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Alzheimer's Disease

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Abstract: *Alzheimer's disease (AD) is a degenerative disorder of the nervous system that progresses over time, leading to cognitive decline, impairment in daily activities, and behavioral changes. It is recognized as the most prevalent form of dementia in both early-onset and late-onset cases. According to estimates by the World Health Organization (WHO), approximately 5% of men and 6% of women over the age of 60 worldwide are affected by this condition. AD initially manifests as subtle memory lapses that are often overlooked but progressively worsen, ultimately leading to significant disability. Current treatment options, such as acetylcholinesterase inhibitors (e.g., rivastigmine, galantamine, donepezil) and NMDA receptor antagonists (e.g., memantine), provide only limited benefits, focusing on symptom management rather than addressing the root cause of the disease. Despite an improved understanding of the neuropathological features of AD, the underlying mechanisms remain elusive, hindering the development of effective preventative or curative therapies. Recent advancements in pathophysiological research have identified potential therapeutic targets, offering hope for interventions that could address the disease process more directly. Expanding knowledge of AD and its management is crucial for enhancing patient care and reducing associated costs. This article reviews recent advancements in understanding and treating Alzheimer's disease.*

Keywords: Alzheimer's disease, dementia, therapeutic strategies, neurode generation, cognitive decline, disease management

I. INTRODUCTION

Alzheimer's disease (AD) is recognized as the leading cause of dementia and is clinically identified by its progression from episodic memory impairment to a gradual and widespread decline in cognitive abilities [1]. In 2013, it was estimated that approximately 44 million people worldwide were affected by dementia, with projections suggesting a sharp increase to nearly 136 million by 2050 [2]. Despite extensive research, no treatments with confirmed disease-modifying effects are available, making AD one of the most significant unmet medical challenges in neurology [1].The pathology of AD involves a multifaceted interaction of various biochemical abnormalities. These include disruptions in amyloid precursor protein metabolism, hyperphosphorylation of tau proteins, oxidative stress, energy deficits, mitochondrial dysfunction, inflammation, lipid membrane dysregulation, and neurotransmitter pathway impairments [3]. Metabolic dysfunction has been increasingly recognized as a pivotal factor in AD [4]. For instance, reduced cerebral glucose uptake—an early and consistent hallmark of AD—can manifest decades before cognitive symptoms appear [5].The neurotoxicity associated with Aβ42 plays a central role in the metabolic impairments observed in AD. This peptide triggers a cascade of pathological processes, including interaction with mitochondrial enzymes, which leads to heightened production of reactive oxygen species (ROS). These ROS disrupt critical metabolic pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, and mitochondrial respiratory-chain activity, by promoting the accumulation of harmful intermediate metabolites within mitochondria [6-7].

A. Alois Alzheimer and Auguste D

The German psychiatrist and neuropathologist Dr. Alois Alzheimer was the first to describe the condition now known as Alzheimer's disease (AD). His groundbreaking work began with a 1906 lecture and a subsequent 1907 publication, where he detailed the case of Auguste D, a 51-year-old woman with a "peculiar disease of the cerebral cortex." Auguste D exhibited progressive memory loss, language difficulties, disorientation, hallucinations, delusions, paranoia, and psychosocial impairments, which collectively highlighted a unique clinical and pathological condition [8–10].

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B. Normal Memory and Ageing

To understand dementia, it is important to first explore normal memory processes and the effects of ageing on cognitive function. Ageing involves biological, social, and psychological changes that often interact. For example, physical changes such as arthritis can limit mobility, which may reduce participation in social activities and affect overall well-being [11]. The overlap between normal and abnormal ageing creates challenges in defining what constitutes "normal" memory decline. Normality lies within a range of variation rather than being a stark opposite of abnormality [11]. Advancements in medicine and technology have extended lifespans, allowing more exposure to ageing-related cognitive changes, leading to evolving perceptions of what is considered normal [12–13]. Cognitive functions, including memory, often show subtle declines with age. Memory impairments, particularly in episodic memory, are among the earliest noticeable cognitive changes. Such changes can be distressing for individuals and their families and may signal the onset of dementia or other conditions [14–18]. Memory decline can result from failure to encode, store, or retrieve information effectively [16]. It is vital to assess the nature and extent of memory dysfunction to determine its underlying cause.

C. Type of Memory

Memory functions are categorized into short-term and long-term memory.

- Short-term memory, or working memory, temporarily holds information, such as a phone number, for immediate use unless interrupted [19].
- Long-term memory stores information over extended periods, enabling recall of details like familiar telephone numbers [20].

Memory can also be classified into:

- Episodic and Semantic Memory: Episodic memory relates to specific events, while semantic memory involves general knowledge, such as the meaning of words [21].
- Declarative and Procedural Memory: Declarative memory encompasses facts (both episodic and semantic), while procedural memory relates to skills and routines, such as driving a car [22].

While older adults can learn new information, they often require more time compared to younger individuals due to slower processing speeds, which may become pronounced with depression or cognitive impairments [23–25]. Significant and persistent memory changes often indicate the presence of dementia or other neurodegenerative disorders [26].

D. Memory Processes

Memory involves four key stages:

1. Registration: Attending to or noticing information.
2. Encoding: Transforming information into meaningful (semantic) or sound-based (phonological) formats [28–29].
3. Storage: Retaining information in the brain.
4. Retrieval: Accessing stored information as needed.

