Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: July 31, 2023

Citation: Patel B, Walker R, et al., 2023. A Review of Alzheimer's Disease and Inflammation: Pathogenesis, Inflammatory Processes, and Novel Insights from the Artificial Intelligence Perspective, Medical Research Archives, [online] 11(7). https://doi.org/10.18103/mra.v11i7.2.3971

DOI
https://doi.org/10.18103/mra.v11i7.2.3971

ISSN: 2375-1924

REVIEW ARTICLE

A Review of Alzheimer's Disease and Inflammation: Pathogenesis, Inflammatory Processes, and Novel Insights from the Artificial Intelligence Perspective

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease which is characterised by the increased deposition and spread of extracellular β-amyloid plaques and intracellular hyperphosphorylated tau as neurofibrillary tangles. This is thought to be driven by the sustained activation of brain microglia and astrocytes. In this review, we will provide an overview of the current understanding of the pathogenesis of Alzheimer's disease, the role of inflammation and associated factors in disease progression as well as current treatments including those in late-stage clinical trials. We will also discuss how machine learning has been previously used to create Alzheimer's disease risk metrics and the potential for blood-based inflammatory factors to be used to create an artificial intelligence-based Alzheimer's disease early warning system. The development of an Alzheimer's disease-based early warning system would enable the improved use of existing and future disease-modifying agents and thereby help to slow or halt disease progression.

Abbreviations:

Aβ, Amyloid beta; AD, Alzheimer's disease; AI, Artificial intelligence; APP, amyloid precursor protein; ARIA, Amyloid-related imaging abnormalities; ASC, Apoptosis-associated speck-like protein containing a caspase-recruitment domain; BBB, Blood-brain barrier; CSF, Cerebrospinal fluid; CNN, Convolutional neural network; CNS, Central nervous system; DL, Deep learning; FDA, Food and drug administration; IgG, Immunoglobulin; IL, Interleukin; MCI, Mild cognitive impairment; ML, Machine learning; MRI, Magnetic resonance imaging; NADPH, Nicotinamide adenine dinucleotide phosphate; NFTs, Neurofibrillary tangles; NLRC, NLR family CARD domain-containing protein; NLRP, Nucleotide-binding oligomerization domain like receptor protein; NMDA, N-methyl-D-aspartate; PET, Positron emission tomography; ROS, reactive oxygen species; SIRT, Sirtuin; sPDGFRβ, Soluble platelet-derived growth factor receptor-β; τ; Tau TLRs, Toll-like receptors.

Introduction

The objective of this review is to provide an overview of problems associated with the diagnosis of Alzheimer's disease (AD), how it progresses and the effectiveness of current treatment options based on disease stage. It also explores the role of inflammation in the development and progression of AD. Additionally, we present an overview of how machine learning (ML) research has already been used to develop AD risk metrics and discuss the potential for inflammatory biomarkers to be used to create an artificial intelligence (AI) early warning system as it is important to be able to both detect and predict the onset of AD.

Alzheimer's disease, the most common form of dementia, accounts for 60-80% of all cases.[1] According to recent estimates, more than 6.5 million individuals are living with AD in the US alone, a number that is expected to rise to 13.8 million by 2060 due to the increasing ageing population.[1] Alzheimer's disease commonly manifests as memory impairment but may also affect expressive speech, visuospatial processing and executive functions impacting activities of daily living. Disease progression varies but on average individuals with AD live 4-8 years following their initial diagnosis.[1] Alzheimer's disease places an enormous burden on individuals, their families, and society in general, with estimated costs of $321 billion annually.[1] Without urgent action to reduce the burden of AD these costs are set to further increase.

A key challenge for clinicians is the lack of effective treatment options for AD. Of the available treatments for AD, few affect the underlying pathology and therefore are capable of reversing disease progression. By identifying those at risk and intervening early it may be possible to halt or slow the progression of AD through a combination of pharmacological drug treatments and lifestyle changes. Initiation of treatment earlier in the disease course could also help to lower overall health care costs with potential savings of approximately $7 trillion in medical and long-term care costs.[1]

The identification of biomarkers that are reflective of the underlying disease pathology could aid in the early detection of AD. Already positron emission tomography (PET) and cerebrospinal fluid (CSF) concentrations of pathological proteins such as amyloid beta (Aβ) and tau (τ) are being utilised clinically in the diagnosis of AD.[2] Magnetic resonance imaging (MRI) can also aid in diagnosis of AD through assessment of brain atrophy which is particularly evident in the medial temporal lobe and temporoparietal cortices.[3] The routine use of these tests in clinical practice is however limited by the invasive nature of the collection procedures and the expense associated with imaging.

