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A Review of Neurological Diseases

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Abstract

Dementia that progressively destroys brain cells is known as Alzheimer's disease (AD). Changes in conduct, impaired capacity to do ADLs, and a gradual deterioration in cognitive capacities are all symptoms. The majority of cases of dementia induced by this illness tend to impact the pre- and senile phases. According to the World Health Organisation, 6% of women and 5% of men experience Alzheimer's type dementia among persons aged 60 and above. A person with dementia, a clinical manifestation of Alzheimer disease (AD), may initially have subtle memory loss that isn't immediately apparent but worsens with time until he or she can no longer care for himself. Memantine and other acetylcholinesterase inhibitors, such as rivastigmine, galantamine, and donepezil, are effective only towards the end of the disease process and have minimal effect on the patient's condition generally. While these drugs do help with symptoms and slow down the disease's progression, they are not a cure. The neuropathological signs of Alzheimer's disease are well-known, although the precise mechanism is still not well understood. It is likely that the lack of understanding of the pathogenic process is to blame for the lack of viable therapies that might arrest the development and progression of the condition. Recent advances in pathophysiology have paved the way for new therapy targets that should allow us to tackle the root cause of sickness head-on. A deeper comprehension of the wealth of data around Alzheimer's disease may lead to improved disease management and reduced healthcare costs. This article makes an effort to summarise some of the most important recent developments in our understanding of Alzheimer's disease and in the methods used to treat it.

KEYWORDS: Alzheimer, Management, Diagnosis, treatment.

Introduction

Clinically characterised by a progressive loss of cognitive function, Alzheimer's disease (AD) is the most common kind of dementia. It starts with episodic memory difficulties and becomes more widespread and severe over time.[1] Worldwide, 44 million individuals were estimated to have dementia in 2013, and scientists predict that figure would surge to 136 million by 2050. The lack of an effective treatment for Alzheimer's disease is the single biggest unmet medical need in the field of neurology.[1] There is a complex web of interconnected pathophysiological processes in Alzheimer's disease (AD), including alterations in the metabolism of amyloid precursor proteins, phosphorylation of tau proteins, oxidative stress, poor energetics, malfunction of the mitochondria, inflammation, dysregulation of membrane lipids, and disruption of neurotransmitter pathways.a subsequent Metabolic dysfunction is now known to play a major role in Alzheimer's disease (AD), and many of the disease's symptoms may have their roots in these dysfunctions.[4] Hypoglycemia in

the brain, for instance, is a characteristic of Alzheimer's disease that persists even decades before the onset of cognitive decline.Various pathogenic processes, starting with Aβ42's interaction with mitochondrial enzymes, which leads to an increase in the production of reactive oxygen species (ROS), are thought to be responsible for the altered neuronal energetics induced by the well-documented neurotoxicity of Aβ42. As a result, toxic intermediate metabolites build up in the mitochondria, which impacts glycolysis, the TCA cycle, and respiratory-chain function in the mitochondria.[6-7]

Alois Alzheimer and Auguste D

It is believed that Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, was the first to describe a dementia ailment that would later be known as Alzheimer's disease (AD). Auguste D., a 51-year-old female patient with a "peculiar disease of the cerebral cortex," was the subject of Alzheimer's groundbreaking 1906 conference talk and 1907 work. Progressive memory and language deterioration, disorientation, behavioural symptoms (paranoia, delusions, and hallucinations), and psychosocial impairment were all things Auguste had shown.(8-10)

Normal memory

In order to grasp the intricacy of the condition, it is vital to distinguish between normal ageing and knowing what may go wrong and produce abnormal diseases like dementia. While studies of ageing may be seen of as belonging to separate disciplines, such as sociology, psychology, and biology, there is often a great deal of overlap and interaction across different domains. For example, if you're experiencing limited mobility as a result of a medical condition like arthritis, it could be challenging to engage in social gatherings or pursue hobbies that you formerly really enjoyed.the eleith When comparing a person's cognitive capacities over various time periods, it is important to bear in mind that one aspect of ageing might impact another.