Each type of memory—episodic and semantic—is stored differently in the brain [20]. Dysfunction in any of these stages may signal cognitive decline, which is a hallmark of dementia [27].

E. Dementia Overview

Dementia is a syndrome characterized by impairments in multiple cognitive domains, including memory, thinking, orientation, comprehension, and judgment. It often progresses alongside changes in emotional control, social behavior, or motivation, without impairing consciousness [30–31]. The progression of dementia can be broadly divided into three stages:

- Early Stage: First 1–2 years, with mild cognitive changes.
- Middle Stage: Spanning 2–4 or 5 years, with worsening symptoms.
- Late Stage: Occurring after 5 years, marked by severe cognitive and functional impairments.

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Dementia manifests uniquely in individuals, influenced by personality, health, and the severity of the disease itself. These periods are given as an approximate guideline and not all persons with dementia will display the same symptoms. Common symptoms experienced by people with dementia syndrome have been illustrated by Table 1:

Table 1: Common symptoms experienced by people with dementia syndrome[32]

Early stage	Middle stage	Late stage
The early stage is often overlooked. Relatives and friends (and sometimes professionals as well) see it as "old age", just a normal part of ageing process. Because the onset of the disease is gradual, it is difficult to be sure exactly when it begins.	As the disease progresses, limitations become clearer and more restricting.	The last stage is one of nearly total dependence and inactivity. Memory disturbances are very serious and the physical side of the disease becomes more obvious.
Become forgetful, especially regarding things that just happened	Become very forgetful, especially of recent events and people's names	Usually unaware of time and place
May have some difficulty with communication, such as difficulty in finding words	Have difficulty comprehending time, date, place and events; may become lost at home as well as in the community	Have difficulty understanding what is happening around them
Become lost in familiar places	Have increasing difficulty with communication (speech and comprehension)	Unable to recognize relatives, friends and familiar objects
Lose track of the time, including time of day, month, year, season	Need help with personal care (i.e. toileting, washing, dressing)	Unable to eat without assistance, may have difficulty in swallowing
Have difficulty making decisions and handling personal finances	Unable to successfully prepare food, cook, clean or shop	Increasing need for assisted self-care (bathing and toileting)
Mood and behaviour: may become less active and motivated and lose interest in	Unable to live alone safely without considerable support	May have bladder and bowel incontinence
activities and hobbies may show mood changes, including depression or anxiety may react unusually angrily or aggressively on occasion.		
	Behaviour changes may include wandering, repeated questioning, calling out, clinging, disturbed sleeping, hallucinations (seeing or hearing things which are not there)	Change in mobility, may be unable to walk or be confined to a wheelchair or bed
	May display inappropriate behaviour in the home or in the community (e.g. disinhibition, aggression).	Behaviour changes, may escalate and include aggression towards carer, nonverbal agitation (kicking, hitting, screaming or moaning)
		Unable to find his or her way around in the home.

Source: World Alzheimer's Report 2009.[33]

II. EPIDEMIOLOGY OF AD

AD is a critical public health issue in the United States and many other countries around the world, with a significant health, social, and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec.8 In the United States, AD is the fifth leading cause of death among older adults, and about $200

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billion are spent annually on direct care of individuals living with dementia. Worldwide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).

AD is a multi-factorial disease, with no single cause known, and several modifiable and non- modifiable risk factors areassociated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling every 5 years after age 65.[34-35] The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (95% of all cases).Rare genetic mutations are associated with the development f AD before age 65, which is known as 'early on set' or 'familial' AD (B5% of all cases).[36] People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, individuals with Down's syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex and less well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD.[37] The prevalence of AD is higher among females, reflecting the longer life expectancy of women.[38] Lower educational attainment has been associated with increased risk of AD dementia,10 consistent with the idea that education serves to increase a person's cognitive reserve and resilience to AD pathology.[39] A large body of evidence suggests that cerebrovascular risk factors play a significant role in both the development and progression of AD; people with a history of diabetes, hypertension, obesity, and smoking have a substantially elevated risk of AD.[40] Family history of AD in first-degree relatives and a history of head injury with loss of consciousness are also risk factors for the development of A.[41]

III. PATHOLOGY

The pathological hallmark of Alzheimer's disease is the presence of Amyloid plaques and Neurofibrillary tangles (NFT). There is diffuse atrophy of the cerebral cortex and secondary dilatation of the ventricles. The deposits are found more at the hippocampus, temporal cortex and nucleus basalis of Meyernet. There is loss of neurons due to the pathological changes leading on to reduced levels of neurotransmitters especially acetylcholine causing cognitive deficits in these patients. The basic pathological cause of Alzheimer's disease is not fully understood and a lot of research is being done to elucidate the basic pathological process. With the current understanding many hypothesis are put forth for the pathogenesis of AD. The widely accepted among them are,

