Alzheimer's disease: Anatomy, Pathogenesis, Early diagnosis and Treatment. Review

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease of the brain that causes dementia in elderly people. In fact, the pathological changes of the disease begin several years in different stages before the clear clinical symptoms of AD's dementia appear. The accumulation of t beta-amyloid plaques outside neurons and tau tangles protein inside neurons mainly in the entorhinal cortex and hippocampus area are the hallmark changes in the brain of patients with AD. A combination of medical, physical and neuropsychological tests is usually used to diagnose and determine the stage of the disease. Until now there is no effective treatment to stop the progression or cure AD and the current approaches aim at decreasing or to stabilizing the progression of the disease. This review discusses the brain anatomy changes associated with the disease, pathogenic hypothesis of the disease, early diagnosis, management and recommended approaches to inhibit the progression the disease.

Keywords: Dementia, Amyloid Plaques, Neurofibrillary Tangles, hippocampus.**ntroduction**

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Alzheimer's disease (AD) is an irreversible progressive neurodegenerative disorder marked by cognitive and behavioral impairment that significantly affects social and occupational functions(Alzheimer's disease facts and figures, 2019). It is considered the most common form of dementia in the elderly population as it affects approximately 12% of elderly individuals (Alzheimer's disease facts and figures, 2019; Hernández-Zimbrón et al., 2017; Maccioni et al., 2018). . In 2015 Alzheimer's Disease International (ADI) announced that 900 million individuals aged 60 years or above were living worldwide, and this number was expected to increase by 138–239% between 2015 and 2050 especially in the middle-income countries such as china(Adlimoghaddam et al., 2018; An et al., 2018). In the united states, research showed that 5.8 million Americans have been diagnosed with Alzheimer's dementia and it is considered as the sixth causing death in the united states among individuals aged 65 years or above (121,404 deaths have been reported from AD in 2017)(Alzheimer's disease facts and figures, 2019). This estimation was based according to the definition of dementia as a severe loss of cognitive functions related to memory, attention, executive function and processing speed beyond the normal aging process.

In the absence of an effective treatment, the researchers responsible for developing strategies to reduce the risk and slow the progression associated with mental aging(An et al., 2018).This review concentrates in anatomy and pathophysiological changes of the brain associated with the disease which can be used as a clinical tool for early diagnosis, management and recommended approaches to inhibit the progression the disease.

1. Brain anatomy changes associated with Alzheimer disease The cerebral cortex is an extensively convoluted with bulges known as gyri and deep fissures known as sulci. It contains sensory, motor and important association regions that are responsible for "complex" functions of the brain including thought, reasoning, sensation, and motion. Each hemisphere of the cerebral cortex consists of a frontal lobe, a parietal lobe, a temporal lobe, and an occipital lobe. It is suggested that each lobe controls certain types of brain activities; however, some overlap does exist between the different lobes. The frontal lobe is mainly responsible for voluntary movement, emotion, planning and execution of behavior, intellect, memory, speech, writing and dictates the personality of an individual. The parietal lobe receives and interprets sensations of pain pressure, temperature, touch, size, shape, and body consciousness. The temporal lobe is responsible for understanding sounds and spoken words as well as emotion and visual memory. The occipital lobe is involved in understanding the visual images and the meaning of the written word (Javed and Lui, 2019). The hippocampus which is part of the limbic system plays a crucial role in learning and processing various forms of information such as long-term memory and formation of new memory. Damage or trauma to the hippocampus region can lead to global loss of memory (Medicalnewstoday, 2019).

In AD, however, damage is widespread in different region, as several neurons stop functioning, lose connections with other neurons, and degenerate. This lead to disruption in certain processes that are vital to neurons and their networks, including communication, metabolism, and repair.

Preclinical features (histopathologic changes) of AD include synaptic degeneration, hippocampal neuronal loss, and aneuploidy, which usually precede the clinical changes (Swerdlow, 2007). The Structural atrophy can be detected via MRI in the preclinical asymptomatic phase of AD while the changes in the molecular and cells of the brain of the patient can be observed by the microscope after death(Raskin et al., 2015). Anatomical signs of AD include progressive brain atrophy, particularly in the hippocampal region. At the early stage of the disease the neurons and their connections in the area of memory including entorhinal cortex and hippocampus are affected and later on the cerebral cortex responsible for language, reasoning, and social behavior gets damaged leading to a gradual loss in the individual's ability to live and function independently over time.