The difficulty of defining "normal" belies the frequency with which "abnormal" and "normal" attitudes and actions overlap. Slowly but surely, obstacles of all kinds—cultural, environmental, and interpersonal—may begin to crumble. The term "normalcy" is really defined as "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 helps to clarify a widespread misconception that normalcy is distinct from abnormality.the eleith Everyone has their own standard of normality, thus when it comes to old age, people's expectations could vary greatly. Thanks to medical and technological breakthroughs, people are living longer than ever before. As a result, more and more people are witnessing and experiencing the many ways in which their friends and family age. As a consequence, people's ideas about what it means to age normally and their expectations of others are in a constant state of flux. Our bodies go through a natural process of ageing, which manifests itself in a variety of ways, including changes to our appearance and, more particularly, to our "cognitive" capacities.parts 12–13 The individual may have misinterpreted the information or the information may not be correctly encoded or retained, both of which may have an effect on memory [14–15].[16] Memory loss, particularly episodic memory, is a common symptom of ageing and may have a negative impact on a person's quality of life, relationships, and career. A decrease in memory function is a hallmark of dementia.[18] in On the other hand, it might indicate other dysfunctions that assessors should look for.

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

As a common and severe symptom, memory loss is what defines dementia. An evaluation is required to ascertain the extent of the problem and the individuals impacted.

Registering, encoding, storing, and retrieval are the four phases that make up the current agreement on how to remember anything. Data must be stored in memory before it can be entered or processed. There are two methods in which information might be "encoded": phonologically, for information that is based on sounds, or semantically, for information that is based on meaning [28, 29]. This is the process by which data is saved to memory. For instance, it is thought that episodic memory (the knowledge that someone ate lunch) and semantic memory (the knowledge that the word "lunch" indicates a mid-day meal) are stored 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 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 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 handling personal finances	Unable to successfully prepare food, cook, clean or shop	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 bowel incontinence
	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 way around in the home.

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

Epidemiology of AD

The financial, social, and health implications of Alzheimer's disease (AD) are enormous, making it a paramount worldwide health problem. With an estimated 5 million Americans impacted, a new diagnosis of Alzheimer's disease is made every 68 seconds.8 As the sixth leading cause of death among Americans 65 and older, dementia accounts for about $200 billion in annual direct care costs. The current global prevalence of dementia and Alzheimer's disease is estimated to be at 35 million. Experts predict that figure will climb to 65 million by 2030 and 115 million by 2050. Though the exact reason why some people are more susceptible to developing Alzheimer's disease (AD) than others is unknown at this time, the condition is known to have many risk factors, some of which can be altered while others cannot. Ageing is the single most critical factor that determines the start of Alzheimer's disease. Risk of developing Alzheimer's disease

(AD) about doubles every five years after age 65 and increases exponentially with age.part 34 and part 35 Most cases of Alzheimer's disease are the 'late-onset' or'sporadic' kind, which affects people aged 65 and above and accounts for 95% of all cases.Rare genetic anomalies cause "earlyonset" or "familial" Alzheimer's disease, which accounts for 5% of all cases, to manifest in individuals younger than 65 years old.[36] In cases when Alzheimer's disease runs in families, autosomal dominant variations are caused by mutations in the amyloid precursor protein (APP) gene on chromosome 21 or the presenilin gene on chromosomes 1 and 14. Those who have Down syndrome (trisomy 21) also have an increased chance of developing early-onset Alzheimer's disease. Less is known about the complex genetics of sporadic Alzheimer's disease. The epsilon 4 allele of the apolipoprotein E (APOE) gene, situated on chromosome 19, is one known risk factor for sporadic AD.[37] Women have a higher frequency of AD than males do due to the fact that women often outlive men.There is an association between lower educational attainment and an increased chance of AD dementia, which is consistent with the concept that education helps to build a person's cognitive reserve and resistance to AD pathology (38).in the text. Evidence from many studies suggests that cerebrovascular risk factors impact both the development and the course of Alzheimer's disease. A increased chance of acquiring Alzheimer's disease is associated with a family history of the disease, high blood pressure, obesity, or smoking.[40] Having a first-degree relative with Alzheimer's disease and a history of catastrophic brain injury leading to a loss of consciousness are additional risk factors for the development of the illness.[41] The