- Amyloid Cascade Hypothesis
- Tau Hypothesis
- Mitochondrial Cascade Hypothesis

A. Amyloid Cascade Hypothesis

This is the most widely accepted hypothesis. The deposition of Aβ42 - amyloid plaques in the brain is considered the basic pathology. Aβ42 is derived from Amyloid Precursor Protein (APP) by the sequential action of β-secretase and γ-secretase. Aβ42 is insoluble and aggregates to form plaques which causes oxidative damage and initiates inflammatory processes leading on to neuronal death. There is hyperphosphorylation of tau proteins and their deposition as neurofibrillary tangles secondary to amyloid deposition. Alzheimer's disease occurs in two forms - familial and sporadic forms. Familial forms have an early onset and are associated with mutations in APP gene (chromosome 21), Presenillin-1 (chromosome 14) and Presenillin-2 genes (chromosome 1). The late onset familial form and sporadic forms of AD are associated with the presence of ApoE4 allele. ApoE is involved in cholesterol transport and has three alleles - 2, 3 and 4. ApoE4 allele is present in 40 - 80 % of the Alzheimer's patients, though the normal distribution in Caucasian population is only 24 - 30%. ApoE4 is shown to increase the production and decrease the clearance of amyloid.

B. Tau Hypothesis

The amyloid cascade hypothesis does not satisfactorily explain sporadic cases of Alzheimer's disease and the level of amyloid deposits does not correlate with the degree of cognitive decline. This lead to the Tau hypothesis which asserts

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that the deposition of tau and formation of neurofibrillary tangles is the basic pathology and the amyloid deposition occur secondary to it. Tau is a microtubule associated protein which binds to and stabilizes the microtubules involved in intracellular transport. The hyperphosphorylation of tau reduces the binding of tau to microtubules, and the sequestration of hyperphosphorylated tau into neurofibrillary tangles (NFTs) reduces the amount of tau that is available to bind microtubules. As a result the microtubules disintegrate leading to reduced axonal transport and cell death.

C. Mitochondrial Cascade Hypothesis

The reduced mitochondrial function to handle the free-radicals is considered the initiating step in Alzheimer's disease.[42]

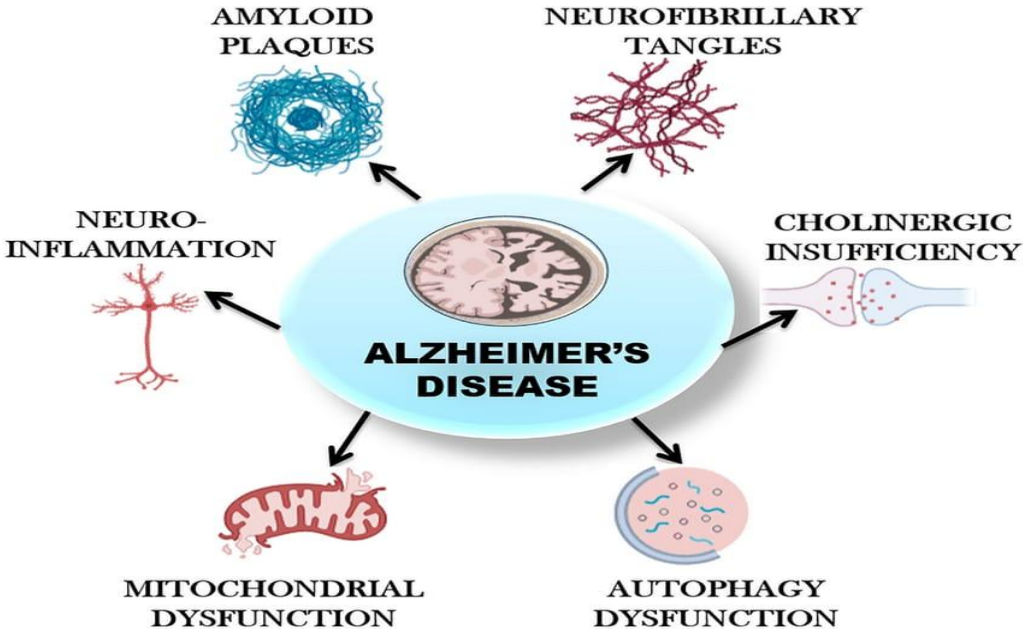

Fig 1. Pathology

IV. DIAGNOSIS OF AD

In clinical settings, the diagnosis of AD is largely based on medical history, physical and neurological examinations, and neuropsychological evaluation, as well as the exclusion of other etiologies using selective ancillary testing. The clinical diagnosis of AD has an accuracy of 70_90%relative to the pathological diagnosis, with greater accuracies being achieved in specialty settings such as memory disorder clinics.[43] The cornerstone of the clinical diagnosis is a set of consensus criteria first established in 1984[44] and last updated in 2011 by the National Institute on Aging _ Alzheimer's Association (NIA_AA) workgroup.[45]

When the patient's cognitive impairment has an atypical clinical course or is suspected to be due to other etiologies in addition to AD, the diagnosis of 'possible' AD dementia is recommended. Patients with AD generally have normal findings on physical and neurological examinations.[46, 47] To help with the differential diagnosis, Table 2 summarizes some of the clinical features that distinguish AD.

A. Establishing the Diagnosis of Alzheimer Disease

Establishing the diagnosis of Alzheimer disease relies on clinical-neuropathologic assessment. Neuropathologic findings on autopsy examination remain the gold standard for diagnosis of AD. The clinical diagnosis of AD (prior to autopsy confirmation) is correct approximately 80%-90% of the time.