2. Pathophysiology

Several studies indicated that the presence of toxic neurofibrillary tangles and extracellular amyloidal protein deposits are the main distinctive features of the brain in patients diagnosed with AD (Epidemiology, pathology, and pathogenesis of Alzheimer disease - UpToDate, 2019; Kumar et al., 2015; Kumar and Tsao, 2019). However, there is still a debate whether these deposits are distinct of AD or part of aging since studies revealed that tangle-and-plaque deposits are also usually present in the brains of the elderly individuals, especially those over the age of 85(Swerdlow, 2007).

Two main pathogenic AD hypotheses have been suggested to explain the development and progression of AD(Mendiola-Precoma et al., 2016), the amyloid cascade hypothesis (which assumes AD is always due to primary amyloidosis)(Suzhen et al., 2012), and the mitochondrial cascade hypothesis (which assumes that most AD results from secondary amyloidosis)(Swerdlow, 2007). The amyloid cascade hypothesis proposes that *"Our hypothesis is that deposition of amyloid β protein (AβP), the main component of the plaques, is the causative agent of Alzheimer's pathology and that the neurofibrillary tangles, cell loss,*

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vascular damage, and dementia follow as a direct result of this deposition"(Ricciarelli and Fedele, 2017). The mitochondrial cascade hypothesis suggests that defect in mitochondrial functions result in the different cellular changes observed in the late-onset AD. This includes Aβ amyloidosis, tau phosphorylation, oxidative stress, synaptic loss, and neurodegeneration(Swerdlow, 2007; Swerdlow and Khan, 2004).

In the last several years the researches have focused their interest on the inflammation hypothesis or the microglia-related pathways to investigate the role of microglial cells in progression of AD. Several human genetic studies of AD indicated that key Alzheimer's risk genes such as TREM2, CD33, ABCA7, and MS4A6A are highly expressed in microglial cells(Hansen et al., 2018; McQuade and Blurton-Jones, 2019). In addition, it is was shown that there is a significant evidence indicating that microglial cells could have both beneficial and harmful effect to the neurons(Hansen et al., 2018). In the early stage of the disease, microglial activity is useful to the brain and prevent the development of AD because microglial serve as housekeeping phagocytes that maintain tissue homeostasis and prevent the formation of Aβ-amyloid plaque in the extracellular space. However, in the late stage of the disease the microglial cells become harmful because they can engulf and remove the synapse via a complement-dependent mechanism; impair tau pathology and activate the secretion of inflammatory factors or neurotoxic astrocytes which lead to nerve injury and neurodegeneration(Hansen et al., 2018; Maccioni et al., 2018)

2.1. Amyloid Plaques

Amyloid precursor protein(APP) are large proteins and the main source for beta-amyloid protein (Aβ). In the healthy brain, the protein fragments of beta-amyloid are broken down and eliminated. In AD, these fragments accumulate forming hard, insoluble protein clumps known as plaques that collect between the neurons and interrupt cell function. These plaques consist of beta-amyloid proteins, which occupies the center of these plaques, surrounded by the fragments of deteriorating neurons, especially those that produce acetylcholine (ACh), a main neurotransmitter essential for processing memory and learning. Different molecular forms of beta-amyloid proteins are involved in AD, the most toxic being the beta-amyloid 42 (Aβ42) (Raskin et al., 2015). Aβ deposits in the brain usually start in the basal neocortex, spreading throughout the hippocampus, and finally spread throughout all the cortex areas (Braak and Braak, 1997; Raskin et al., 2015). Current research is focused on elucidating how the various forms of beta-amyloid influence the development and progression AD and are their roles at the different stages of the disease (Raskin et al., 2015).

According to the amyloid hypothesis, the accumulation of Aβ in the brain tissues is a crucial stimulus in the AD pathogenesis and its development. The next stages of the disease and its progression depend on the formation of neurofibrillary tangles inclosing tau protein Accordingly, this hypothesis suggests that AD is caused as a result of an imbalance between the Aβ production and their clearance(Hardy, 2002).

