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A Review of Alzheimer Disease

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Abstract

Dementia that gradually affects brain cells is known as Alzheimer's disease (AD). Symptoms include a steady decline in cognitive abilities along with diminished ability to carry out ADLs and changes in behaviour. Dementia affecting the pre- and senile stages is most often caused by this condition. The World Health Organisation reports that among adults aged 60 and above, 6% of women and 5% of men suffer with Alzheimer's type dementia. Dementia, the clinical manifestation of Alzheimer disease (AD), usually starts with mild memory loss that isn't immediately noticeable but gradually becomes worse and finally makes a person unable to care for himself. Treatments like memantine, which targets late stages of the illness, and acetylcholinesterase inhibitors like rivastigmine, galantamine, and donepezil, have little influence on the condition overall. These medications slow the disease's course and alleviate symptoms, but they don't cure the condition completely. Although Alzheimer's disease is known for its neuropathological symptoms, the exact process is still poorly understood. The absence of effective treatments that may halt the development and progression of the illness is probably due to the fact that the pathogenic process is not well understood. New treatment targets should make it possible to approach the underlying illness process directly, thanks to significant development in pathophysiology in the previous few of years. Better disease management and lower healthcare expenses may be achieved by gaining a better understanding of the breadth of information around Alzheimer's disease. Some of the most significant new insights into and approaches to treating Alzheimer's disease are attempted to be highlighted in this article.

Keywords: Alzheimer, Management, Diagnosis, treatment..

Introduction

The most prevalent form of dementia, Alzheimer's disease (AD) is clinically defined by a gradual loss of cognitive function that begins with episodic memory issues and progresses to a more widespread and severe form over time.[1] The projected number of people afflicted by dementia worldwide was 44 million in 2013, and experts expect that number would skyrocket to 136 million by 2050. The most unfulfilled medical need in neurology is a therapy for Alzheimer's disease, although no such medication has been developed to yet.[1] Amyloid precursor protein metabolism changes, tau protein phosphorylation, oxidative stress, impaired energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation, and disruption of neurotransmitter pathways are all intricately interwoven in AD pathology.the third It is now well-established that metabolic dysfunction is a significant component of AD, and most of the clinical characteristics may be directly associated with metabolic abnormalities.[4] As an example, one consistent hallmark of Alzheimer's disease is reduced cerebral glucose absorption, which happens decades before cognitive loss begins.It is believed that the impaired neuronal energetics caused by the well-documented neurotoxicity of

Aβ42 is the result of a series of pathological events that begin with the interaction of Aβ42 with mitochondrial enzymes, which in turn increases the release of reactive oxygen species (ROS). This, in turn, affects glycolysis, the TCA cycle, and mitochondrial respiratory-chain activity by causing the accumulation of harmful intermediate metabolites in the mitochondria.[6-7]

Alois Alzheimer and Auguste D

The initial description of a dementing disorder that would eventually be recognised as Alzheimer's disease (AD) was supposedly made by the German psychiatrist and neuropathologist Dr. Alois Alzheimer. Alzheimer recounted the case of Auguste D, a 51-year-old woman suffering from a "peculiar disease of the cerebral cortex," in his seminal 1906 conference lecture and 1907 article. Auguste had shown signs of progressive memory and language impairment, disorientation, behavioural symptoms (hallucinations, delusions, paranoia), and psychosocial impairment.[8-10]

Normal memory

Identifying normal ageing and understanding what might go wrong and cause abnormal disorders like dementia is essential for comprehending the complexity of the disease. Although the fields of biology, sociology, and psychology may be considered distinct when discussing ageing, there is often substantial overlap and interaction across these areas. For instance, if you're less mobile due to a condition like arthritis, you could find it harder to participate in social events or pursue other interests that you used to love.the eleventh Keep in mind that one part of ageing might have an effect on another; this is particularly true when comparing a person's cognitive abilities from different eras.

It is astonishing how frequently 'normal' and 'abnormal' behaviours and attitudes coincide, and defining 'normal' is no easy undertaking. Cultural, environmental, and even interpersonal barriers may become more porous with time. "Normality" really means "the range around the middle of a dimension (e.g., height) with two extremes at opposite ends (very tall and very short), rather than one extreme," which is a common misunderstanding that normalcy is separate from abnormality.the eleventh Expectations in old age are seen differently by various people since everyone has their own idea of what constitutes normalcy. People are living longer because to medical advancements and technological advancements, which means that more people are seeing older people and experiencing the many ways in which friends and family age. The result is that people's expectations of themselves and others, as well as their views on what constitutes normal ageing, are always evolving.
As we get older, our bodies naturally undergo changes—not just in how we look, but also in how our brains work, specifically in what are known as "cognitive" capabilities.sections 12–13] Additionally, memory may be impacted,[14–15] either because the person has misunderstood the knowledge or because it is no longer adequately encoded or preserved.[16] As people become older, they may notice changes in their memory, especially episodic memory, which may be upsetting for both the individual and those closest to them, as well as for their professional and personal lives. Dementia is characterised by a decline in memory function.[18] However, it may also suggest additional dysfunctions that need to be taken into account during any evaluation.