- Clinical signs. Slowly progressive dementia
- Neuroimaging

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- Gross cerebral cortical atrophy on CT or MRI
- Diffuse cerebral hypometabolism on PET

Neuropathologic findings. Microscopic β-amyloid neuritic plaques, intraneuronal neurofibrillary tangles (containing tau protein), and amyloid angiopathy at postmortem examination. The plaques should stain positively with β-amyloid antibodies and negative for prion antibodies, which are diagnostic of prion diseases. The numbers of plaques and tangles must exceed those found in age-matched controls without dementia. Guidelines for the quantitative assessment of these changes exist. Aggregation of alpha-synuclein in the form of Lewy bodies may also be found in neurons in the amygdala.

Cerebrospinal fluid (CSF). Decreased Aβ amyloid 42 and increased tau.

S. No	Clinical feature	Alzheimer's dementia	Vascular dementia	Parkinson's dementia	Dementia with Lewy bodies	Frontotemporal dementia
1	Patient profile	>65 years old	>40 years old Vascular risk factors	>65 years old	75 years old (mean)	50_70 years old 50% autosomal dominant
2	History	Gradual onset and deterioration	Acute onset, stepwise deterioration	Gradual onset and deterioration	Gradual onset and deterioration	Gradual onset and deterioration
3	Initial symptoms	Memory loss	Executive dysfunction	Visual hallucinations	Visual hallucinations Fluctuating attention	Memory intact Disinhibition, apathy or aphasia
4	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)	Usually none (rarely associated with motor neuron disease)

Table 2. Clinical features that distinguish AD from other dementias –

Notes: Pyramidal (upper motor neuron) signs include hyperreflexia, spasticity, weakness, and extensor plantar responses (Babinski sign). Parkinsonism refers to the following features: bradykinesia, cogwheel rigidity, resting tremor, and postural instability.[41,44]

V. NEUROPATHOLOGY AND CLINICAL SIGNS OF ALZHEIMER'S DISEASE

The clinical diagnosis of Alzheimer's disease is said to be correct 75% to 90% of the time.[48] According to,[49] accuracy is highest for neurologists specializing in memory disorders and lowest for general practitioners, who has a tendency to over diagnose Alzheimer's disease. The clinical accuracy also tends to be lower for older patients' who often have mixed pathology rather than a single cause of dementia.[50] The only clinical means of establishing a definite diagnosis is by microscopic examination of brain tissue as there are no laboratory tests and neither sophisticated imaging techniques nor detailed neuropsychological evaluation can specify Alzheimer's disease categorically.[51] Typically, the onset is from 40 years of age onwards with insidious degeneration until death at about sixty years following onset.[52-54] The brain invariably displays a degree of atrophy; however, age-associated a trophy and the normal variability in brain size preclude a diagnosis based solely on gross examination of the brain.[55] Atrophy of the medial portion of the temporal lobe is often disproportionate to other areas of the cortex. In most cases, the primary sensory and motor cortices are relatively spared and on sectioning the brain, the lateral ventricles are usually dilated and the hippocampus and amygdale are atrophic.[56] More specific neuronal alterations accompany neuronal and synaptic loss. The most important of these alterations is pair etherical filaments which are intra neuronal proteinaceous structures that are composed by an abnormal form of tau protein.[57-58]

The neuropathological hallmarks of Alzheimer's disease is the intracellular neurofibrillary tangles of tau protein and amyloid plaques, primarily composed of aggregated amyloid beta peptide. At high concentrations vesicular amyloid beta aggregates to form high molecular weight species which are capable of seeding amyloid fibril growth[59] suggest

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that it is these aggregate that seed the extracellular amyloid plaque formation seen in the pathogenesis of Alzheimer's disease.

VI. PHASES OF ALZHEIMER DISEASE

Each person with Alzheimer's disease will vary slightly in presentation according to personality. Emotional, behavioral and cognitive changes will also vary, but generally accepted by clinicians and researchers are stage model which describes broad characteristics.[60] In the first phase, the 'forgetfulness phase', there is usually difficulty in recalling recent events, and a tendency to forget where objects have been placed.[27] Names of people and places, previously familiar, may be poorly recalled and a general disorientation persists and poor short-term memory.[61] The second recognized phase is known as the 'confusional phase'. Increasingly poor attention span and a decline in generalized intellectual performance are seen with a deteriorating memory. Disorientation in place, word-finding difficulty and other changes to speech may be seen.[61] Complex tasks are performed with difficulty, sometimes in a clumsy or inaccurate manner and often the skills the person learned last will be lost first. Lack of interest in news and surroundings follows relatively quickly and can be extremely distressing to family and friends.[62] The third phase, the 'dementia phase', is characterized by a lack of purpose in the person's behavior which appears disjointed and sometimes bizarre. Remaining intellectual and self- care abilities require constant supervision as people in this phase undergo further deterioration in memory capacity, calculating ability (dyscalculia) and aspects of language are severely affected and eventually lost. Constant assistance is required for self-care skills such as grooming, dressing, and toileting and for feeding. A progressive physical wasting can also be seen which will mean help with walking. Sometimes one or two years of life will follow in an almost vegetative state until death. Environmental factors may have a role in triggering Alzheimer's disease in susceptible individuals. An association between Alzheimer's disease and aluminium has been formulated for several years.

VII. RISK FACTORS FOR AD

Table 3: Factors that modify the risk of Alzheimer Disease.

