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Pathway to Accurate Alzheimer's Diagnosis

Insights on enhancing diagnostic proficiency

Alzheimer's disease (AD) is a progressive brain disorder characterised by a loss of thinking ability and memory[1]

An increasingly important global public health issue[1]

- 1 in 9 individuals ≥65 years of age affected
- 5th leading cause of death

Projected to reach 71 million by 2050 in the Asia-Pacific regions[2]

Disease stages of AD[1]

- Preclinical
- Mild cognitive impairment (MCI)
- Dementia
  - Mild
  - Moderate
  - Severe

Pace of disease progression is determined by[1]:

- Age
- Genetics
- Sex
- Environmental factors
- Severity of AD pathology
- Presence of other brain pathology (e.g., cerebrovascular disease)

AD accounts for 60% to 80% of all dementias[1]

75% of people with dementia are not diagnosed[1]

Pathophysiology of AD[3]

First neuropathological hallmarks

- Accumulation and formation of amyloid β (Aβ) plaques
- Intracellular neurofibrillary tangles of tau protein

Earliest symptoms

Memory loss | Depression and apathy | Disorientation | Confusion | Behavioural changes | Problems with speech or language

Recently, newer disease-modifying treatments (DMTs) that target key pathological processes of AD have been developed and approved[1] → Anti-amyloid treatments slow disease progression

Early diagnosis and timely intervention can now help improve long-term outcomes for patients with AD[1]

Challenges in diagnosing AD[1]

- Lack of definitive diagnostic tests
- Limited or delayed access to healthcare
- Similarity to other types of dementia or age-related cognitive decline
- Overlapping conditions like vascular dementia or Parkinson's disease
- Stigma and denial
- Variability of symptoms

Early diagnosis is especially challenging, as changes in the brain may occur long before clinical symptoms are detected[1]

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Current diagnostic measures evaluate patients presenting with cognitive or behavioural impairment concerning AD-related dementias and make use of[1]:

- Medical history
- Cognitive assessments
- Routine lab tests
- Imaging studies
  - Computed tomography scans
  - Magnetic resonance imaging (MRI)
  - Positron emission tomography (PET) scans

Diagnosis can now be made of prodromal and non-symptomatic stages preceding dementia[3]

AD-P	First pre-clinical stage of AD – asymptomatic cerebral amyloidosis can be detected in abnormal ↓**CSF Aβ1-42** concentration or high amyloid PET
AD-P	Second pre-clinical stage of AD – **amyloidosis + neuronal injury** or degeneration observable: FDG-PET/MRI,↑**total tau/pTau181** in CSF, cortical thinning/hippocampal atrophy on SMRI
AD-P	Third pre-clinical stage of AD – **cumulative of two previous stages** with very mild and subtle cognitive decline
MCI-AD	MCI due to AD (prodromal AD) – observable memory impairment and decline of other cognitive functions,↓**Aβ1-42,↑total tau/pTau181 in CSF**, e.g., cortical thinning
ADD-mild	Dementia due to mild AD – some of everyday activities are disrupted. Significant interference with the ability to function at work or at usual activities, but still able to carry out basic activities
ADD-moderate	Dementia due to moderate AD – the longest stage of ADD everyday life and activities become problematic to handle independently
ADD-severe	The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria

AD-P, preclinical stages of Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural MRI; pTau181: plasma phosphorylated tau 181

Guidelines for diagnostic assessment involves the collection of[4]:

- History of present illness
- History of cognitive symptoms
- History of mood and/or behavioural symptoms
- Impact on instrumental activities of daily living (IADLs) and ADLs
- Review of cognitive, behavioural, and sensorimotor systems
- History of sleep disturbance
- Examination

Medical history and cognitive assessment tests are subjective, and they lack sensitivity, specificity, and consistency[1]

Validated instruments with structured questionnaires aid in reporting symptoms, and the best-suited test(s) should be chosen depending on:

