Mild cognitive impairment and dementia in neuro-degenerative disorders

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Incidence of Common Neurological Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence (per 100,000)</th>
<th>New Cases (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>268</td>
<td>670,000</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>188</td>
<td>470,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>200</td>
<td>500,000</td>
</tr>
<tr>
<td>Seizures</td>
<td>50</td>
<td>124,000</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>16</td>
<td>40,000</td>
</tr>
<tr>
<td>Primary neoplasm</td>
<td>15</td>
<td>37,500</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>6</td>
<td>15,000</td>
</tr>
<tr>
<td>Primary brain tumor</td>
<td>6</td>
<td>15,000</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2</td>
<td>5,000</td>
</tr>
<tr>
<td>Gullain Barre’</td>
<td>1</td>
<td>2,500</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>0.3</td>
<td>750</td>
</tr>
</tbody>
</table>
Timely Diagnosis of AD Is an Unmet Need

• Diagnosis is delayed by an average of 2-3 years after symptom onset\(^1,2\)
• 25% of patients clinically diagnosed with probable AD during their lifetime did not have AD pathology at autopsy\(^3,4\)
• 50% of patients with any form of dementia are not formally diagnosed\(^5\)

AD=Alzheimer’s Disease
Concept #1

- Subjective memory complaint is no longer considered the “worried well”
- The ICD10 code is R41.3
- A self report of a memory complaint should not be dismissed or downplayed but should be evaluated

Subjective memory complaint has predictive value

- A Brazilian study examined 248 subjects. They were asked whether they had memory complaints and underwent a cognitive impairment screening.
- A total of 147 patients presented with subjective memory complaints, and 43 were further classified as demented or "cognitively impaired not demented". Subjective memory complaints presented a sensitivity of 100% and a negative predictive value of 100%. This suggests that subjective memory complaints are an indicator for cognitive impairment screening.

Subjective memory complaints in the elderly: a sign of cognitive impairment? Jacinto AF, Brucki SM, Porto CS, Arruda Martins Md, Nitrini R. - Clinics (Sao Paulo) - March 1, 2014; 69 (3); 194-7
SMC is predictive of progression and pathology

- SMC is associated with increased risk of progression
- SMC is associated with higher amyloid burden on PET
- ApoE4 carrier status influences the effect of SMC on burden and progression
- SMC associated with neuropathology of AD

Concept # Mild Cognitive Impairment could be the prodrome of AD Dementia

- Cognitive
  - Mild Cognitive Impairment MCI (memory)
    - 10% - 15% conversion to AD per year
    - 50% Conversion after 5 yrs >90% conversion by 10 years
  - Criteria
    - Memory difficulties corroborated by informant that interfere with adaptive functioning
    - Selective deficit as measured by neuropsychological tests; other functions normal or near normal
    - Intact IADLs
    - Not demented

Petersen 98 Neurology; Fisk 03 Neurology, Morris 01, Neurology
Diagnostic Criteria of MCI

Clinical and cognitive criteria
- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (historical or observed evidence of decline)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (formal or bedside testing)
- Preservation of independence in functional abilities
- Not demented

Examine etiology of MCI consistent with AD pathophysiology
- Rule out vascular, traumatic, medical causes of cognitive decline
- Provide evidence of longitudinal decline in cognition
- Report history consistent with AD genetic factors

Clinical Criteria for MCI of AD Type

- Subjective memory complaint reported by subject or informant
- Global cognition intact (MMSE >25)
- Memory impairment confirmed objectively
- ADL impairment is insufficient for diagnosis of dementia; IADL may be effected (GDS = 3 or CDR = 0.5)
- No medical / other etiology for memory deficit.

Albert et al, Alzheimer’s and Dementia 2011
MCI: Definitions and Categories

- **Amnestic Forms**
  - Single Domain
  - Multiple Domains

- **Non Amnestic Forms**
  - Single Domain
  - Multiple Domains

Albert 2011, Alzforum.org
Diagnosis of MCI

- Not established by consensus criteria
- Clinically apply Petersen criteria 2004 recast by Albert 2011
- Neuropsychological assessment
- Apo E genotyping
- Screening eval (imaging, standard labs) low yield

Prediction of Conversion from MCI to AD

- MCI conversions to AD can be predicted by
  - Worse memory scores (<<1.5 SD below age and education adjusted norms)
  - Smaller hippocampi on NeuroQuant (5th percentile or below)
  - Low CSF Aβ and high tau (ADNI reports that 33/37 subject converting to AD within one year had the CSF profile)
- ApoE4 positivity
- PIB uptake
Follow-Up of PiB-Positive ADNI MCI’s N = 65, 12 mo. follow-up