Other biomarkers that have been the focus of research include blood based inflammatory factors.[4] Inflammation has long been known to play a key role in the pathogenesis of several neurodegenerative diseases including AD.[5,6] Indeed, several inflammatory biomarkers have already been shown to be altered early in the pathogenesis of AD including soluble tumour necrosis factor receptor 2, IL-6, monocyte chemoattractant protein-1 and IL-8.[7] It is hoped these biomarkers could provide a simple, non-invasive, and more cost-effective alternative to PET imaging and CSF biomarkers.

Progression of Alzheimer's disease

The clinical course of AD is complex and often varies considerably between individuals. Pathologically AD is characterised by the extracellular accumulation of β-amyloid plaques and the intracellular accumulation of τ-containing neurofibrillary tangles (NFTs). Amyloid beta is derived by the proteolytic cleavage of amyloid precursor protein (APP) by γ-secretases and β-secretases. The Aβ42 peptide has a high propensity to aggregate and form higher order oligomers, fibrils, and plaques owing to the increased hydrophobicity of its C-terminus. Amyloid beta

oligomers may play a direct role in AD pathogenesis by impairing both synaptic function (e.g., long-term potentiation) and synaptic structure (e.g., dendritic spines) through a range of different mechanisms.[8] However, there is minimal correlation between phases of amyloid deposition and degree of cognitive decline and therefore it is unlikely that Aβ pathology alone is responsible for inducing cognitive impairment.[9] In addition, evidence suggests that racial and ethnic differences found in amyloid PET positivity in people with mild cognitive impairment (MCI) and dementia may indicate differences in the underlying etiology of cognitive impairment.[10] For example, the proportion of amyloid positive PET scans was greater in white than in black or Asian participants in this study. [10]

According to the amyloid cascade hypothesis, deposition of Aβ may be the initiating step in AD pathology.[11] Amyloid beta aggregation is thought to activate kinases which lead to the hyperphosphorylation of microtubule-associated τ protein and its polymerisation into NFTs.[11] Neurofibrillary tangles typically contain a mixture of the 3R and 4R isoforms of the τ protein. Unlike Aβ pathology, τ pathology has been shown to correlate well with the degree of cognitive impairment in AD sufferers.[9,12] However, the co-occurrence of Aβ, τ and abnormal microglia are a strong predictor of cognitive impairment.[13]

The formation of Aβ plaques and NFTs may also contribute to AD pathology through the activation of microglial cells and astrocytes resulting in the production of inflammatory mediators. Further details about the role of inflammation in the pathogenesis of AD is discussed in the section on inflammation.[14] Alzheimer's disease related neuroinflammation also contributes to the neuronal loss and synaptic dysfunction seen in AD patients.

Alzheimer's disease severity is generally based on the degree of cognitive impairment and ranges from mild to severe dementia. At an early stage of the disease Aβ-containing plaques can be found widely distributed throughout the isocortex while τ-NFTs are mainly observed in the allocortex of the medial temporal lobe.[15] Early AD is characterised predominantly by impairments in memory which are accompanied by behavioural changes such as increased anxiety or agitation but these are often not severe enough to interfere with daily life.

Alzheimer's disease is particularly difficult to diagnose based on clinical symptoms alone during the early stages of the disease. As a result, CSF and PET imaging markers are commonly used along with cognitive assessments to diagnose AD. Cerebral spinal fluid biomarkers such as aggregated Aβ, total-τ, and phospho-τ, reflect key elements of AD pathophysiology and show high diagnostic accuracy even in the early stages of the disease.

As AD progresses cognitive impairment becomes more profound. Alzheimer's disease progression is associated with the spread of τ-NFTs from the medial temporal lobe to the lateral temporal, parietal and frontal isocortex.[15] At this later stage there are more obvious impairments in language, spatial cognition, executive function, and memory which do impact daily life. There are also noticeable behavioural changes such as confusion, disorientation, aggression, agitation, and at a late-stage delusions and hallucinations.

Even early AD represents an advanced stage in the pathogenesis of the disease. By the time some cognitive impairment is evident significant and irreversible synaptic and neuronal loss has likely already occurred.[16] The clinical phase of AD is preceded by a protracted preclinical phase in which AD pathology has been shown to accumulate 15–20 years prior to the onset of clinical symptoms.[17] This preclinical stage of the disease presents a unique opportunity to identify those at risk, to start pre-emptive interventions and alter disease trajectory.

