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REVIEW ARTICLE **OPEN ACCESS**

Alzheimer's disease: A Systematic Review

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ABSTRACT
Alzheimer's disease, the most common type of dementia, is a serious global health issue with far- reaching implications for both individuals and society. This paper summarizes the current understanding of Alzheimer's disease epidemiology, genetics, pathology, and pathophysiology before analyzing its clinical presentation and current treatment strategies. Finally, the report emphasizes how our enhanced understanding of Alzheimer's etiology, not ably the discovery of a protracted preclinical stage, is leading innovative therapeutic techniques targeted at transitioning from treatment to protection.
Keywords*: Alzheimer's disease, epidemiology, pathogenesis, pathology, treatment.*

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INTRODUCTION

The World Health Organization has designated Alzheimer's disease (AD) as a worldwide public health concern. Due to significant advances in our understanding of AD pathophysiology and how the illness is understood since Alois Alzheimer reported the first case in 1907, we still have a long way to go [1].
The most frequent kind of dementia is Alzheimer's disease (AD) [2] it affects as least 27 million individuals and accounts for 60to 70%ofalldementia cases. The incidence of this disorder has a significant influence on the lives of the patient's family as well as a significant financial cost to society [3].
Primary care doctors and specialists will increasingly meet dementia patients throughout their careers. Because dementia has serious consequences for patients, their families, and our society, well-rounded clinicians must be well-versed in the subject. The goal of this review article is to offer a quick overview of Alzheimer's disease and the associated notion of moderate cognitive impairment (MCI) [4].
The paper focuses on clinical and neurobiological features of AD and MCI that young doctors should be aware of. Furthermore, the article discusses improvements in the application of biomarkers for the detection of Alzheimer's disease and emphasizes current attempts to create innovative therapeutics [5].

Dementia

Dementia is a psychological disorder (a collection of coexisting signs and symptoms) characterized by a gradual decline in mental function. 4 Dementia can affect a variety of cognitive capacities, including memory, language, reasoning, decision-making, visuospatial function, attention, and orientation. Cognitive deficits in dementia patients are frequently linked o changes in personality, emotional control, and social behaviors [6].
There are numerous reversible and irreversible causes of dementia.[4] Reversible dementias (also known as 'pseudo-dementias') are relatively uncommon but potentially preventable and happen as a result of another serious illness, such as depression, nutritional deficiencies (e.g., vitamin B12), metabolic and endocrine disorders (e.g., hypothyroidism), or space-occupying lesions [7].

Epidemiology

According to current estimates, 44 million individuals worldwide suffer with dementia. This is expected to more than treble by 2050, when the yearly expense of dementia in the United States alone maysur pass US$600 billion. Dementia is the top cause of mortality in England and Wales, responsible for 11.6% of all

deaths recorded in 2015 [8].

Recent research has shown that the prevalence of dementia, especially in males, is decreasing in Western nations; it is unknown which causes of dementia are reducing, although this might be due to better management of vascular risk. The greatest increase in dementia prevalence is projected in poor and medium income nations, which have rising rates of cardiovascular disease, hypertension, and diabetes.[9]

AD is a complex illness with no single cause recognized, and various modifiable and non- modifiable health issues are linked to its growth and progression. The most important risk factor for the occurrence of AD is age. The probability of having Alzheimer's disease grows rapidly with age, about increasing every 5 years after the age of 65 [10].

The great majority of people with Alzheimer's disease are 65 or older and have 'late-onset' or 'sporadic' Alzheimer's disease (95% of all cases). Uncommon genetic mutations are associated with the onset of Alzheimer's disease (AD) before the age of 65, a condition known as 'early onset' or 'familial' AD [11].

Persons with familial Alzheimer's disease (AD) have an autosomal dominant variation in either one of the presenilin genes on chromosomes 1 and 14, or in the amyloid precursor protein (APP) gene on chromosome [12].

