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Navigating Alzheimer's Disease

Insights on the pathophysiological continuum, diagnostic techniques, therapeutic strategies, treatment guidelines, and adverse effects

Understanding the pathophysiological journey of Alzheimer's disease (AD) is crucial as it transitions from silent biological changes to symptomatic stages

Pathophysiological–clinical continuum of AD

- Hallmarks of AD pathology involve the accumulation in the brain of:[1] • Amyloid-beta (Aβ) • Tau protein
- AD biomarkers develop and evolve in a predictable and sequential manner, similar to the pathology of AD
- Aβ biomarkers are state biomarkers and indicate the presence of disease
- Some tau biomarkers can indicate both disease presence and disease progression

Phases of AD[1]

Asymptomatic phase

- Genetic and environmental factors induce the accumulation of Aβ peptides in the brain
- Early Aβ accumulation increases rates of Aβ fibril accumulation in the brain's default mode network[2]
- Accumulation of Aβ peptides begins as early as 25 to 30 years before the appearance of AD clinical symptoms

Progression of asymptomatic AD and its association with biomarkers[1]

- The first measurable evidence of AD is abnormally reduced levels of Aβ1 or Aβ42 in the cerebrospinal fluid (CSF)
- This is followed by increased Aβ tracer retention during positron emission tomography (PET) scans
- Elevated levels of some fluid biomarkers indicate neuronal injury
- Evidence of neurodegeneration can be observed in neuroimaging modalities
- Aβ accumulation linked with cognitive decline and progression towards symptomatic AD

Early symptomatic phase (or mild cognitive impairment (MCI) due to AD)[1]

- MCI due to AD is characterised by:
  - Not much change in Aβ accumulation
  - Tau accumulation and neurodegeneration is directly proportional to the degree of cognitive impairment
- Progression from MCI to AD dementia is influenced by various risk factors including cardiovascular disease, metabolic syndrome, psychiatric illness, and apolipoprotein e4 (*APOE ε4*) gene

AD dementia[1]

Advanced stage of AD disease, characterised by:

- ✔ High Aβ distribution in the brain
- ✔ Maximum tau accumulation
- ✔ Neurodegeneration in medial temporal regions (amygdala, hippocampus, and neocortex)

The complex sequence of events, including tauopathy and abnormalities in biomarkers

Classification schemes for the AD continuum

- US National Institute on Aging–Alzheimer's Association Classification (NIA-AA)[1]
- International Working Group Classification[1]

- Standardises research settings
- Enables diagnosis via symptoms and biomarkers

Importance of timely diagnosis of AD[1]

- Improves quality of life
- Early evaluation of reversible causes (e.g., depression, anxiety, vitamin deficiency, sleep disturbances)
- Enables patient and family education and counselling
- Allows for potential pharmacologic and non-pharmacologic interventions
- Controls comorbidities contributing to cognitive decline
- Delays nursing home admission

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Clinical phenotypes and imaging biomarkers – structural, functional, and molecular[3]

Amnestic syndrome is the most common characteristic phenotype of AD and is observed in approximately 85% of AD cases

Rare phenotypes of AD[3]

- Logopenic variant of primary progressive aphasia
- Posterior cortical atrophy

Atypical phenotypes of AD[2]

- Dysexecutive variant of frontal AD
- Non-fluent primary progressive aphasia
- Semantic variant primary progressive aphasia
- Behavioural variant of frontal AD

Biomarker profiles for typical and atypical phenotypes of AD[3]

- AD biomarkers can aid clinicians in identifying, differentiating, and diagnosing AD phenotypes
- Classified into pathophysiological biomarkers and topographical biomarkers
- Pathophysiological biomarkers include:
  - Amyloid PET[2]
  - Detection of Aβ fibril accumulation for identifying early-stage AD
  - CSF concentrations of amyloid and tau proteins
  - Plasma levels of amyloid, tau, and other protein biomarkers
- Topographical biomarkers are indicative of regional hypometabolism pattern of AD pathology and include:
  - Fluorodeoxyglucose (FDG)-PET
  - Atrophy pattern in structural magnetic resonance imaging (MRI)

Structural neuroimaging biomarkers[4]

Computed tomography

- Differential diagnosis of AD
- Easily accessible, inexpensive, and faster than MRI

Structural MRI

- Provides accurate details of the structural changes in the brain
- Serial structural MRI is commonly used to find specific atrophy patterns of many dementia disorders and other disorders causing dementia (vascular, traumatic, etc.), and also to to measure disease progression of AD