Alzheimer's disease drug development pipeline

There are currently seven Food and Drug Administration (FDA) approved drugs available for the treatment of AD (Table 1). These include the cholinesterase inhibitors donepezil, rivastigmine and galantamine, the N-methyl-D-aspartate (NMDA) antagonist memantine and the amyloid beta antibodies aducanumab and lecanemab. Except for the recently approved Aβ antibodies, these drugs all treat AD symptoms with little effect on the underlying disease pathology or AD progression. Even the available Aβ therapeutics have shown limited efficacy in modifying the clinical course of AD.[18] However this failure may not be surprising given that Aβ plaque accumulation is already usually associated with significant neuronal changes.[18]

There are also numerous promising therapeutics currently in the late stages of clinical development as shown in Table 2 & 3, but these will not be discussed in detail in this review. These include other disease-modifying therapeutics targeting τ

aggregates and apolipoprotein E, which could prove more effective.[18] Given its role in the AD pathogenesis, inflammation is also attracting interest as a potential target in the treatment of AD. Those inflammatory targets of interest include tumour necrosis factor α, triggering receptor expressed on myeloid cells 2, CD33, proinflammatory cytokines and cyclooxygenase.[19] As more becomes known about the mechanisms involved in the pathogenesis of AD undoubtedly additional targets and new therapeutic strategies will emerge.

Table 1. Food and Drug Administration approved drugs for the treatment of Alzheimer's disease

Drug (Brand name)	Year of approval	Indication	Mechanism of action	Common adverse effects
Cholinesterase inhibitors				
Donepezil (Aricept)	1996	Mild, moderate, and severe dementia due to AD	Prevents breakdown of acetylcholine	Nausea, vomiting, loss of appetite, muscle cramps, diarrhoea
Rivastigmine (Exelon)	1997	Mild to moderate dementia due to AD	Prevents breakdown of acetylcholine	Nausea, vomiting, loss of appetite, diarrhoea
Galantamine (Razadyne)	2001	Mild to moderately severe dementia due to AD	Prevents breakdown of acetylcholine; Enhances action of acetylcholine on nicotinic receptors	Nausea, vomiting, loss of appetite, diarrhoea
N-methyl-D-aspartate receptor antagonists				
Memantine (Namenda)	2003	Moderate to severe dementia due to AD	Modulates effect of tonic levels of glutamate	Dizziness, confusion, headache, constipation
Amyloid beta monoclonal antibodies				
Aducanumab (Aduhelm)	2021	MCI or mild dementia due to AD	Promotes clearance of Aβ plaques	ARIA, headaches, falls
Lecanemab (Leqembi)	2023	Early AD	Promotes clearance of Aβ plaques	ARIA, infusion-related reactions
Combination drugs				
Memantine + Doneprezil (Namzaric)	2014	Moderate to severe AD	Prevents breakdown of acetylcholine; Modulates effect of tonic levels of glutamate	Diarrhoea, headache, dizziness, constipation, nausea, vomiting, loss of appetite, muscle cramps, diarrhoea

Table 2. Promising small molecule therapeutics in late-stage clinical trials for Alzheimer's disease

Drug candidate	Sponsor	Target indication	Proposed mechanism of action
Atuzaginstat (COR388)	Quince Therapeutics (formerly Cortexyme)	AD	Inhibits the bacterial protease gingipain to reduce neuroinflammation and hippocampal degeneration
ABG101 (low dose levetiracetam)	AgeneBio/ National Institute for Aging	AD	Modulates synaptic vesicle glycoprotein 2A reducing neuronal hyperactivity
ALZT-OP1 (Cromolyn & ibuprofen)	AZ Therapies	Early AD	Combined anti-inflammatory compounds
Blarcamesine (ANAVEX2-73)	Anavex Life Sciences	AD	Sigma-1 & muscarine receptor agonist reducing oxidative stress, Aβ accumulation and τ phosphorylation
BPDO-1603 (Donepezil & Memantine)	Hyundai Pharmaceutical	Moderate to severe AD	Combined angiotensin-converting-enzyme inhibitor and NMDA receptor antagonist
NE3107	Neurmedix	Mild to moderate AD	Binds to ERK1/2 kinases inhibiting inflammation and improving insulin sensitivity

Nilotinib BE	KeifeRx	Early AD	Inhibits tyrosine kinase to promote clearance of Aβ and τ plaques
Oligomannate (GV-971)	Shanghai Greenvalley	Mild to moderate AD	Alters intestinal bacteria to reduce inflammation and reduces Aβ plaque burden
Semaglutide	Novo Nordisk	Early AD	Antagonist of GLP-1 receptor reducing neuroinflammation and improving insulin sensitivity
Simufilam (PTI-125)	Cassave Sciences	Mild to Moderate AD	Binds to filamin A stabilising its interaction with the α7 nicotinic acetylcholine receptor
Tricapillin	Cerecin	Mild to moderate AD	Improves cerebral cellular metabolism
TRx0237	TauRx Therapeutics	AD	Inhibits τ protein aggregation into toxic oligomers
Valiltramiprosate (ALZ-801)	Alzheon, National Institute for Aging	Early AD in APOE4/4 homozygotes	Inhibits Aβ protein aggregation into toxic oligomers

Table 3. Promising antibody therapeutics in late-stage clinical trials for Alzheimer's disease