Memory functioning has been recognized as followsShort-term and long-term memory

Short-term memory, now elaborated into the concept of working memory,[19] is the system which allows one to remember a new telephone number while one is dialling it, so long asone is not distracted.

Long-term memory allows one to remember a familiar telephone number from day to day and year to year.[20]

Semantic and episodic memory – It would suggest that various forms of information are preserved in different ways. The idea of differentiating between procedural and declarative memories has recently gained traction, building on earlier work that distinguished between episodic and semantic memories [21].[22] is a While semantic memories store knowledge independent of

context, episodic memories store specific occurrences. Knowing that "breakfast" denotes a morning meal is an example of a semantic memory, but recalling exactly what I ate for breakfast is an example of an episodic memory.[20]

"Declarative and procedural memory" include not only episodic memories (representing facts) but also semantic memories (representing concepts). Some sensory impulses may be a part of procedural memory, which is used for routines and skills. Knowledge about the inner workings of an engine is declarative, but knowledge of how to operate a vehicle is an example of procedural memory.[20] In most cases, older adults are just as capable of learning as younger ones,[23] but it takes them longer to reach the same level of proficiency since they 'absorb' and process knowledge at the same rate as younger ones.[24]

This slowing down might be subtle at first, but it can become more pronounced when sadness sets in.[25] When other cognitive abilities are also impaired, a change in memory that is both noticeable and ongoing may be an indicator of dementia.[26]

Problems with memory

Dementia is characterised by memory loss, which is a frequent and serious symptom. To determine the severity of the issue and the people affected, it is necessary to conduct an assessment.

The present consensus holds that the process of remembering anything consists of four steps: registering, encoding, storing, and retrieval. Prior to being registered or beattended to, information must be saved in memory. Information may be "encoded" in one of two ways: either in terms of meaning (semantically) or in terms of sound (phonologically) [28, 29]. Information is stored in memory via this method. As an example, knowing that a person's lunch was eaten (episodic memory) and knowing that the term "lunch" denotes a mid-day meal (semantic memory) are both believed to be retained differently.

Dementia

Disruptions to many brain processes such as memory, cognition, direction, understanding, computation, learning ability, language, and judgement are hallmarks of dementia, a sickness. There is no haze around awareness. Negative changes in motivation, social behaviour, or emotional regulation often precede or accompany cognitive function deficits.The numbers 30–31 The effects of dementia on an individual might vary, and the disease's course can be influenced by the individual's health, personality, and other factors. The three phases of dementia are as follows:

-Early stage – first year or two
-Middle stage – second to fourth or fifth years
-Late stage – fifth year and after

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 clearerand 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 justhappened	Become very forgetful, especially of recent eventsand people's names	Usually unaware of time andplace
May have some difficulty with communication, such asdifficulty 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 familiarplaces	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 withoutassistance, may have difficulty in swallowing

Have difficulty making decisions and handlingpersonal finances	Unable to successfully prepare food, cook, clean orshop	Increasing need for assisted self-care (bathing andtoileting)
Mood and behaviour: may become less active and motivated and lose interest in activities and hobbies may show mood changes, including depression or anxiety may react unusuallyangrily or aggressively on occasion.	Unable to live alone safely without considerablesupport	May have bladder and bowelincontinence
	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 confinedto a wheelchair or bed
	May display inappropriate behaviour in the home or inthe 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 wayaround in the home.

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

Epidemiology of AD

Alzheimer's disease (AD) is a major global health concern that has a substantial monetary, social, and health impact on society. A new diagnosis of Alzheimer's disease is made every 68 seconds, affecting an estimated 5 million Americans.8 About $200 billion is spent every year on direct care for those with dementia, and Alzheimer's disease is the sixth largest cause of mortality among older adults in the US. Roughly 35 million individuals throughout the world suffer from Alzheimer's disease or another kind of dementia; by 2030, that number is projected to rise to 65 million, and by 2050, it is projected to reach 115 million.