2.2. Neurofibrillary Tangles

Tau is an abundant protein in the central nervous system and it is found in the neurons responsible for stabilizing of the cellular microtubules. It has been found that in AD patients there is a defective in chemical changes cause tau to detach from microtubules and stick to other tau molecules, thus, forming thread-like structures protein known as" neurofibrillary tangles". These accumulation of these tangles block the neuron transport system and

damage the synaptic communication between neurons(Mandelkow et al ., 2003; Mandelkow and Mandelkow, 2012; Raskin et al., 2015). It is also suggested that the accumulation of tau proteins and beta –amyloid plaques, especially in memory sites of brain, is the main cause of Alzheimer disease (Chen et al., 2018; Chirita et al., 2005; Mandelkow et al., 2003; Tong et al., 2018).

3. Causes and risk factors of AD

The main cause of AD is still indistinct and most studies suggested that it is due to combination of genetic factors (Nicolas et al., 2018; Takatori et al., 2019; Wang et al., 2019), vascular and environmental factors that accumulate with age (Mayeux et al., 1995; Munoz and Feldman, 2000). Age is considered the strongest risk factor for AD (Rivera et al., 2019) as the majority of individuals with AD are 65 years of age or older(Almeida and Carrettiero, 2018). 10% of AD patients, almost all being early-onset familial inheritance AD(Grossberg and Desai, 2003). Other risk factors include diabetes type 2(Mendiola-Precoma et al., 2016) (Salas and De Strooper, 2019), hypertension(Mendiola-Precoma et al., 2016), hypercholesterolemia(Mendiola-Precoma et al., 2016), vitamin D deficiency (Dursun and Gezen-Ak, 2019), obesity(Jones and Rebeck, 2018), mild cognitive impairment (MCI)(Petersen, 2016) and brain injuries(Kokiko-Cochran and Godbout, 2018).

4. Symptoms of AD

AD normally develops and progresses slowly in three stages; mild (initial stage), moderate (middle stage), and severe (late stage). The decline in cognitive and functional abilities distends over 5–8 years with an average of 2–20 years(Grossberg and Desai, 2003). The pathological changes in the affected area of the brain begin at least 10-20 years before the clear symptoms of the disease appear(Holtzman et al., 2011).

During the initial mild stage, the patient illustrates short-term memory impairment accompanied by signs of anxiety and depression. This stage usually persists 2–3 years(Grossberg and Desai, 2003) . In the moderate stage of AD, the neuropsychiatric symptoms (NPSs) such as apathy(Breitve et al., 2018), depression, psychosis, sleeping disturbance, hallucinations and delusions, anger, agitation and aggression, loss of inhibitions, appetite as well as anger are the main signs of AD patients(Chen et al., 2018; Lanctôt et al., 2017; Li et al., 2014). The moderate stage usually lasts for 2-4 years(Holtzman et al., 2011). The severe and more advanced stage is characterized by loss of certain motor functions as a result of stark loss of brain function. At this stage, the patient is unable to dress, lacks urinary and defecation control; therefore, the patient becomes completely dependent on others for their care. The physical care and the neuropsychiatric care are highly recommended at this stage (Grossberg and Desai, 2003; Holtzman et al., 2011; Neugroschl and Wang, 2011)

5. Diagnosis

Early and accurate diagnosis of disease is very important stage in treatment of AD patients especially in younger individuals (Barnes et al., 2018). Current new practices performed more than one evaluation method c to detect the primary symptoms of AD to differentiate it from other types of dementia. Medical history, physical examination, blood and urine tests, a psychiatric assessment, neuropsychological tests (to assess memory and thinking abilities) and brain scan using CT,MRI and PET methods have been recommended for assessment and diagnosis of AD

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patients(Johnson et al., 2012; Panegyres et al., 2016). These tests also are used to evaluate memory impairment, thinking skills, and functional abilities as well as detect behavior changes for AD patient. Recent developments in the diagnostic skills and instruments lead to improvements in the early diagnosis of AD and differentiating it from other types of dementia, especially frontotemporal dementia (FTD).