Neuropathology

The normal structure and function of the brain are significantly disrupted by AD, a neurodegenerative brain illness that progresses over time. A gradual loss of cortical neurons, particularly pyramidal cells that mediate higher cognitive tasks, is a biological feature of AD [13].

Significant evidence also points to the possibility that AD disrupts connectivity among brain circuits crucial for memory and other cognitive functions early in the disease process. The entorhinal cortex and hippocampal regions of the medial temporal lobe are where AD-related degeneration first manifests itself.[20]Memoryand learning problems are common in early clinical signs of Alzheimer's disease when these brain regions are damaged [14].

Clinical features

The most frequent kind of Alzheimer's disease is an elderly person with gradual, progressive issues with episodic memory. The patient may meet the criteria for amnestic mild cognitive impairment at this point (MCI).

Topographical issues, as well as challenges with multitasking and lack of confidence, are common outcomes. As the illness worsens, cognitive impairments become deeper and more extensive, interfering with daily tasks; at this point, a patient might be diagnosed with AD dementia. The norm is increasing reliance, and later in the disease, behavioral changes, reduced mobility, hallucinations, and seizures may appear. Death occurs after a median of 8.5 years from appearance [15].

These conditions include posterior cerebral atrophy (PCA), logopenic aphasia (LPA), and the frontal version of Alzheimer's disease (AD). While amyloid is extensively dispersed in PCA, the load of tau pathology and atrophy is first concentrated in the parieto-occipital lobes, and patients often appear with substantial visuospatial and visuoperceptual difficulties, as well as dyspraxia, with somewhat retained recall [16].

Diagnosis

An autopsy-based (post-mortem) pathological investigation is the gold standard for diagnosing Alzheimer's disease. The existence and dispersion of amyloid plaques and NFT in the brain are utilized to make a 'definitive' diagnosis of AD and stage the disease. In medical settings, the identification of Alzheimer's disease is mostly dependent on a medical history, physical and neurological tests, and cognitive evaluation, as well as the elimination of other etiologies through the use of selective auxiliary testing. Clinical diagnosis of Alzheimer's disease has an accuracy of 70-90% when compared to pathological diagnosis, with higher accuracies achieved in specialization settings such as memory problem centers [17].

When a patient's cognitive impairment follows an unusual clinical path or is considered to be caused by something other than AD, the identification of 'possible' AD dementia is advised. Physical and neurological exams of patients with Alzheimer's disease are typically normal. Table 1 outlines some of the clinical aspects that discriminate to aid in differential diagnosis [18].

Table1.Clinical features that distinguish AD from other dementias

Clinical features	Alzheimer's dementia	Vascular dementia	Parkinson's dementia	Dementia with Lewy bodies
Patient profile	>65 years old	>40-year-old	>65 years old	75yearsold (mean)
History	Gradual onset and deterioration	Acute onset, step-wise deterioration	Gradual onset and deterioration	Gradual onset and deterioration
Initial symptoms	Memory loss	Executive dysfunction	Visusal hallucinations	Visusal hallucinations Fluctuating attention
Physical findings	No motor impairment (until late stage)	Pyramidal (upper motor neuron signs)	Parkinsonism (precedes dementia by > 1 year)	Parkinsonism (presents within 1 year of dementia)

Notes: Pyramidal (upper motor neuron) signs include hyper reflexia, spasticity, weakness, and extensor plantar responses (Babinski sign). Parkinsonism refers to the following features: bradykinesia, cogwheel rigidity, resting tremor, and postural instability.[6]

The American Academy of Neurology recommends only three laboratory tests as part of a dementia work-up: serum B12, thyroid stimulating hormone (TSH), and free thyroxine (T4) levels. 26 To rule out normal pressure hydrocephalus, cerebral hematomas, brain tumors, and cerebrovascular lesions, structural magnetic resonance imaging (MRI) or non-contrast computed tomography (CT) may be beneficial [19].

