AD, which is significantly under-represented in drug development.
4. Employing combination therapy strategies in AD clinical trial design.

6. Conclusion

Research of Alzheimer's disease is at a unique stage in which theory is abundant but effective therapy has not been found. Emphasizing its heterogeneity and complex pathobiology, AD occurrence is related with age of patients, the challenges in clinical treatment still need to be taken into account.

Clinical manifestations of AD, including memory impairment, aphasia, executive dysfunction, and behavioral changes, bring plenty of inconvenience to patients, even cause their death. The progression of neuropathological changes in different AD stages is explored, suggesting a spreading pattern of pathological alterations in the brain.

There are various hypotheses about AD's pathogenesis, emphasizing genetic, epigenetic, and environmental factors. Key components include the accumulation of amyloid-beta (Aβ) peptides, tau protein abnormalities, synaptic dysfunction, and neuroinflammation. Genetic studies reveal mutations in genes like APP, PS-1, and PS-2, while transgenic animal models help understand molecular mechanisms in vivo.

The primary neuropathologic criteria for AD diagnosis involve extracellular β-amyloid deposition and intracellular accumulation of hyperphosphorylated tau. Biomarkers are now included in revised diagnostic criteria, stressing the importance of personalized medicine in adapting therapies to individual needs. Targeted therapy for Alzheimer's disease aims to improve efficacy and minimize negative effects by targeting A β peptides and tau proteins. Personalized clinical trials play a crucial part in treatment, detailing key topics such as defining objectives, participation requirements, randomization, blinding, and ethical issues. Amyloid positron emission tomography (PET) imaging is a big step forward in visualizing amyloid disease in the living human brain. This approach promotes early identification, accurate diagnosis, and potential therapy development.

A host of future possibilities for disease-modifying therapies are raised, including anti-amyloid treatments in preclinical stages, non-amyloid-based therapies targeting tau and ApoE, modulation of neuroimmune responses, and combination therapy strategies in clinical trials. Overall, the comprehensive exploration sheds light on the complexities of Alzheimer's disease and the evolving landscape of research and treatment strategies. Because of the limitation of literature review, some issues may be neglected. Human will do research on AD intensively, making it a curable disease in the future.

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