Functional imaging biomarkers[4]

PET markers

FDG-PET

- Differentiates typical and atypical AD
- Robust biomarker of overall brain metabolism
- Identifies nerve cell injury, loss of synaptic activity, and impairment of the blood-brain-barrier in patients with AD

Molecular imaging biomarkers

Amyloid PET

- Detects insoluble Aβ plaques in the brain, but not other forms of Aβ peptide

Tau PET

- Indicates neurofibrillary tangles
- Allows for quantification of tau neuropathology *in vivo*

Fluid biomarkers[2,4]

CSF biomarkers

- Detects both Aβ24 and hyperphosphorylated tau
- CSF-tau can reveal neuronal death
- CSF biomarkers include Aβ42/Aβ40, p-tau217, tp-tau181, and total tau

Neurofilament light protein (NfL)

- Sensitive biomarker of neuroaxonal damage
- CSF-NfL can be used as a prognostic biomarker to track neurodegeneration in AD

Blood-based biomarkers[2,4]

- Assessment of AD biomarkers in blood is performed via specific immunoassays
- Plasma Aβ levels positively correlate with Aβ levels in the CSF and Aβ content in the brain of patients with AD
- Plasma p-tau181 can indicate clinical severity of AD and is a promising biomarker candidate
- Plasma p-tau217 can capture earliest cerebral amyloid-beta changes and is a promising biomarker

Prospective biomarkers[4]

Digital biomarkers refer to the medical data collected through wearable devices and mobile

Retinal imaging[5]

- Optical coherence tomography can provide two-dimensional cross-sectional images and three-dimensional volumetric details of retina
- Retinal changes in AD: loss of retinal ganglion cells, thinning of retina, reduced optic nerve volume, Aβ plaques in the retina

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Expert opinions on biomarkers for AD[4]

Structural imaging
- ✔ MRI is the main tool for brain imaging and is particularly valuable with normative data tailored for Asian populations
- ✔ Advanced technologies combining volume measurement and machine learning assist in detecting early AD and other dementia types

CSF biomarkers
- ✔ Tests for Aβ42, p-tau181, and others: crucial for early diagnosis and differential diagnosis
- ✔ Normative data and standardisation: essential for broader use, especially in Asian populations

Functional imaging
- ✔ FDG-PET tracks dementia progression and distinguishes AD types, crucial in resource-limited settings
- ✔ Amyloid-PET confirms amyloid deposits in MCI and early dementia, useful for patients under 65 years of age
- ✔ Tau-PET diagnoses dementia types and monitors progression, which is vital as new therapies emerge

Blood-based biomarkers
- ✔ Aβ42/Aβ40 ratio and p-tau181 for screening, monitoring progression, and predicting treatment response
- ✔ Promotes equity in AD research and diagnosis
- ✔ p-tau217 is in evolution

Prospective biomarkers
- ✔ Digital and AI-based tools for early detection, genetic tests complement biomarker panels

Differential diagnoses of the different phenotypes of AD[3]

Amnestic syndrome	• Dementia with limbic-predominant age-related TDP-43 encephalopathy • Dementia with Lewy bodies • Frontotemporal lobar dementia
Logopenic variant of primary progressive aphasia	• Non-fluent primary progressive aphasia • Semantic variant primary progressive aphasia
Posterior cortical atrophy	• Dementia with Lewy bodies • Cortical basal degeneration • Prion diseases like Creutzfeldt-Jakob disease
Corticobasal syndrome	• Cortical basal degeneration • Progressive supranuclear palsy • Creutzfeldt-Jakob disease
Behavioural variant of frontal AD	Behavioural variant of frontotemporal dementia (FTD)
Dysexecutive variant of frontal AD	Behavioural variant of FTD

Biomarkers should complement clinical assessment for AD diagnosis[3]

'ATN' research framework by NIA-AA
- Defines AD based on three key biomarkers
  - ✔ Amyloid abnormalities ('A')
  - ✔ Tau protein changes ('T')
  - ✔ Evidence of neurodegeneration ('N')
- Clinical phenotypes and cognitive symptoms of AD are not considered within this framework