Treatment

There is currently no cure for Alzheimer's disease and medication therapy for the condition is still in its early stages. Approved drugs for the treatment of probable Alzheimer's disease help control symptoms but do not slow or reverse the disease's progression. At the moment, medicines that target neurotransmitter systems in the brain remain the main stay of AD therapy [20].

Acetylcholinesterase inhibitors increase memory function and attention in Alzheimer's disease patients by interfering with the breakdown of acetylcholine, hence raising the neurotransmitter levels at the synapse. There are now three FDA-approved drug class: rivastigmine and galantamine (for mild to moderate Alzheimer's disease), and donepezil(for severe Alzheimer's disease) (for all stages of AD). Memantine is yet another FDA-approved treatment for moderate to severe Alzheimer's disease, although it belongs to a separate class of pharmaceuticals known as NMDA (glutamate) receptor antagonists. Both kinds of medicines are usually well-tolerated, with the most frequent side effects being gastrointestinal discomfort, dizziness, and headache [21].

Secretase inhibitors, for example, inhibit the secretase (protease) enzymes that cleave APP to generate Ab. Another technique that has been tried is the use of medicines that increase Ab clearance by active or passive vaccination. 30 However, several completed phase three trials with various amyloid-lowering medicines had failed to establish clinical efficacy as of the publication of this article [22].

Other key source of possible Alzheimer's treatments is the pool of medications already on the market for non-AD reasons such as diabetes, hypertension, and infectious disease. This drug repurposing or repositioning technique can considerably accelerate the identification of novel AD medicines and has previously been employed for many other neurodegenerative conditions (e.g., the anti-viral drug amantadine for use in Parkinson's disease). Given that the disease can begin years or even decades before the onset of dementia, early detection and treatment are crucial [23].

Immunotherapy for AD

The immune system has a significant role in the aetiology of Alzheimer's disease. AD is an autoimmune illness marked by increasing memory loss, cognitive impairment, and a personality paradigm change. 25

Defective microglias are also thought to be risk factors for Alzheimer's disease. Although a disturbance in microglial activity and alterations in microglial response to A are connected with higher AD risk, there is growing evidence that microglia inhibit the onset of AD. On the contrary, substantial evidence shows that active microglia can harm neurons. Microglia normally function as housekeeping phagocytes, maintaining tissue homeostasis and keeping the extracellular space free of A, so guarding against AD. Microglia ingest and clear A aggregates when A levels rise, and when A activity is reduced, microgliacondense A into thick plaques and block it from neurons.

Several immunotherapies are now in clinical trials, with many more set to begin soon. A immunotherapy, which combined both active and passive administration of anti-A antibodies, reduced A deposition and averted AD-like pathology in a transgenic mouse model. Active vaccination with intact A42 peptide stimulates T-cell, B-cell, and microglial immune responses, whereas active vaccination with synthetic A fragments conjugated with carrier protein stimulates T-cells to release cytokines that allow B-cells to mature and produce antibodies.26

Biomarkers

In the brief term, biomarkers of Alzheimer's disease are required to improve patient selection in clinical trials; in the long run, biomarkers are necessary to identify high-risk people for proper diagnosis as well as to detect disease progression and response to therapy. This section discusses some of the most often utilized biomarker techniques as well as associated findings in AD and MCI.[24]

Diagnostic markers

Today, imaging techniques such as structural MRI to visualise brain atrophy, 18F-2-fuoro-2- deoxy-D-glucose ([18F]FDG) PET to measure brain metabolism, amyloid-PET to quantify insoluble A deposits (plaques), Tau-PET [18F] for taucipir to quantify pathogenic Tau, and CSF biomarkers (CSF A42 and Tau) are recognized as valid screening methods [27].