Drug candidate	**Sponsor**	**Target indication**	**Proposed mechanism of action**
Donanemab	Eli Lilly	Early AD	Monoclonal antibody specific for the pyroglutamate form of Aβ aiding in the clearance of Aβ plaques
Donanemmmab & Aducanumab	Eli Lilly	Early AD	Combination of monoclonal antibodies specific for Aβ plaques and oligomers promoting their clearance
Gantenerumab	Hoffmann- La Roche	Early AD	Monoclonal antibody specific for Aβ plaques and oligomers promoting their clearance
Gantenerumab & Solanezumab	Eli Lilly, Hoffmann-La Roche, National Institute of Aging	Early AD	Combination of monoclonal antibodies with specificity for Aβ monomer oligomers and plaques promoting their clearance
Solanezumab	Eli Lilly, Alzheimer's Therapeutic Research Institute	Early dominantly inherited AD	Monoclonal antibody specific for Aβ monomers helping promote plaque clearance

Donepezil

Donepezil is a reversible inhibitor of acetylcholinesterase which helps to increase the availability of acetylcholine at the synapses. Donepezil is used to treat symptoms associated with mild to moderate AD. A recent meta-analysis found evidence of a small benefit in cognitive function, activities of daily living and clinician-rated global clinical state in those taking donepezil compared to placebo.[20] However, they found no difference between those taking donepezil and placebo in terms of behavioural symptoms, quality of life or patient total healthcare resource utilisation.[20] Higher doses (≥10mg) of donepezil were associated with a slight improvement in cognitive function but lower quality of life and more adverse events.[20]

Rivastigmine

Rivastigmine is a pseudo-irreversible inhibitor of acetylcholinesterase and butyrylcholinesterase, which helps to increase acetylcholine availability at the synapses. Rivastigmine is currently approved by the FDA for the treatment of symptoms associated with mild to moderate AD. A meta-analysis of studies evaluating rivastigmine compared to placebo reported better cognitive function, activities of daily living and clinicians rated global impression of changes but no change in behavioural symptoms or impact on carers.[21] Additionally, patients taking rivastigmine were twice as likely to experience adverse gastrointestinal events compared to placebo, although these risks were slightly less for patients using patches compared with capsules.[21]

Galantamine

Galantamine is a reversible inhibitor of acetylcholinesterase, which helps to increase the availability of acetylcholine at the synapses. Galantamine is also an allosteric modulator of nicotinic cholinergic receptor sites, helping to potentiate cholinergic nicotinic neurotransmission. Galantamine is FDA-approved

for the treatment of symptoms relating to mild to moderately severe AD. One meta-analysis reported a significantly greater reduction in cognition at all dosing levels in patients with AD and MCI taking galantamine compared to placebo, with the greatest effect seen over six months.[22] Galantamine has similar adverse effects to the other cholinesterase inhibitors which include mainly gastrointestinal symptoms.[22]

Memantine

Memantine is a low affinity uncompetitive NMDA receptor antagonist. Memantine is thought to inhibit glutamate mediated neurotoxicity that occurs in response to neuronal cell death.[23,24] A recent meta-analysis confirmed the efficacy of memantine with a small beneficial effect on cognition, activities of daily living and behavioural symptoms in those with moderate to severe AD.[25] No clinical benefit was observed in those with mild AD and consequently it is not recommended that memantine be prescribed in these patients.[25] Memantine is generally well tolerated in those with moderate to severe AD, but is associated with dizziness and headache in some patients.[25]

Aducanumab

Aducanumab is a human immunoglobulin (IgG) 1 antibody that binds to Aβ aggregates aiding in the removal of Aβ plaques. Aducanumab is the first drug approved by the FDA that targets the underlying pathology of AD. The FDA approval of aducanumab was initially denied due to weak efficacy data pending further confirmatory studies. Controversially, the FDA then approved aducanumab under their accelerated pathway following reanalysis of phase III data which demonstrated its ability to slow cognitive decline and reduce brain amyloid and CSF phospho-τ in patients with mild AD.[26] The most common adverse event associated with aducanumab is amyloid-related imaging abnormalities (ARIA) which can indicate brain swelling.[26] The phase IV trial required by the FDA recently began to confirm the clinical efficacy of aducanumab.

Lecanemab

Lecanemab is a human IgG1 antibody that binds specifically to Aβ protofibrils aiding in the removal of Aβ plaques. A phase III clinical study of lecanemab reported a reduction in markers of amyloid in early AD and moderately less decline on measures of cognition and function than placebo at 18 months.[27] The most common adverse events during this study were infusion reactions and ARIA.[27] As a result of its Phase II clinical data lecanemab was approved by the FDA through their accelerated approval pathway, based on the likelihood of a clinical benefit in early AD.