Antecedent	Direction	Possible mechanism
Cardiovascular disease	Increased	Parenchymal destruction Strategic location ↑ beta (symbol) deposition
Smoking	Increased	Cerebrovascular effects Oxidative stress
Hypertension	Increased and decreased	Cerebrovascular disease
Type II diabetes	Increased	Insulin and A beta (symbol)compete for clearance
Obesity	Increased	Increased risk of type II diabetes inflammatory
Traumatic head injury	Increased	↑A beta (symbol) and amyloid precursor protein deposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti- inflammatory
Physical activity	Decreased	Activates brain plasticity, promotes brain vascularization

Source: *Epidemiology of Alzheimer Disease*[6]

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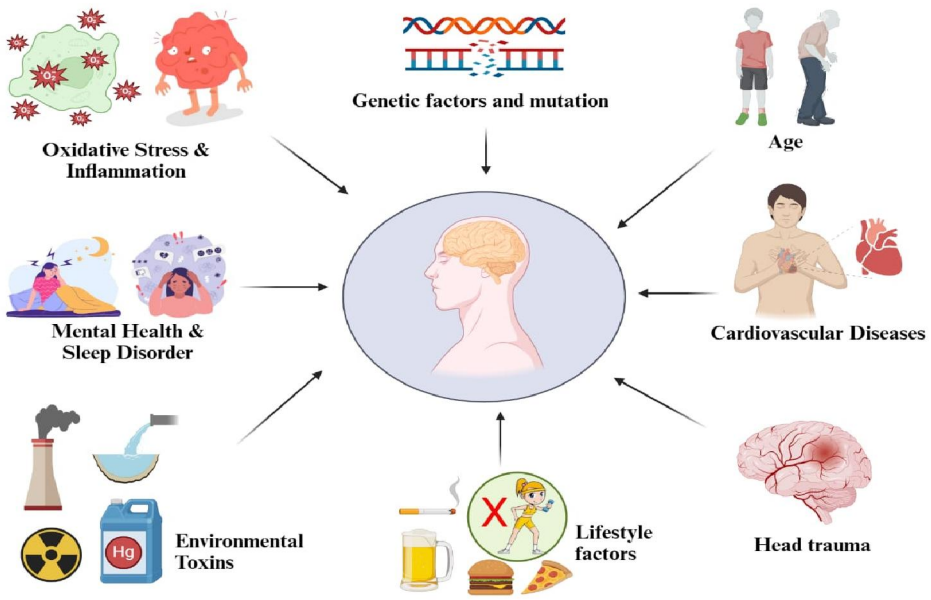

Fig. 2. Risk Factor of AD

VIII. PHARMACOLOGICAL THERAPY REVIEW FOR AD

The current pharmacologic therapy for AD only provides short-term improvement for a short period of time, six to eighteen months.[65] The only medicines approved in the US and several parts of Europe for short term alleviation of symptoms are cholinesterase inhibitors and memantine.[66] These drugs do not affect the pathology of AD, but allows the brain to compensate for the loss of neurones that communicate via acetylcholine, a neurotransmitter.[67] This section reviews the clinical efficacy of approved and possible pharmacological therapies for AD.[68] The new Medicines under development for Alzheimer disease has been illustrated in Table 4.

Table 4: New Medicines under Development for Alzheimer disease:

Drug name	Indication	Company	Development Status
ABT-126 acetylcholinesterase inhibitors	Alzheimer disease	Abbott	Phase 2
ABT-126	Alzheimer disease	Abbott	Phase 2
LY2886721	Alzheimer disease	Eli Lilly and Company	Phase 1
AZD3480	Alzheimer disease	Targacept Inc.	Phase 2
AVP-923 (dextromethorphan/quinidine)	Alzheimer disease, mild cognitive impairment	Avanir Pharmaceuticals	Phase 2
MABT5102A	Alzheimer disease	Genentech	Phase 2
AZD5213	Alzheimer disease	AstraZeneca	Phase 2
Gantenerumab	Alzheimer disease	Hoffmann-La Roche	Phase 3
AAB-003 (PF-05236812)	Alzheimer disease	Pfizer	Phase 1
BMS-241027	Alzheimer disease	Bristol-Myers Squibb	Phase 1
MABT5102A	Alzheimer disease	Genentech	Phase 2
BIIB037	Alzheimer disease prodromal or mild AD	Biogen Idec	Phase 1
GSK2647544	Alzheimer disease,	GlaxoSmithKline	Phase 1

Sources: Evaluation of Medicinal Products (EMEA) http://www.ema.europa.eu/ema/[69] and the US Food and Drug Administration (FDA) http://www.fda.gov/[70]

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IX. STRUCTURAL CHANGES RELATEDTO AD DEMENTIA

As indicated by Alzheimer et al. (1995), the presence of two main aberrant structures, senile plaques and neurofibrillary tangles, precede the neuronal death and brain degeneration found later on the disease. Plaques are aggregates of beta amyloid peptide that progressively appear during the development of the disease following a specific pattern (Thal et al., 2002). This pattern starts in the neocortex and continues through the allocortex, hippocampus, basal ganglia, midbrain, and cerebellum. This pathway starts many years before clinical diagnostic (Bateman et al., 2012). Later on, it can be found by the presence of neurofibrillary tangles (tau protein aggregates), that also propagate, but follow a different pathway (Braak and Braak, 1991), starting at the transentorhinal region and expanding through the entorhinal cortex, hippocampus and neocortical areas. In this way, there are two different pathologies (amyloid and tau pathologies, with different structural changes) that appear at different times during the development of the disease. Indeed, it has been suggested that the disorder can become a unique disease when both amyloid and tau pathologies overlap (Hojjati et al., 2021). Before that time, different features may be related to the presence of only plaques in some brain region