- PiB(+) = 47
- Converters to AD = 14
- PiB(-) = 18
- Converters to AD = 3

PiB-Positivity in Predicting Clinical Conversion in MCI

- Melbourne Cohort N = 28, 21 mo. follow-up
  - PiB(-) = 13
    - Converters to AD = 1
  - PiB(+) = 15
    - Converters to AD = 12
- Pittsburgh Cohort N = 23, 24 mo. follow-up
  - PiB(-) = 10
    - Converters to AD = 0
  - PiB(+) = 13
    - Converters to AD = 5
Diagnostic Criteria of Dementia

A. Dementia
   • Interferes with ability to function at work or at usual activities
   • A decline from a previous level of functioning
   • Not delirium or psychiatric disorder
   • Diagnosed by history, examination
   • Involves at least 2 cognitive domains:
     • Memory
     • Reasoning and judgment
     • Visuospatial
     • Language
     • Personality, behavior, comportment

McKhann et al, Alzheimer's and Dementia 2011

Diagnostic Criteria of AD

A. Probable AD [based on clinical criteria]
   • Dementia
   • Insidious onset
   • Worsening of cognition over time
   • Amnestic vs. non-amnestic presentation
   • Not due to another dementia diagnosis

B. Probable AD with evidence of AD pathophysiology
   • Ab (CSF or amyloid PET)
   • Neuronal injury (CSF tau, FDG-PET, structural MRI)

McKhann et al, Alzheimer’s and Dementia 2011
Concept #3 ATN Criteria will reframe our approach clinically

<table>
<thead>
<tr>
<th>A/T/N score</th>
<th>NIA-AA classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-/T-/N-</td>
<td>Dementia, unlikely due to AD</td>
</tr>
<tr>
<td>A+/T-/N-</td>
<td>Intermediate likelihood; probable AD dementia based on clinical criteria</td>
</tr>
<tr>
<td>A+/T+/N-</td>
<td>High likelihood; probable AD dementia; based on clinical criteria</td>
</tr>
<tr>
<td>A+/T-/N+</td>
<td>High likelihood; probable AD dementia; based on clinical criteria</td>
</tr>
<tr>
<td>A+/T+/N+</td>
<td>High likelihood AD pathophysiology</td>
</tr>
<tr>
<td>A-/T+/N-</td>
<td>Probable AD dementia; based on clinical criteria</td>
</tr>
<tr>
<td>A-/T-/N+</td>
<td>Intermediate likelihood; probable AD dementia based on clinical criteria</td>
</tr>
<tr>
<td>A-/T+/N+</td>
<td>Intermediate likelihood; probable AD dementia based on clinical criteria</td>
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</table>
Concept # 4 The Differential Diagnosis of Dementia is broad

- Alzheimer’s Disease (AD)
- Dementia with Lewy Bodies (DLB)
- AD & Vascular Dementia (mixed)
- Vascular Dementia
- Frontotemporal Dementia (FTD)
- Parkinson’s Disease
- Huntington’s Disease
- Other Degenerative Diseases (PSP, OPCA, ALS with dementia)
- Dementias Secondary to Alcohol
- Depression/Pseudodementia
- Normal Pressure Hydrocephalus (NPH)
- Structural Lesions
- Metabolic Disorders (Hypothyroidism)
- Infections (e.g. neurosyphilis, AIDS, CJD)
- Drug Intoxication
Dementia with Lewy Bodies

- Parkinsonism coexisting with cognitive decline
- Visual hallucinations
- Clinical fluctuations
- Neuroleptic sensitivity
- Newest criteria: REM behavioral disturbance
- Cognitive pattern may be subcortical or mixed cortical/subcortical with prominent visuospatial abnormalities
- Prone to other neuropsychiatric features
- May possibly progress faster
- Pathologically characterized by worse cholinergic loss, fewer plaques and tangles, neocortical Lewy bodies, lower Braak stages.
- Treatment could include cholinesterase inhibitors and L-dopa

Vascular Dementia

- May start abruptly immediately after a cerebrovascular accident
- Multi-focal distribution of cognitive decline
- Focal neurologic exam
- Gait disturbance, incontinence, and fluctuating changes are common (aka Binswanger’s [290.12]
- Vascular changes on imaging obligatory
- NINDS-AIREN criteria applicable
- Most vascular dementia mixed with AD
- Hachinski Score ≥ 7
- Treatment involves management of stroke risk factors and ChEIs
Frontotemporal Dementias

- Also known as Pick’s disease
- Now many linked to Chromosome 17 (“the tau-opathies”)
- Usually earlier age of onset compared to AD (average 40-65 years old)
- Early prominent language changes including anomia, aphasia, echolalia, and perseverative speech
- Social skills lost early
- Inappropriate behavior and judgment, disinhibition, and lack of insight
- Personality changes and withdrawal prominent