Neuroinflammation and Alzheimer's disease

Neuroinflammation has been linked to numerous neurological and somatic disorders, such as AD, Parkinson's disease, and depression. Neuroinflammation is the immune response mechanism of the central nervous system (CNS) to various stimuli and threats, including infection, injury, and toxic protein accumulation. While an acute inflammatory response can be beneficial for clearing pathogens and cellular debris, chronic inflammation can lead to neuronal damage, synaptic dysfunction, and cognitive decline.[28]

Increasing evidence from genetic, epidemiological, and experimental studies indicate a strong association between neuroinflammation and AD.[29–31] Genome-wide association studies have identified several risk genes associated with AD, including *ATP8B4* and *ABCA1* together with rare variants of *ADAM 10* gene, many of which are involved in immune processes and inflammation regulation.[32–34] Furthermore, epidemiological studies suggest that long-term use of nonsteroidal anti-inflammatory drugs may reduce the risk of AD.[35]

Inflammation in AD occurs as a result of the binding of Aβ and activation of microglia and astrocytes receptors. Amyloid beta binding results in the production of a range of inflammatory mediators which contribute to progressive neurodegeneration as observed in AD. [36–40] Amyloid beta can also be cleared by microglia through receptor-mediated phagocytosis and degradation. The receptor for advanced glycation end product activates microglia and is involved in the production of proinflammatory molecules following Aβ binding. Activation of toll-like receptors (TLRs), particularly TLR2 and TLR4, and CD14, a member of the scavenger receptor class B family, can also do this.

However, it should be noted that the functions of microglia in the CNS are complex since in addition to their neurotoxic effects microglia can be neuroprotective.[37] It is this balance between the pro- and anti-inflammatory roles of microglia which can determine the onset and progression of AD. It is persistent overactivation that can result in a proinflammatory state.

A leaky blood-brain barrier (BBB) is known to contribute to the onset of AD.[39,41] A leaky BBB allows the entry of fibrinogen into the brain

parenchyma and its interaction with microglia and astrocytes. Fibrinogen can then interact with Aβ to form deposits in the brain parenchyma which increase the reactive microglial proinflammatory response and induce neuronal damage in AD individuals. Consequently, a leaky BBB is an early sign of cognitive dysfunction in AD sufferers.[42] Using a novel cerebrospinal fluid biomarker of the BBB associated with capillary pericytes and vascular smooth muscle cells, soluble platelet-derived growth factor receptor-β (sPDGFRβ) one study found that individuals with early cognitive dysfunction develop brain capillary damage and BBB breakdown in the hippocampus irrespective of changes in Aβ and/or τ. This suggests that BBB breakdown is an early biomarker of human cognitive dysfunction, independent of Aβ or τ. In individuals with MCI increased CSF sPDGFRβ correlates with dynamic contrast-enhanced MRI measures of BBB dysfunction in specific brain regions.[43]

Additionally, Nation *et al.*[42] found that brain vasculature is an important new biomarker of cognitive dysfunction in both individuals with or without Aβ and τ. There is also evidence for age-dependent BBB breakdown in the hippocampus.[43] In this study, it was shown that BBB breakdown in the hippocampus and its CA1 area and dentate gyrus deteriorated with MCI that correlated with injury to BBB pericytes.[42] These results enforce the idea that BBB breakdown is an early event in the ageing human brain which begins in the hippocampus, and may contribute to cognitive impairment.

Inflammatory factors and their role in Alzheimer's disease

Activation of microglia and astrocytes results in the production of a range of different inflammatory mediators including cytokines, chemokines and reactive oxygen species (ROS) all of which play a role in the pathogenesis of AD. Inflammasomes cleave precursors of cytokines, such as, interleukin (IL) -1β and IL-18 to produce their active forms. An inflammasome is an intracellular multiprotein complex which is the platform for proIL-1β and proIL-18.[38] Well-characterised inflammasomes are Nucleotide-binding Oligomerization Domain (NOD)-like Receptor Protein (NLRP) 1, NLRP2, NLRP3 and CARD domain-containing protein (NLRC) 4.[44,45] Other components of the inflammasome include the adaptor protein, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), which recruits the effector protein procaspase-1.[38] Following recruitment of procaspase-1, it self-cleaves to form caspase-1 and cleaves the precursor of the proinflammatory molecules to form IL-1β and IL-18.[38] The role of microglia and NLRP3 in the innate immune response to AD is reviewed by Hanslik and Ulland.[40]