X. FUNCTIONAL CHANGES RELATED TO AD DEMENTIA

Memory loss, cognitive impairment, loss of executive functions, and loss of consciousness, among others (Masters et al., 2015; Jack, et al., 2018), occur in AD dementia. They can appear at different times during disease development, step by step through a continuum that ends in dementia and an extensive brain degeneration. Being aware of one's surroundings and considering social behavior as part of the interaction with that environment, it is important to note that it changes with aging (Rosati et al., 2020), which is relevant taking into account that aging itself constitutes the main risk for dementia. Indeed, there is a loss of consciousness, related to loss of individual awareness or awareness related to the world around those future patients.

XI. MILD COGNITIVE IMPAIRMENT

We now know that before dementia there is a mild cognitive impairment (MCI), that could be more related to tau pathology. At the end of the past century (Petersen et al., 1999), it was suggested that before dementia and probably related to the onset of the first Braak stages, MCI could result in changes in cognition, while maintaining the capacity for executive functions and the independence to carry out daily activities. MCI definition can be classified into two different types, amnesic and non amnesic. The first one is more related to memory changes, the second one may maintain an intact executive functionality (Carmasin et al., 2021). Moreover, MCI could be related to Braak stages 1 and 2 and CA1 region could be involved in the appearance of MCI. The existence of a so-called AD continuum could indicate the presence of MCI before AD (Petersen et al., 1999). Although there are several types of MCI, including amnestic, non-amnestic, and mixed, that could behave differently to progress into dementia, we will mainly comment on MCIasawhole. Around 10–15% of subjects with MCI could progress to dementia per year (Petersen, 2000) and it has been estimated that overall more than 40% of subjects with MCI could develop dementia (Panpalli Ates and Yilmaz Can, 2020). Thus, it is paramount to know why the other 60% do not progress similarly. The percentage of transition from MCI to dementia depends on factors like age, education, family history of dementia, vascular risk factors or ApoE4 status (Kryscio et al., 2006). Also, lifestyle-related factors like alcohol consumption have a role on this proportion (Xu et al., 2009). Some of these factors could be modified to prevent the development of the disease (Sanz-Blasco et al., 2021).

XII. SUBJECTIVE COGNITIVE DECLINE

It has been suggested that subjective cognitive decline (SCD), expressed by a frequent confusion and transitory memory loss could be a cognitive decline without being an objective (testable) mild cognitive impairment. Thus, it has been suggested that SCD could be a previous step to MCI (Jessen et al., 2014).

XIII. TRANSITION FROM SUBJECTIVE COGNITIVE DECLINE TO MILD COGNITIVE IMPAIRMENT

In a 7-year longitudinal study, it was described that around 20% of SCD subjects can progress to MCI (Bessietal.,2018). Similar results were found in other studies (Avila-VillanuevaandFernandez-Blazquez,2017). Thus, SCD is a clear risk factor for MCI, like MCI is a risk factor for dementia. Again, it will be of interest to identify the causes for the transition of that 20%SCDsubjects to MCI, looking for a possible prevention

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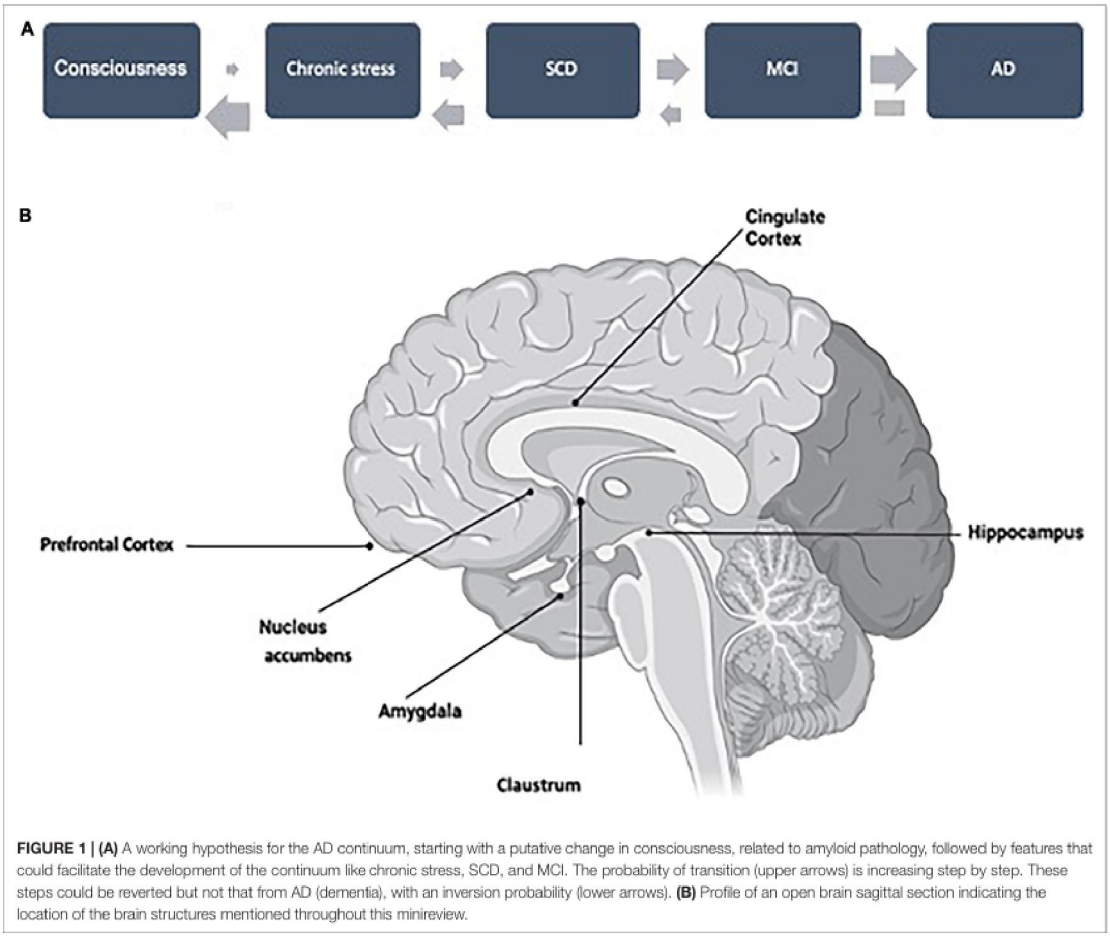