In the past, the clinician followed several steps to increase the accuracy of AD diagnosis; however, recently the diagnosis of AD depends mainly on the presence of brain amyloidosis or neural injury, which are considered as critical landmarks associated with AD. The confirmation of the diagnosis can only be done post mortem by examination of the brain tissue to identify the plaques and tangles(Benussi et al., 2018). Positron emission tomography (PET) scans are one of the most common methods used by clinicians to detect and monitor the plaques and tangles formation in the patient brains with 96% sensitivity and 100% specificity(Weller and Budson, 2018). Also, obtaining lumbar puncture sample from patients is useful for measuring the concentration of abnormal proteins in cerebrospinal fluid (CSF) such as Aβ42 and tau- protein and is considered a predictive test for AD(Hampel et al., 2008; Petersen, 2018; Souza et al., 2014). Even though measuring the protein concentrations in CSF method is less expensive than the PET method, obtaining a lumbar puncture has lower diagnostic accuracy (85–90%) than the PET method, is more risky for the patient and it usually takes weeks to acquire the results (Weller and Budson, 2018).

6. Treatment

Currently, there is no effective medication nor therapeutic approach to completely treat AD. Moreover, early diagnosis of the AD is considered the most critical factor in the treatment and limiting the progression of the disease(Weller and Budson, 2018).The current medications used in the treatment of AD either stabilize or inhibit the progression of the disease, particularly the symptoms related to memory and thinking functions(Briggs et al., 2016). The cholinesterase inhibitors such as donepezil , rivastigmine , and galantamine are suggested for managing for patients diagnosed with mild, moderate, or severe AD in order to decrease the agitation or depression symptoms(Briggs et al., 2016). Namenda (Memantine), also an acetylcholinesterase inhibitor, is used in moderate and severe stages to inhibit the development of behavioral symptoms(van Marum, 2009). Also, it is recommended to supplement the diet of AD patients with food rich in vitamin D and omega-3 fatty acids. Early diagnosis of the AD is the most risk factor in treatment and limitation the progression of the disease(Weller and Budson, 2018).

Some investigators are currently focusing on managing the beta-amyloid plaques and (Aβ-plaque) and neurofibrillary tangles (p-tau)(Weller and Budson, 2018). For instance, it was shown that anti-amyloid drugs can prevent the beta-amyloid fragments from clumping into plaques by inhibiting the activity of the beta-secretase enzyme; and using antibodies against beta-amyloid to remove it from the brain (Briggs et al., 2016; Kozin et al, 2018; Schenk et al., 1999; Weller and Budson, 2018; Wisniewski and Konietzko, 2008). Whereas, anti- tau drugs has been investigated to prevent the aggregation of tau and twisting into tangles (Briggs et al., 2016). Moreover, animals studies demonstrated that tau vaccines are safety and effective and present a promising treatment of AD (Weller and Budson, 2018).

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7. Prevention

Although there is of research performed on identifying the risk factors of AD, there is still no specific knowledge on how to prevent it. Certain risk factors such as age and familial inheritance cannot be controlled. However, life style modifications (exercise(Ginis et al., 2017), healthy diet, stop smoking, avoiding head and heart injuries) and the treatment of other related diseases including s hypertension and diabetes can be lead to hindering the development or progression of AD (Norton et al., 2014; Patterson et al., 2008) Several studies indicated that the use of nonsteroidal anti-inflammatory drugs (NSAIDs), vitamin supplements, estrogens in women and other anti-inflammatory drugs has the potential to reduce the risk of developing AD(Hodes et al., 2019; Mendiola-Precoma et al., 2016; Patterson et al., 2008)

Conclusion

AD is the most common type of dementia in elderly people, and its incidence is increasing universally. The pathological changes of the disease begin years before the clear symptoms appear. The clinicians usually depend on a wide- spectrum of neuropsychological evaluation, brain imaging, and cerebral spine fluid biomarkers tests to diagnose the disease with high accuracy. Even though there are currently no therapy for treating the AD completely, researchers are in constantly attempting to develop drugs and therapeutic approaches to control the cognitive and behavioral symptoms and limit the progression of the disease.References

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