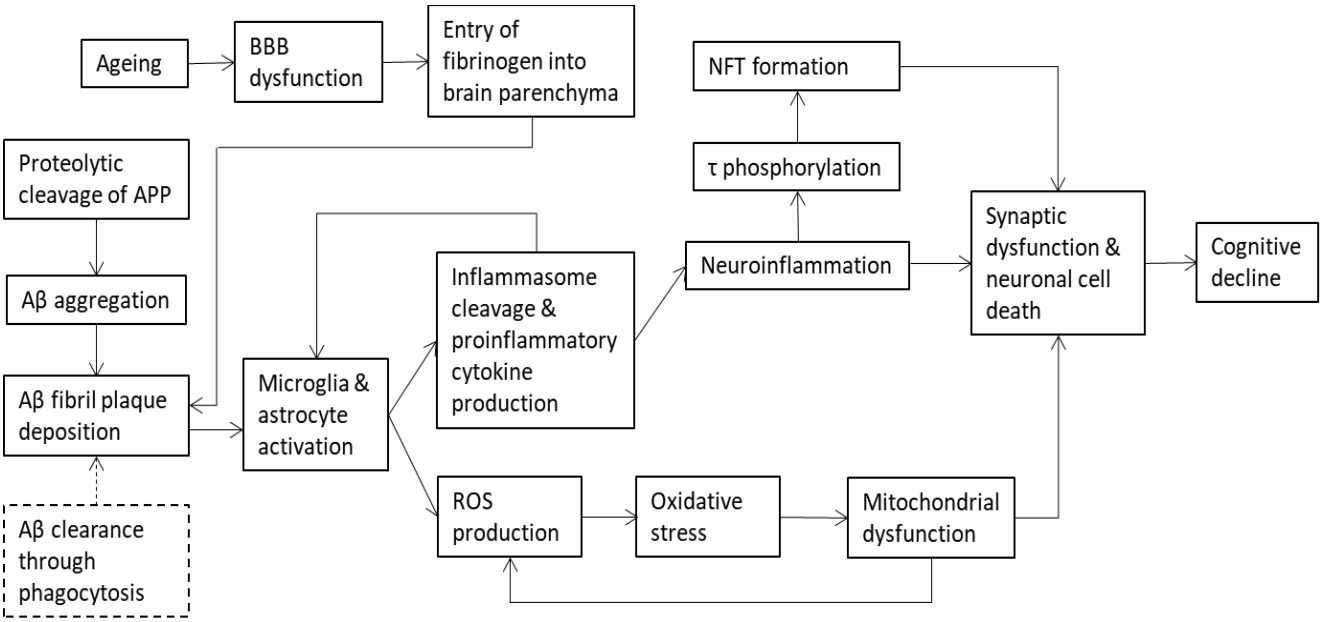

Figure 1. The role of inflammation in the pathogenesis of Alzheimer's disease

Both IL-1β and IL-18 are released from microglia and astrocytes and have been implicated in the onset and development of AD and the literature has been reviewed by Liu and Chan. [38,46–49] Following their release IL-1β and IL-18 can activate more astrocytes and microglia to secrete more inflammatory molecules, including cytokines, growth factors, complement molecules, chemokines and cell adhesion molecules resulting in further neuronal death. This activation may result from a microglial reaction associated with deposition of Aβ. In contrast, other cytokines, for example, IL-1 receptor antagonist, IL-4, IL-10 and transforming growth factor-β, can suppress proinflammatory cytokine production and their actions.[50,51] For example, when mice showing both Aβ and τ pathology were treated with an IL-1 receptor blocking antibody, this treatment regulated brain inflammatory responses through reduction of nuclear factor kappa-light-chain-enhancer of activated B cells activity.[52] There was also a partial reduction in fibrillar and oligomeric Aβ species although the overall Aβ plaque burden was unaffected.[52] However, neuronal τ pathology was reduced and blocking IL-1 signalling was shown to rescue hippocampal-dependent cognitive impairment.[52]

Interleukin-6 is another cytokine with a key role in brain inflammation. It can cause microgliosis and astrogliosis, and has a role in BBB integrity.[53] Interleukin-6 levels are raised in AD patients and in animal models of AD but levels also rise with age. Toll like receptor 2 can bind Aβ which can then induce IL-6 production in both microglia and astrocytes and lead to the production of inflammatory mediators in astrocytes. In their review, Spooren *et al.*[53] conclude that IL-6 cannot be labelled "beneficial" or "detrimental" in normal brain function.

Fatty acids are involved in the activation of the inflammasome and development of AD.[38] For example, palmitate will activate NLRC4 in astrocytes to release IL-1β and ASC assists in the activation of the NLRC4 inflammasome. If levels of either NLRC4 or ASC are reduced in palmitate-treated astrocytes, the production of IL-1β is reduced. Both the levels of NLRC4 and ASC are upregulated in brains of individuals suffering from AD. Fatty acids are involved in the release of IL-1β from microglia.