FIGURE 1 | (A) A working hypothesis for the AD continuum, starting with a putative change in consciousness, related to amyloid pathology, followed by features that could facilitate the development of the continuum like chronic stress, SCD, and MCI. The probability of transition (upper arrows) is increasing step by step. These steps could be reverted but not that from AD (dementia), with an inversion probability (lower arrows). **(B)** Profile of an open brain sagittal section indicating the location of the brain structures mentioned throughout this minireview.

XIV. EXECUTIVE FUNCTIONS

In addition to episodic memory loss, related to changes in the CA1hippocampal region, a main feature on the development of AD is the loss of executive functions, like planning, working memory, self-control, flexible thinking, or organization. Executive functions have been mainly located in prefrontal regions (Stuss, 2011), although other regions like nucleus accumbens (NAcc) could also play a role in such functions (Floresco,2015;Prasad,2018).More recently, this role has been proposed again(Jenkinsetal.,2021).SincehippocampalCA1can connect to NAcc (Zhouetal.,2020),adamageinCA1couldlater on have an effect on NAcc and on executive functions or specific types of memories(Prasad,2018). In this way, it will be of interest to know if some features of cognitive decline relatedto CA1 damage could take place, or not, earlier than those specific executive functions. Further analysis should be done to test if it is the case.

XV. IS THERE A CHANGE BEFORE SUBJECTIVE COGNITIVE DECLINE? COULD BE THAT CHANGE CHRONIC STRESS

We have previously discussed the role of chronic stress as a trigger for the AD continuum, being a possible step before SCD (Avila-Villanuevaetal.,2020). Structurally, chronic stress may affect structures like amygdala (Liuet al., 2020).Amygdala could activate other brain areas, such as hypothalamus and brainstem, altering prefrontal cortex (PFC) function (Arnsten, 2009). Also, chronic stress may induce changes in the sympathetic nervous system altering the hypothalamic-pituitary-adrenal axis and producing an increase of cortisol, a compound that can cross the brain-blood barrier and is able to bind to hippocampus, amygdala, or prefrontal cortex receptors (de Kloet et al., 1999; Li et al.,

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2019). Thus, damage in those structures may be a previous step to SCD. Indeed, people with chronic stress in midlife could have a higher risk for SCD and MCI(Avila-Villanueva et al., 2020). This also agrees well with the fact that subjects with SCD tend to have a higher level of cortisol, a marker for chronic stress (Fiocco et al., 2006). Additionally, depression or anxiety could be functional factors, taking place before MCI or dementia and they may correlate with changes in structural areas like amygdala (Liu et al., 2020). Chronic stress in turn can be consequence of the lifestyle, being poverty, the main cause of chronic stress (Fernandez Blazquez et al., 2021). On the other hand, cortisol secretion is linked to circadian rhythm and a relation between sleeping time, cortisol secretion, and dementia has been recently indicated.

XVI. CONSCIOUSNESS AND "HIDDEN" STRUCTURES THAT COULDBE INVOLVED BEFORE THE APPEARANCE OF COGNITIVE IMPAIRMENT

In Familial Alzheimer Disease (FAD), consciousness changes have been considered as an early marker of the disease (Aschenbrenner et al., 2020), and claustrum has been proposed to be a brain area controlling consciousness (Crick and Koch, 2003). Claustrum is a "hidden" structure, located below the insula cortex, that can only be visualized when other parts of the cortex are pulled aside. Claustrum dysfunction may precede amyloid accumulation and aggregation in FAD (Goutagny et al., 2013). Additionally, claustrum can establish connections with entorhinal cortex (Kurada et al., 2019) and hippocampal areas (Amaral and Cowan, 1980), which have been related to tau pathology, and cognitive impairment. Thus, we suggest that further studies analyzing the possible role of claustrum in very early stages of AD should be performed, not only on FAD, but also in sporadic Alzheimer's disease (SAD). If there is a role of claustrum in SAD, a very early functional change in the AD continuum could be related to controlling consciousness (Figure 1A).