There is currently no known cause of Alzheimer's disease (AD), although the development and progression of the illness are linked to a number of risk factors, some of which may be changed and others of which cannot. The most important determinant for the onset of AD is becoming older. After age 65, the risk of acquiring Alzheimer's disease (AD) about doubles every five years, increasing exponentially with age.sections 34 and 35 The 'late-onset' or'sporadic' forms of Alzheimer's disease account for 95% of all instances, and the great majority of those affected are 65 and over."Earlyonset" or "familial" Alzheimer's disease (B5% of all cases) occurs in people who do not reach the age of 65 because of rare genetic abnormalities.[36] Amyloid precursor protein (APP) gene mutations on chromosome 21 or presenilin genes on chromosomes 1 and 14 cause autosomal dominant variants of Alzheimer's disease in people with family forms of the disease. Furthermore, the likelihood of having early-onset AD is higher among those who have Down's syndrome (trisomy 21). Sporadic Alzheimer's disease genetics are less known and more complicated. One recognised risk factor for sporadic AD is the epsilon four allele of the apolipoprotein E (APOE) gene, which is located on chromosome 19.[37] Because women tend to live longer than men, the prevalence of AD is greater in this gender.Consistent with the hypothesis that education contributes to strengthen a person's cognitive reserve and resistance to AD pathology, lower educational attainment has been related with an increased likelihood of AD dementia (38).[39] The onset and progression of Alzheimer's disease are both influenced by cerebrovascular risk factors, according to a wide body of research. Those who have a history of diabetes, hypertension, obesity, or smoking are at a much higher risk of developing AD.[40] Additional risk factors for the development of AD include a first-degree relative with the disease and a history of traumatic brain injury resulting in loss of consciousness.[41]

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

Amyloid Cascade Hypothesis

Almost everyone agrees with this theory. Plaques of Aβ42 - amyloid in the brain are thought to be the fundamental disease. The Aβ42 is produced from the APP by the successive activity of the β-secretase and γ-secretase enzymes. The insoluble Aβ42 builds up as plaques, which trigger oxidative damage, inflammatory processes, and ultimately the death of neurones. After amyloid deposits, tau proteins undergo hyperphosphorylation and eventually accumulate as neurofibrillary tangles. Both hereditary and sporadic types of Alzheimer's disease may manifest. In hereditary forms, mutations in the APP, Presenillin-1, and Presenillin-2 genes are related with an early onset and are located on chromosomes 21, 14, and 1, respectively. Having the ApoE4 allele increases the risk of developing late-onset familial or sporadic Alzheimer's disease. There are three different alleles for ApoE, and all three play a role in cholesterol transport. Although the typical distribution in the Caucasian population is just 24-30%, 40-80% of Alzheimer's patients possess the ApoE4 allele. Researchers have discovered that ApoE4 increases amyloid production and lowers clearance.

Tau Hypothesis

Random occurrences of Alzheimer's disease defy the amyloid cascade theory, as there is no correlation between amyloid deposit levels and cognitive deterioration. Amyloid deposition is considered a byproduct of the primary disease, tau deposition and neurofibrillary tangle development, according to the Tau hypothesis. Tau is a protein that attaches to microtubules and helps to stabilise them so that they can continue to carry cargo throughout cells. Tau hyperphosphorylation decreases tau binding to microtubules, while tau sequestration into neurofibrillary tangles (NFTs) further decreases tau availability for microtubule binding. Reduced axonal transport and cell death ensue from microtubule disintegration.

Mitochondrial Cascade Hypothesis

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

Diagnosis of AD

Clinical diagnosis of Alzheimer's disease relies heavily on the patient's medical history, neurological and physical exams, cognitive testing, and the elimination of other possible causes via the use of specific auxiliary tests. With higher accuracies reached in specialised settings like memory problem clinics, the clinical diagnosis of AD has a relative accuracy of 70–90% compared to the pathological diagnosis.[43] The National Institute onAging _ Alzheimer's Association (NIA_AA) workgroup last revised its set of consensus criteria in 2011, however they were first created in 1984[44]. These criteria form the basis of the clinical diagnosis.[45] It is suggested to diagnose 'possible' AD dementia when the patient's cognitive impairment has an unusual clinical history or is thought to be caused by other causes than AD. Results from neurological and physical exams in patients with AD are often unremarkable.(46, 47) Table 2 provides a summary of some clinical characteristics that differentiate AD, which might aid in the differential diagnosis.

Establishing the Diagnosis of Alzheimer Disease

A clinical-neuropathologic evaluation is necessary to confirm an Alzheimer disease diagnosis. When it comes to diagnosing Alzheimer's disease, the gold standard is still the neuropathologic evidence seen at autopsy. The accuracy of the clinical diagnosis of Alzheimer's disease (before autopsy confirmation) is about 80% to 90% of the time.

-Clinical signs. Slowly progressive dementia

-Neuroimaging

-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.