Oxidative stress is closely linked with inflammation and contributes to many diseases including AD. Oxidative stress may play a role linking the entry of fibrinogen through a leaky BBB and subsequent synaptic and neuronal damage in AD.[39] It is suggested that microglia are activated following fibrinogen binding to CD11b receptor which in turn activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and release of neurotoxic ROS.[54] The monoclonal antibody 5B8 has been found to suppress fibrin-induced NADPH oxidase, ROS and proinflammatory gene expression.[54] Using a mouse animal model of AD, 5B8 entered the brain, bound to parenchymal fibrin and reduced innate immune activation and neurodegeneration.[54] These authors concluded that fibrin acts as a dual inflammatory and oxidative stress signal in the brain and that fibrin immunotherapy could prevent neurodegeneration following BBB disruption.[54]

Neuroinflammation and mitochondrial impairment may also trigger a cycle ending in neuronal death.[55] Abnormalities of mitochondria have been found in neurones and astrocytes in brains of AD patients. Both APP and Aβ accumulate in mitochondria membranes resulting in functional and structural damage.[56] This may increase the number of defective mitochondria and decrease mitochondrial trafficking, resulting in abnormal mitochondrial dynamics in neurons of AD patients. There is also evidence for abnormal intracellular calcium regulation in neurons from AD patients.

Artificial intelligence/machine learning approaches and inflammatory factors in Alzheimer's disease

With an ever-growing amount of data being collected daily, AI and ML are becoming ubiquitous in a variety of settings in modern society, healthcare being one of them.[57] The processing/analysis of such a vast amount of information and the intricacies that lay behind it, are difficult tasks for single individuals and are much more suited to being handled by machines and algorithms. Tremendous progress has been made in recent years in the development and application of AI and ML tools, and these advances present an exciting opportunity for the healthcare sector.

There are however several challenges that lay between state-of-the-art computational and data analytic techniques and the translation of these aspects into effective clinical practice.[58] Medical data are highly sensitive private information and accessibility is often an object of debate as there are privacy concerns surrounding handling of these types of data. Information is often extremely fragmented, being collected in different contexts

by different people with different platforms and following different standards, leading to the scarcity of very high-quality large datasets. Bias is also a challenge and needs to be properly addressed to evaluate the applicability of the results obtained. In addition, lack of transparency in the interpretation of the models (especially with deep learning (DL) approaches, typically referred to as "black boxes") often exacerbates another existing issue which is the lack of understanding from the medical professional/clinical side of what AI and ML models can and cannot do. Finally, the absence of regulations on how to use AI in healthcare complicates matters even further and in conjunction with all the above hampers the efficacious use of these approaches in clinical practice.

Nevertheless, the potential of AI in medicine has still to be fully explored and a growing number of examples are demonstrating its possibilities.[59] Benefits include improvement in diagnosis and treatment of medical conditions, virtual assistance, and the more efficient use of resources by speeding up processes, reducing costs, prioritising tasks, and focusing efforts (as in the case of computational drug discovery and development), just to name a few.

Due to the availability of larger and more high-quality data, ML application in AD and, in general, neurodegenerative diseases-related research has imploded in the last decade. Machine learning has the potential to play a significant role in the early prediction of neurodegenerative diseases, as it can aid in the analysis of large amounts of data, including medical imaging, genetics, and lifestyle information, to identify patterns and correlations that can lead to early detection of the disease.

A wide variety of ML approaches have been used to both understand the complex relationships between inflammatory factors and AD, as well as for developing multi-source risk metrics for such a condition. Next, we will summarise some of the interesting results in this field in terms of the different areas of ML research:

1. **Association rule mining:** In the context of AD and inflammation, association rule mining can help identify relationships between different inflammatory factors and AD, such as presented in the work of Chaves *et al.*, Happwana *et al.* and Szalkai *et al.*.[60–62] Among other results, in this line of research Szalkai *et al.*[62] determined some novel and also some already well-established relations connected to good or bad cognition. Among other findings, new associations of mean corpuscular haemoglobin, alkaline phosphatase and aspartate aminotransferase levels to cognition are proposed. Furthermore, it has been suggested that high cholesterol levels seem to be beneficial in an elderly population to contravene bad cognition. This type of technique has also been extrapolated to image inputs, for instance Chaves *et al.*[60] proposed a methodology based on association rules to extract relations among activated brain areas in single photon emission computed tomography imaging. The results of this work have been used to characterise the perfusion patterns of normal subjects and to make use of them for the early diagnosis of AD (reported 94.87% classification accuracy).[60]

2. **Supervised learning:** This approach involves training a model on a labelled dataset (i.e., a dataset where the outcome of interest is known) to predict the outcome of interest for new, unlabelled data. In the context of AD and inflammation, supervised learning can be used to predict the risk of developing AD based on multiple inflammatory factors and other clinical and genetic variables.[63] For instance, Kavitha *et al.*[64] developed a variety of supervised learning models, namely decision trees, random forests, support vector machines, gradient boosting, and voting classifiers for early AD detection via longitudinal MRI data and achieved an average accuracy of 83%. Furthermore, Gaetani *et al.*[65] used different statistical approaches and Lasso models to both identify protein biomarkers reflecting neuroinflammation in AD and determine patients with MCI due to AD (Area under the curve=0.906). Their findings suggest an association between AD pathology and the sirtuin (SIRT) 2 pathway, astrocyte and microglia activation, and BBB dysfunction, as reflected by concentration changes in the CSF of SIRT2, hepatocyte growth factor, matrix metalloproteinase 10, and CXC ligand 5.[65]