Progressive Aphasias

- Early prominent language changes including anomia, aphasia, echolalia, and perseverative speech
- Three subtypes now recognized (logopenic progressive aphasia-frontal variant, semantic dementia, progressive non fluent aphasia
- Progressive non fluent aphasia
  - Involves effortful speech with agrammatism and frequent apraxia of speech
  - Post-hoc comparisons with HC showed bilateral GM atrophy in the caudate, putamen and thalamus, in bvFTD; a left-confined GM reduction in the amygdala in SD; and bilateral GM atrophy in the caudate and thalamus, and left-sided GM reduction in the putamen and amygdala in PNFA. Left insula and adjacent inferior frontal gyrus
  - Pathologically associated with CBD or FTLD pathology with tau inclusions or PSP
- Semantic dementia
  - Characterized by loss of word and object meaning and understanding
  - Abnormalities in the left rostral temporal lobes
  - Ubiquitin positive TDP proteinopathy pathology have both been associated with it
- Logopenic Progressive Aphasia
  - Speech rate was slow, with long word-finding pauses.
  - Grammar and articulation were preserved, although phonological paraphasias could be present. Moderate anomia
  - Repetition and comprehension were impaired for sentences but preserved for single words, and naming was moderately affected.
  - Atrophy or decreased blood flow was consistently found in the posterior portion of the left superior and middle and posterior temporal gyri and inferior parietal lobule.
  - Recent studies suggest that Alzheimer disease may be the most common pathology underlying the LPA clinical syndrome.
Degenerative Dementias

- AD
- DLB
- FTD
- Mixed Dementias
- Prion Diseases
- Parkinson’s Disease
- Huntington’s Disease
- Progressive Supranuclear Palsy
- Guamanian ALS-PD-AD

Dementias Possibly Amenable to Treatment

- Hypothyroidism
- Neurosyphilis/ Infectious Etiologies
- Normal Pressure Hydrocephalus
- Vascular Dementia
- Vitamin B12 Deficiency
- Structural Lesions
- Metabolic Disorders
- Drug Intoxication
- Depression/Pseudodementia
- Wilson’s Disease
- Alcohol Related Dementias
Dementias Associated with Other Neurological Signs and Symptoms

- AIDS (neuropathy, myopathy)
- Normal Pressure Hydrocephalus (gait disturbance, incontinence)
- Tumors/Mass Lesions (stroke-like symptoms that are subacute and evolving)
- Subdural Hematoma (stroke-like symptoms that are acute or subacute and evolving)
Dementias Associated with Other Neurological Signs and Symptoms

- **Huntington’s Disease** (chorea, depression, psychosis, parkinsonism)
- **Creutzfeldt Jakob Disease** (myoclonus, rapid dementia, EEG changes)
- **Parkinson’s Disease** (rigidity, bradykinesia, gait disturbance, tremor)
- **B12 Deficiency** (Often associated with subacute combined degeneration: proprioceptive loss, paresthesias, hyper-reflexia)

The Current Approach for Evaluation of Patients With Dementia

**Routine**
- History
- Mental Status Exam
- Neurological Exam
- Chemistry Panel
- Complete Blood Count
- Vitamin B12 level
- Thyroid function studies
- CT/MRI

**Optional**
- Syphilis serology
- Sedimentation Rate
- Chest X-Ray
- Electrocardiogram
- Urinalysis
- Drug Levels
- HIV testing
- Lyme Serology
- EEG
- PET/SPECT
- ApoE genotyping
- CSF (Aβ42/tau or 14-3-3 for CJD)

**Initial consultation:** $350
**Screening labs:** $200
**CT/MRI:** $1500 to $2000

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CT/MRI=computed tomography/magnetic resonance imaging; CJD=Creutzfeldt-Jakob disease; EEG=electroencephalogram; SPECT=Single photon emission computed tomography.

Concept # 5: The Clinical Diagnosis of AD is not accurate

- Of 57 individuals clinically diagnosed with AD:
  - 23% (n=13) had no (n=7) or sparse (n=6) Aβ plaques at autopsy
  - Neuropathologically, 12 were diagnosed with a dementia disease other than AD, most frequently caused by aggregation of tau
- **Thus, diagnostic accuracy is 77% for a clinical diagnosis of AD, even among the experts**
- Florbetaben PET was consistent with histopathology in all 12 patients for whom cSUVRs were available


cSUVRs = composite standardized uptake value ratios

Concept # 6 AD Biomarkers Are Available, But Not Routinely Used in Clinical Practice in the US