- Clinician proficiency
- Patient's level of education and occupation

Advanced diagnostic modalities

- Imaging and fluid biomarkers are the more objective measures of neuropathological processes[3]
- Exclude reversible causes of cognitive decline and other intracranial pathology by structural imaging[5]
- Amyloid burden associated with disease progression[6]
  Unimpaired → MCI → Dementia
- PET radiotracers that detect amyloid plaques and tau tangles[7]
  - Identify AD disease-defining lesions
  - Deemed appropriate for use in diagnosis or AD management
- However, there is limited use of amyloid PET in routine practice because of[8,9]:

Limited accessibility

High cost

Non-coverage by insurance

There is a need for accurate, cost-effective, and easily accessible biomarkers for widespread clinical use, facilitating timely AD diagnosis[9]

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Blood-based markers (BBM)

pTau at threonine 217 (pTau217)

- Increased by 80–350% in cognitively unimpaired subjects with positive amyloid status
- 20 years before the onset of cognitive decline[8]

In individuals with cognitive impairment[9]:

- pTau217 with Aβ42/40 is more sensitive than pTau217 alone

CSF biomarkers[3]

Biomarkers in CSF represent evidence of neuropathological changes developing in the brain of patients with dementia

- Correlated with PET biomarkers and cognitive decline
- Detect pathological changes before the onset of cognitive symptoms with high accuracy, sensitivity, and specificity

↑ **Aβ 1-42 or Aβ 1-42/Aβ 1-40 ratio +**
↓ **Tau and pTau181 levels**

→ **Accurately predict progression from MCI to dementia**

Limitations of CSF biomarkers

Invasive lumbar puncture for CSF collection

Higher medical risk → Legal concerns of informed consent

- MCI with a normal biomarker profile[10] 5-year dementia risk: **10%**
- Patients with MCI with a full AD profile (amyloid and tau pathology)[10] 5-year dementia risk: **>90%**

In individuals with MCI, the key decision-making skills essential for capacity to consent are often already significantly impaired[10]

Supported decision-making involving patients, caregivers, and physicians aids in timely biomarker-based diagnosis and initiation of DMT[10]

Integration of existing and potential AD diagnostic measures[3,8,9]

- Patient medical history
- Cognitive and neuropsychological assessment
- Non-invasive BBM pre-screening tool Aβ42/Aβ40 ratio, pTau181, pTau217

- CSF biomarkers: amyloid, Tau/pTau181
- Imaging for neurodegeneration
  - MRI measuring brain atrophy
  - FDG-PET
- Treatment initiation

Potential integration of BBM[8]

- Best for primary care setting
- Annual screening for older adults
- Monitoring of at-risk groups

- Prognosis
- Identify candidates for early intervention

- Accelerate clinical trial enrolment
- Reduce trial cost

- Assess treatment efficacy
- Facilitate treatment selection and patient stratification

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Standardisation and unified interpretation of biomarkers

Accurate diagnosis relies on standardised interpretations of biomarker levels detected in patients with AD

Variability associated with AD stages and clinical presentation makes it challenging to interpret observed biomarker value ranges

Determine pre-analytical conditions to improve reproducibility of fluid biomarker measurements[3]

- Technological advances bringing automation
- Establish unified cut-off values and reference limits

Standardise the interpretation of fluid biomarkers with respect to clinical presentation of AD and MCI[3]

Expert consensus and guidelines on the interpretation of fluid biomarkers

Collaborative strategies to enhance diagnostic accuracy[4,10]

Supported decision-making

- Involves patients, caregivers, and healthcare providers
- Crucial when decision-making capacity is impaired (e.g., in MCI)
- Fosters a shared understanding of diagnosis, prognosis, and available treatment options
- Supports ethical and timely initiation of DMTs

Multidisciplinary care teams

- Includes neurologists, geriatricians, neuropsychologists, and primary care physicians
- Enables a comprehensive evaluation of cognitive, behavioural, and functional domains
- Improves coordination for long-term management and follow-up care

Key messages

DMTs with the potential to alter the course of disease progression highlight the urgent need for improved diagnostic methods that can successfully diagnose AD in its earlier stages

Fluid biomarkers reflect the neuropathological changes developing in the brain of patients with dementia, and serve as objective diagnostic measures

Establishing unified biomarker reference ranges and standardisation of interpretation in the clinical context of AD will promote biomarker use in routine clinical practice, ensuring rapid and accurate diagnosis with improved outcomes for patients with AD

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