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

S.No	Clinical feature	Alzheimer's dementia	Vascular dementia	Parkinson's dementia	Dementiawith Lewy bodies	Frontotemporal dementia
1	Patient profile	>65 yearsold	>40 yearsold 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	Memoryloss	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 withmotor neuron disease)

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]

Neuropathology and clinical signs of Alzheimer'sdisease

It is believed that between 75% and 90% of the time, a clinical diagnosis of Alzheimer's disease is accurate.[48] General practitioners have a propensity to overdiagnose Alzheimer's disease, while neurologists who specialise in memory problems have the best accuracy ([49]). Because elderly individuals generally have many pathologies rather than just dementia, clinical accuracy is often worse in this population.[50] Since there are currently no laboratory tests, advanced imaging methods, or thorough neuropsychological evaluation that can definitively identify Alzheimer's disease, the only clinical method for making a diagnosis is by microscopic inspection of brain tissue.[51] In most cases, symptoms begin around the age of 40 and progress subtly until death occurs about sixty years after symptoms first appear.pp. 52–54 The brain always shows signs of shrinkage, but a diagnosis can't be made just by looking at it because of age-related shrinkage and the typical variation in brain size.[55] When compared to other regions of the brain, atrophy in the medial temporal lobe is often more pronounced. After a brain slice, you'll normally see dilated lateral ventricles and atrophy in the hippocampus and amygdale, but the major sensory and motor cortices are usually unharmed.[56] Loss of neurones and synapses is accompanied by more targeted changes in neurones.Paired helical filaments, intraneuronal proteinaceous structures made up of an aberrant type of tau protein, are the most significant of these changes.References 57 and 58

Intracellular neurofibrillary tangles of tau protein and amyloid plaques, mostly made of aggregated amyloid beta peptide, are the neuropathological hallmarks of Alzheimer's disease. The pathophysiology of Alzheimer's disease is thought to begin with the production of extracellular amyloid plaques, which are believed to be seeded by high molecular weight

species that form aggregates of vesicular amyloid beta at high concentrations [59].

Phases of Alzheimer disease

There will be significant personality differences in how Alzheimer's disease manifests in each individual. Changes in mood, conduct, and thinking may also differ from person to person, but a stage model that outlines commonalities is widely used in the medical and academic communities.[60]

During the first stage, known as the "forgetfulness phase," individuals often struggle to remember recent events and have trouble remembering the exact location of things.[27] A lack of short-term memory, overall confusion, and trouble remembering even familiar names and locations may all contribute to memory loss.[61]

The 'confusional phase' is the middle stage that has been identified. As memory loss progresses, other symptoms such as a shorter attention span and worse overall cognitive function become more noticeable. Some people may notice changes to their speech, such as trouble finding words or disorientation in their surroundings.[61]

Complicated activities are executed imperfectly or with clumsiness, and the most recent acquired abilities tend to be forgotten earliest. A rapid decline of interest in one's environment and news may be devastating to those closest to the sufferer.[62] In the third stage, known as the "dementia phase," the individual's actions seem disorganised and even strange since they lack a clear goal. People in this stage have additional decline in memory capacity, calculation skills (dyscalculia), and parts of language are significantly impaired or lost altogether; as a result, their remaining intellectual and self-care abilities require continual monitoring. Grooming, clothing, toileting, and eating are all examples of self-care abilities that need constant support. Additionally, there is a noticeable trend of physical waste, which will need assistance with walking. After then, a person may spend the next year or two in an almost vegetative condition until they pass away. Some people may be more prone to developing Alzheimer's disease if certain environmental conditions are present. There has been speculation for a while that aluminium may be related to Alzheimer's disease.[63]

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 brainvascularization

Source: *Epidemiology of Alzheimer Disease*[64].

Pharmacological therapy review for AD

Existing pharmacologic treatment for AD only offers temporary relief, lasting approximately six to eighteen months at most.[65] The Cholinesterase inhibitors and memantine are the only medications authorised in the US and several regions of Europe to provide temporary symptom relief.[66] I While these medications do nothing to ameliorate AD pathology, they do help the brain make up for the death of neurones that normally would have communicated via the neurotransmitter acetylcholine.the 67th] Reviewing the clinical effectiveness of both authorised and potential pharmacological treatments for AD, this section concludes.[68] Table 4 shows the novel medications that are being developed to treat Alzheimer's disease.

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]

Conclusion

Any clinical evaluation tool for dementia has its limits, whether used to the general population or to those with learning difficulties. With this information in hand, we can make educated scientific decisions on how to modify our neuropsychological battery or come up with other assessments.

Despite these caveats, scientific knowledge has painted a clearer picture than ever before of the progression of dementia, suggesting that a compromise may be possible. Neuropsychological assessments given at critical intervals, including follow-ups, together with imaging modalities like fMRI and MRI, PET and SPET scans, and other technological advances, put the clinician in a stronger position to establish an accurate diagnosis and prognosis than in the past. It is believed that this will shed light on how service providers might better accommodate individuals with learning difficulties and dementia.

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