XVII. REVERSION IN THE AD CONTINUUM

In this commentary, we have suggested the possible AD continuum shown in Figure 1, but we would like to discuss whether it is unidirectional in all steps or it could be bidirectional in some of them (Figure 1A). We know, that it is not possible to revert dementia, but subjects from the previous step, MCI, could revert to normal condition in a significant proportion (Sanz-Blasco et al., 2021). Ahigh proportion of MCI subjects can progress to dementia. Curiously, a similar proportion could revert to a normal cognitive situation (Sanz-Blasco et al., 2021). Some features that could be involved in one or the opposite direction have already been suggested (Sanz-Blasco et al., 2021), but further studies should be carried out. One example could be that circadian rest activity could predict cognitive decline in MCI subjects (Targa et al., 2021). Additionally, a good characterization of previous stages of MCI (like SCD), of MCI itself, and dementia should be carried out [see for example Yang et al. (2021)], to accurately determine the transition among stages. On the other hand, it should be discussed that psychological tests are more focused on changes in cognitive or executive dysfunctions than changes in emotional or social behavior. In this way, it can be proposed that for AD development, at very early steps, Aß and tau pathologies could follow different structural and functional pathways, being those of Aß pathology, probably, more related to emotions (less present in clinical tests) whereas tau pathology is more related to cognitive impairment or memory decrease. Accordingly, Figure1Bshowsapossiblerelationbetweenspecific structural changes with specific functional (cognitive, behavioral, or emotional) changes.

XVIII. REVERSION FROM MILD COGNITIVE IMPAIRMENT TO NORMAL COGNITION

Recently, it has been shown that the likelihood of progression from MCI to dementia is very similar to the reversion from MCI to normal cognition (Sanz-Blasco et al., 2021). Some factors involved in that reversion have been described (Sanz Blasco et al., 2021), but there are other features that should be analyzed, based on the previous history of the patient. For instance, we have previously commented on this minireview the possible role of chronic stress as a very early risk factor for dementia. Suitably, reversion of chronic stress correlates with reversion to a normal healthy cognition. However, in some cases that stress results in the irreversible atrophy of dentate gyrus neurons (Bai et al., 2012), which remains as a risk signature that could facilitate the future progression to dementia. In addition, morphological (unreversible?) reorganization, in hippocampus, nucleus accumbens, and amygdala has been reported after corticosterone administration (Morales-Medina et al., 2009). In this way, we would like to comment that new psychological tests to determine changes in social and emotional behavior may be needed to account for possible

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changes related to the presence of amyloid plaques at specific brain locations at very early times of the continuum. Recently, changes in emotion and generosity in older adults have been reported (Carstensen and Chi, 2021), but little was done in MCI/AD patients, especially at early stages of the disorder. In humans, social and emotional processing is mainly localized at cerebral neocortex in areas like the orbital frontal cortex. In the first Thal stage, this area already shows an evident amount of amyloid aggregation. Although it has been reported that orbital frontal cortex is involved in emotional enhancement of memory (Kumfor et al., 2013), there are not many studies looking for possible behavioral changes at those early Thal stages. Curiously, orbital frontal cortex pathology related to AD has been probably more analyzed by examining at tau pathology than amyloid pathology (Tekin et al., 2001). It has also been indicated that damage on the orbitofrontal cortex and the anterior cingulate cortex correlate with behavioral changes, for example dealing with empathy (Avila-Villanueva et al., 2021). Thus, we suggest the possibility of preparing behavioral psychological tests to explore changes at very early timepoints of the continuum. These tests may analyze behavioral changes, expressed by symptoms like agitation, disinhibition, elation, anxiety, or depression (Cajanus et al., 2019), and other features related to subjective wellbeing (van Zonneveld, 1961), similar to EuroQoL-5D (Dolan, 1997). These tests could be a good complement for the previous ones measuring memory changes, cognition, or executive functions, more related to the development of tau pathology, even though during the development of the disease there is an overlapping of both pathologies. Indeed, there such overlapping during the spreading of tau pathology is linked to the fact that tau spreading is favored by the presence of amyloid aggregates (Busche and Hyman, 2020). This tau spreading from the hippocampal area to cerebral cortex is related to an initial memory (and cognitive) impairment, which endpoint could be dementia. Thus, in Figure 1B, we have shown a relation between structural changes (with the presence of amyloid, tau, or both pathologies) with specific functional (behavioral, emotional, memory, or cognitive) changes, occurring at different times of the AD continuum.

XIX. CONCLUSION

The use of any measure for the clinical assessment of dementia, whether in people with learning disabilities or in the 'normal' population carries with it limitations. Informed knowledge of these limitations allows use scientific choices which enable us to tailor our neuropsychological battery or adopt alternative measures. Ultimately, there may be a compromise because of these limitations; however, scientific understanding has given us a better picture of the course of dementia than ever before. With the advancement of technology, such as MRI and fMRI, and PET and SPET scans, used in conjunction with neuropsychological tests administered at key time points including follow- ups, the clinician is better placed to make a more reliable diagnosis and prognosis than in the past. It is hope that this will also enlighten service providers in widening access to people with learning disabilities who also have dementia.

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