AD treatment strategies

Challenges affecting AD treatment[2,6]
- Pathological changes occur 15–20 years before symptoms leading to irreversible damage
- Variability in symptoms and progression complicates treatment development
- Neuropathological changes in AD, including Aβ plaques and hyperphosphorylated tau protein, complicate therapeutic targeting
- Underlying mechanisms for amyloid hypothesis and other pathological effects of AD need to be mapped and elucidated accurately

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Symptomatic and disease modifying treatments

Cholinesterase inhibitors (ChEIs)[5,6]
- Increase synaptic acetylcholine levels to improve cognitive and memory functions
- Approved for mild-to-moderate AD
- Ineffective for long-term progression; not recommended for MCI due to AD

Anti-N-methyl-D-aspartate (NMDA) receptor antagonist[6]
Memantine
- Modulates NMDA receptors to reduce glutamate toxicity
- Effective for moderate-to-severe AD; not recommended for mild AD

Aβ-directed therapeutics[2,6]
- Reduce Aβ levels and amyloid deposits; requires effective models and trials
- Monoclonal antibody treatment

Tau-directed therapeutics[6]
Includes tau kinase inhibitors and antisense oligonucleotides to target tau pathology

***ApoE*-directed therapeutics[6]**
Studies in animals show that lowering *ApoE* can reduce amyloidosis and tau pathology; gene therapy may address *Apoε4* function loss

Overview of treatment guidelines[7]

The guidelines integrate pharmacological and non-pharmacological interventions tailored to regional healthcare systems and patient needs

Guidelines	Key features
NICE Dementia[7]	Evidence-based recommendations; criteria for ChEIs and memantine; emphasis on cost-effectiveness; management of behavioural and psychological symptoms of dementia (BPSD)
American Academy of Neurology[7]	Screening and diagnosis protocols; recommendations on cognitive testing tools; caution against routine biomarker use; focus on reversible causes and differential diagnoses
Korean Dementia Association[7]	Use of *APOE* genotyping in diagnosis and prognosis; role of amyloid PET and FDG-PET; non-pharmacological interventions like exercise
Danish MCI Guidelines[7]	Biomarker testing for diagnostic certainty; importance of assessing activities of daily living; structural and functional imaging recommendations
World Health Organization[7]	Non-pharmacological approaches: exercise, diet, smoking cessation; management strategies for BPSD; support for caregivers and families
Indian Dementia[7]	Diagnosis and management strategies specific to the Indian context; cultural considerations in care
TCM Chinese Guidelines[7]	Traditional Chinese medicine (TCM) approaches integrated with modern practices; prevention strategies
European Association of Nuclear Medicine[7]	Role of PET imaging in dementia diagnosis; recommendations on neuroimaging techniques

Treatment-related adverse events: amyloid-related imaging abnormalities (ARIA)[8]

Radiological features
Monoclonal antibodies targeting Aβ reduce brain deposits but can lead to ARIA, characterised by MRI abnormalities

Two classes of ARIA
- ARIA-E (oedema/effusion): characterised by MRI signal abnormalities indicating fluid accumulation in the brain
- ARIA-H (haemosiderosis/microhaemorrhages): identified by MRI signals indicating blood products or microhaemorrhages

Clinical detection and classification challenges
- ARIA can be asymptomatic or symptomatic, with symptoms typically related to ARIA-E
- Challenges include distinguishing ARIA from disease progression and other neurovascular conditions

Pathophysiology
- Shares pathophysiological features with AD and cerebral amyloid angiopathy
- Treatment-induced clearance of Aβ may disrupt the blood-brain barrier, leading to fluid extravasation or microvascular damage
- Cerebral amyloid angipathy-related inflammation

Underlying biological mechanisms
- Vascular permeability
- Microvascular integrity
- Cerebral amyloid angiopathy-related inflammation

Risk factors/predictors
- *APOE* alleles increase susceptibility to ARIA, particularly ARIA-E
- Higher doses of anti-amyloid therapies
- Baseline microhaemorrhages

Key messages

- **AD progresses through identifiable stages marked by biomarker changes, from asymptomatic to symptomatic phases, highlighting the importance of early detection**
- **Diagnostic biomarkers can effectively identify AD pathogenesis which can then be validated with a clinical evaluation**
- **Neuroimaging biomarkers offer high accuracy, accessibility, and sensitivity in detecting AD, aiding in precise diagnosis and disease monitoring**
- **The complex pathology of AD, including Aβ accumulation and tau pathology and the poorly understood disease mechanisms have resulted in the failure of numerous clinical drugs**

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