Pathology

In Alzheimer's disease, neurofibrillary tangles and amyloid plaques are the pathological hallmarks. The brain's cortex shrinks all around and the ventricles enlarge as a result. More deposits are located in the nucleus basalis of Meyernet, temporal cortex, and hippocampus. Cognitive impairments manifest in these individuals as a result of neuronal death brought on by pathogenic alterations, which in turn diminish levels of neurotransmitters, particularly acetylcholine. There is a great deal of research being conducted to clarify the fundamental pathological process of Alzheimer's disease, but the underlying pathological aetiology remains a mystery. The present state of knowledge has led to several theories on the causes of Alzheimer's disease (AD). They generally agree that

Amyloid Cascade Hypothesis

Tau Hypothesis

Mitochondrial Cascade Hypothesis

Amyloid Cascade Hypothesis

This hypothesis is widely accepted. It is believed that the underlying condition is caused by Aβ42-amyloid plaques in the brain. The β-secretase and γ-secretase enzymes sequentially work to create Aβ42 from the APP. Neurones die as a result of oxidative damage, inflammation, and the accumulation of insoluble Aβ42 as plaques. Neurofibrillary tangles form when tau proteins, after amyloid deposition, are hyperphosphorylated. There are two possible forms of Alzheimer's disease: familial and sporadic. Mutations in the APP, Presenillin-1, and Presenillin-2 genes, which are found on chromosomes 21, 14, and 1, respectively, are associated with an early onset in hereditary types. Possessing the ApoE4 allele raises the probability of acquiring familial or sporadic Alzheimer's disease at a later stage. Each of the three ApoE alleles contributes to cholesterol transport in its own unique way. The ApoE4 allele is present in 40-80% of Alzheimer's patients, despite a usual distribution of about 24-30% in the Caucasian population. New evidence suggests that ApoE4 upregulates amyloid formation and decreases clearance.

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

The clinical diagnosis of Alzheimer's disease is based on a number of tests, including the patient's medical history, neurological and physical examinations, cognitive testing, and the use of particular auxiliary tests to rule out other potential causes. The relative accuracy of the clinical diagnosis of AD is 70-90%, which is lower than the pathological diagnosis,

although it is greater in specialist settings such memory difficulty clinics.[43] The consensus criteria were first established in 1984[44], however the most recent revision was made by the National Institute on Ageing and the Alzheimer's Association (NIA_AA) workgroup in 2011. It is from these factors that the clinical diagnosis is formed.[45] Diagnosing "possible" Alzheimer's disease dementia is recommended when a patient's cognitive impairment is suspected to have an atypical clinical history or be caused by anything other than AD. Neurological and physical examination results in Alzheimer's disease patients are often unimpressive.positions 46 and 47} To help with the differential diagnosis, Table 2 summarises a few clinical features that distinguish AD.

Establishing the Diagnosis of Alzheimer Disease

To confirm a diagnosis of Alzheimer's disease, a clinical-neuropathologic assessment is required. Still, neuropathologic evidence presented at autopsy remains the gold standard for Alzheimer's disease diagnosis. There is an 80% to 90% success rate for clinical diagnoses of Alzheimer's disease prior to postmortem confirmation.

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	Dementia with Lewy bodies	Frontotemporal dementia
1	Patient profile	>65 yearsold	>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	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 with motor 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