In the last few years, a large amount of DL-based models have been published for early detection of AD via image inputs.[66,67] Cheung *et al.*[66] developed a convolutional neural network (CNN)-based model with an 83.6% accuracy for detecting AD-dementia using retinal photographs. Furthermore, such a model was able to differentiate between participants who were Aβ positive and those who were Aβ negative - accuracies ranged from 80.6 to 89.3%.[66] On the other hand, Venugopalan *et al.*[67] used a variety of supervised learning approaches, such as 3D CNNs, to analyse imaging (MRI), genetic (single nucleotide polymorphisms), and clinical test

data to classify patients into AD, MCI, and controls. This study identified hippocampus, amygdala brain areas, and the Rey Auditory Verbal Learning Test as top distinguished features.[67] Pan *et al.*[68] designed a novel approach combining CNN architectures and Ensemble Learning and applied it to some of the most commonly acquired anatomical MRI of the brain, i.e., T1WI. The proposed model achieved average classification accuracies (± standard deviation) of 0.84 ± 0.05 for AD vs. healthy cognition and 0.79 ± 0.04 for MCI patients who will convert to AD vs. healthy cognition. A comprehensive review containing the most relevant research work done in this area (DL techniques for AD prediction) has been carried out by Shastry *et al.*[69]

3. **Unsupervised learning:** This approach involves identifying patterns in a dataset without prior knowledge of the outcome of interest. In the context of AD and inflammation, unsupervised learning can be used to identify subgroups of patients based on their profiles.[70] In this sense, Liu *et al.*[71] developed an unsupervised learning methodology to discriminate between scans from cognitively normal and people with AD using a limited number of labelled structural MRI scans. They used two-sample t-tests to detect the AD-relevant regions and then employed an unsupervised learning neural network to extract features from the regions. Finally, a clustering algorithm was implemented to discriminate between control and AD data based on the extracted features. The proposed method yielded an accuracy of 84%.

More importantly, there is a vast amount of literature aiming to stratify AD patients into multiple subtypes via a plethora of clustering algorithms and metrics. A more detailed review of this research area is available in Alashwal *et al.*.[72] Such stratification has allowed researchers to determine several features to explain, among other things, why some individuals may progress to AD while others do not. These features include low CSF Aβ42 and impaired immediate recall.

4. **Network analysis:** This approach involves constructing networks of interacting variables (e.g., genes, proteins, pathways) and analysing their properties. For AD and inflammation, network analysis can be used to identify key inflammatory pathways involved in AD and to predict novel targets for drug development. For instance, Wang *et al.*[73] developed a transcriptomic network analysis of 19 brain regions. This approach provides a comprehensive assessment of the critical molecular pathways associated with AD pathology and offers new insights into molecular mechanisms underlying selective regional vulnerability to AD at different stages of the progression of cognitive impairment.[73] Analogously, Canario *et al.*[74] utilised functional near-infrared spectroscopy to analyse brain activity in different regions and then construct minimum spanning tree-based regions to characterise the brain topologies of participants with AD, MCI, and normal controls. Their results showed the AD group to have strong correlations between the Hamilton depression rating scale and different graph metrics, suggesting a link between network organisation and the recurrence of depression in AD.

Overall, ML/AI can significantly help with the early prediction of AD by analysing large amounts of data and identifying early signs of the condition before symptoms are apparent. To achieve this goal recent research has been focused on the analysis of a large variety of multi-source databases that range from medical imaging data, such as MRI and PET scans, to cognitive tests and genetic inputs. Depending on the nature of the database, different types of algorithms have been proposed in the areas of association rule mining, supervised learning, unsupervised learning and network analysis. The application of AI/ML could also aid in the identification of inflammatory blood biomarkers which could form the basis of AD risk metrics.

Conclusion

Undoubtedly the successful treatment of AD will likely depend on the early identification and the administration of disease-modifying therapeutics before symptom onset in order to slow disease progression. Considering the clear role inflammation plays in the pathogenesis of AD, AI/ML could play an important role in helping to identify potential inflammatory blood biomarkers that could form the basis of an AD risk metric. This metric could also provide an easy method for monitoring disease progression and the effectiveness of disease-modifying therapeutics as well as enabling more tailored and personalised treatment. Such a metric could transform the way AD is managed and help relieve the significant personal and financial burden that AD places on both patients and healthcare providers.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

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