A wide number of amyloid-PET studies claim over 90% sensitivity and specificity in diagnosing Alzheimer's disease, with very slight differences across the many different radioligands [28]. Tau PET also beats MRI indications in terms of diagnostic accuracy in separating AD dementia from other neurodegenerative disorders. CSF A1-42, hyper phosphorylated Tau peptide (P-Tau), and total Tau protein (T-Tau) have good diagnostic accuracy, exceeding 90% when used together.[29]

Blood and body fluid biomarkers

Blood-based and fluorescent biomarkers are being developed, notably for the detection of Tau in plasma. Blood-based biomarkers have the advantage of being compatible with basic health care use since blood samples are easy and do not require much training. A blood-based biomarker analysis might be an acceptable starting step in a multi-stage diagnostic method. Primary care facilities may screen patients to detect those who may require additional evaluation by professionals, such as CSF diagnostic analysis, MRI, or amyloid PET diagnostics [30].

Occular markers

Eye scans that use high-resolution imaging technologies, such as optical coherence tomography (OCT), to diagnose Alzheimer's disease at an early stage are becoming increasingly common. Several studies in Alzheimer's disease animal models have revealed degenerative changes in the retina.[31]

Blood-based biomarkers of protein pathology Aβ in plasma

The major component of the insoluble protein inclusions, or plaques, seen in Alzheimer's disease brains is Aβ. The protein exists in two forms: pathogenic A42 (found in diffuse amyloid aggregates) and A40 (found in the centre of mature plaques) [32].

Numerous studies demonstrate that plasma A could be a more cost-effective alternative to standard CSF-based markers for detecting Alzheimer's disease. Yet, practical adoption has been hampered by results variability and negligible gains in A42 and A40 levels in blood plasma relative to CSF A in Alzheimer's chronic conditions [33].

This problem might be connected to A β epitope masking by binding to plasma proteins, which is an analytical limitation of enzyme-linked immunosorbent assay (ELISA) or other conventional immunoassays routinely used to detect A β levels in plasma. It is likely that the absence of contact between A in plasma and CSF is due to A β expression by cells in peripheral organs such as platelets. Yet, despite the development of sensitive anaylsis methods, the use of plasma Aβ as a biomarker is most likely to become a feasible screening tool, primarily in combination with other clinical measures [34].

PlasmaTau

Tau's main physiological role is to keep microtubules in neuronal axons stable. In Alzheimer's disease, neuroaxial degeneration produces increased Tau release from neurons. Tau is also shortened and phosphorylated, causing it to collect in the proximal axoplasm's neuro fbrillary tangles. The primary component of neurofbrillary tangles in Alzheimer's disease and other tauopathies is inappropriately phosphorylated and truncated tau protein [35].

CSF total Tau may be a non-specific test since it is elevated as an indication of neuronal death following traumatic brain injury and severe stroke. Elevated levels of phosphorylated Tauin CSF and blood, such as P-Tau181, P-Tau217, and P-Tau231, are thought to be AD-specific biomarkers.[36]A recent study of both the ADNI and Bio Finder data demonstrated that P-Tau levels in people with SCD or MCI reliably predicted their development to AD [37].

CONCLUSION

Since Alois Alzheimer documented the first case of Alzheimer's disease more than a century ago, tremendous progress has been made in understanding the illness's biology and clinical characteristics. Significant progress has been achieved in describing pre-dementia phases of Alzheimer's disease, such as MCI, and enhancing the diagnostic and treatment options for controlling Alzheimer's disease. Our capacity to identify a "cure" for Alzheimer's disease largely depends not only on a precise understanding of the cellular and molecular mechanisms that go wrong, but also on having adequate biomarkers to enable

accurate diagnosis and timely treatment methods in at-risk people. Recognizing the critical need for clinically significant neuro imaging and other biomarkers for early identification of Alzheimer's disease, the NIA launched the Alzheimer's disease Neuroimaging Initiative (ADNI) in 2004. The ADNI is a public-private partnership that aims to collect longitudinal neuro imaging data, clinical data, neuropsychological tests, and biological materials (e.g., blood and CSF) from people with MCI, Alzheimer's disease, and healthy older people. It is the most extensive endeavor of its sort.[38]

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