A clinical diagnosis of Alzheimer's disease is thought to be accurate 75% to 90% of the time.[48] Neurologists who focus on memory issues tend to be more accurate in their diagnoses of Alzheimer's disease than general practitioners, who tend to overdiagnose the condition ([49]). The clinical accuracy is often worse in the aged population due to the fact that they typically have many illnesses rather than only dementia.[50] Microscopic examination of brain tissue is the only clinical tool for diagnosing Alzheimer's disease at this time due to the lack of conclusive laboratory testing, sophisticated imaging technologies, or comprehensive neuropsychological assessment.[51] Typically, symptoms start showing up around the age of 40 and gradually worsen until the patient passes away around 60 years after the symptoms first manifest.pages 52–54 There is usually some shrinking in the brain, but due to age-related shrinkage and normal fluctuation in brain size, a diagnosis cannot be determined only by looking at it.[55] Atrophy in the medial temporal lobe is often more noticeable than in other areas of the brain. While a brain slice often reveals atrophy in the amygdale and hippocampus as well as dilated lateral ventricles, the main sensory and motor cortices are typically unaffected.[56] More specific alterations in neurones occur with synaptic and neuronal loss.These alterations are most noticeably shown as paired helical filaments, which are intraneuronal proteinaceous structures composed of an abnormal tau protein.Articles 57 and 58 cited Amyloid plaques, mostly composed of aggregated amyloid beta peptide, and intracellular neurofibrillary tangles of tau protein are the neuropathological features that characterise Alzheimer's disease. High molecular weight species are hypothesised to seed the creation of extracellular amyloid plaques, which in turn form aggregates of vesicular amyloid beta at high concentrations, and this is the first step in the pathogenesis of Alzheimer's disease [59].

Phases of Alzheimer disease

The effects of Alzheimer's disease on each person's personality will vary greatly. Although each individual may experience changes in mood, behaviour, and thought processes at their own unique rate, the medical and academic sectors often refer to a stage model that identifies shared characteristics.[60] The first stage, called the "forgetfulness phase," is characterised by a general lack of memory for recent events and specific places.[27] Memory loss may be caused by a variety of factors, including a decrease in short-term memory, general disorientation, and problems recalling even familiar names and places.[61]

An intermediate step known as the "confusional phase" has been found. Memory loss is accompanied by additional symptoms that become more apparent as the disease advances, including a diminished ability to focus and general cognitive decline. Alterations to one's speech pattern, such as difficulty articulating ideas or becoming disoriented, may be noticeable to others.[61] Complex tasks are often carried out clumsily or incorrectly, and the most recently learned skills are often lost first. Those closest to a person who suddenly stops caring about their surroundings and the news may find it unbearable.Stage three, the "dementia phase," is characterised by a loss of purpose and an overall sense of disorganisation in the individual's behaviour [62]. Individuals in this stage have further deterioration in their memory capacity, arithmetic skills (dyscalculia), and certain portions of their language are severely affected or gone completely. Consequently, their remaining cognitive and self-care abilities need to be closely monitored. Ability to dress oneself, use the restroom, eat, and groom oneself are all examples of self-care skills that need ongoing assistance. Also, there's a clear pattern of physical waste, so you'll probably need someone to help you walk. A person may then remain in a nearly vegetative state for the subsequent year or two until they eventually die. Certain environmental factors may increase the risk of Alzheimer's disease in certain persons. An association between aluminium and Alzheimer's disease has been the subject of conjecture for some time.[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 forclearance
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

At best, the current pharmacologic treatments for AD only provide short-term respite, ranging anywhere from six months to eighteen months.For short-term symptom alleviation, the only drugs approved in the United States and certain parts of Europe are cholinesterase inhibitors and memantine [65].In [66], I Despite the fact that these drugs have no effect on AD pathology, they aid the brain in compensating for the loss of neurones that would have otherwise communicated via acetylcholine.that 67th This section wraps up by reviewing the clinical success of Alzheimer's disease pharmacological therapies, including both active and future options.[68] The innovative drugs now in development for the treatment of Alzheimer's disease are shown 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]

CONCLUSION

There are limitations to any clinical assessment method for dementia, whether it is employed with the general public or those with learning disabilities. This data will allow us to make well-informed scientific judgements on the future of our neuropsychological battery and other evaluation tools.

Despite these limitations, our understanding of dementia's course is now more complete than previously, which raises the prospect of a workable solution. Due to technology advancements, imaging modalities such as fMRI and MRI, PET and SPET scans, and neuropsychological evaluations administered at important intervals (including follow-ups), the clinician is now better able to determine an accurate diagnosis and prognosis than in the past. Service providers may be able to better accommodate persons with learning challenges and dementia if this holds true.

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