**Biomarkers of Aβ amyloid deposition**
- Low CSF Aβ42
- PET amyloid imaging

**Biomarkers of neuronal injury**
- High CSF tau/phosphorylated tau
- Hippocampal volume or medial temporal atrophy
- Rate of brain atrophy
- FDG-PET imaging
- SPECT perfusion imaging
- Less well-validated: fMRI activation studies, resting BOLD functional connectivity, MRI

**Associated biochemical change**
- Inflammatory biomarkers (cytokines)
- Oxidative stress (isoprostanes)
- Other markers of synaptic damage and neurodegeneration

BOLD = blood oxygen level-dependent; FDG = fluorodeoxyglucose; fMRI = functional magnetic resonance imaging.
Differential Diagnosis of Neurodegenerative Diseases Using Structural MRI Data

Abstract

Different neurodegenerative diseases can cause memory disorders and other cognitive impairments. The early detection and the stratification of patients according to the underlying diseases are essential for an efficient management of the disease. This emphasizes the importance of differential diagnostics. Most studies compare patients and controls, or Alzheimer’s disease with one other type of dementia. Such a bilateral comparison does not resemble clinical practice, where a clinician is faced with a number of different possible types of dementia. Here we studied which features in structural magnetic resonance imaging (MRI) can be used to distinguish four types of dementia, Alzheimer’s disease, frontotemporal dementia, vascular dementia, and dementia with Lewy bodies, and control subjects. We extracted an extensive set of features quantifying volumetric and morphometric characteristics from T1 images, and vascular characteristics from FLAIR images. Classification was performed using a multiclass classifier based on Disease State Index methodology. The classifier provided continuous probability indices for each disease to support clinical decision making. A dataset of 504 individuals was used for evaluation. Different quantification methods provided complementary information, and consequently, the best results were obtained by utilizing several quantification methods. The results prove that automatic quantification methods and computerized decision support methods are feasible for clinical practice and provide comprehensive information that may help clinicians in the diagnosis making.

“The cross-validated classification accuracy was 70.6% and balanced accuracy was 69.1% for the five disease groups using only automatically determined MRI features. Vascular dementia patients could be detected with high sensitivity (96%) using features from FLAIR images. Controls (sensitivity 82%) and Alzheimer’s disease patients (sensitivity 74%) could be accurately classified using T1-based features, whereas the most difficult group was the dementia with Lewy bodies (sensitivity 32%). These results were notable better than the classification accuracies obtained with visual MRI ratings (accuracy 44.6%, balanced accuracy 51.6%).”

Age and ApoE Genotype Influence Amyloid PET Positivity

PET Amyloid and Tau Imaging highly sensitive in detecting target pathology but are expensive

**Amyloid PET:**
- The negative predictive value is very high. A negative scan excludes AD
- A positive PET can occur in NC subjects
- It is not considered diagnostic, only an adjunct
- It is very expensive and has very limited coverage worldwide

**Tau PET:**
- Likely correlates better with clinical progression than amyloid PET, but the clinical utility has yet to be determined

IWG-2 Criteria

NIA-AA Criteria

IAP=isolated amyloid pathology; SNAP=suspected non-Alzheimer pathophysiology.


IT’S TIME TO CONSIDER
RESTRUCTURING THE DIAGNOSTIC
APPROACH FROM
A DIAGNOSIS OF EXCLUSION TO…
A DIAGNOSIS OF INCLUSION

The imprimatur would be to increase specificity and sensitivity without a commensurate increase in cost.
Why do we need biomarkers for Alzheimer’s Disease?

- Clinical criteria for AD have poor diagnostic accuracy (70%-80% sensitivity and specificity)
- Except for plaques and tangles, late onset AD cases pathology:
  - 65% TDP-43 pathology
  - 29% Microscopic infarcts
  - 32% Arteriolosclerosis
  - 25% Lewy bodies
  - 11% Hippocampal sclerosis

Biomarkers are needed for:

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Clinical research</th>
<th>Theragnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select true AD cases for inclusion in clinical trials</td>
<td>Study disease pathogenesis directly in patients to understand the temporal evolution and contribution to symptoms of the different pathologies</td>
<td>Identify downstream effects on neurodegeneration by anti-Aβ (and tau) drugs</td>
</tr>
<tr>
<td>Make a correct diagnosis for initiation of treatment</td>
<td>Minimal change in the preclinical stage – very long trials needed</td>
<td>AD=Alzheimer's disease; TDP-43=transactive response DNA-binding protein 43.</td>
</tr>
</tbody>
</table>

FLUID BIOMARKERS FOR AD: CSF
The Core CSF biomarkers for Alzheimer’s disease

- **Phospho tau**: Phosphorylation state of tau / development of tangles
- **Total tau**: Neuronal/axonal degeneration
- **Aβ 42+40**: β-amyloid metabolism / deposition into plaques

**CSF=cerebrospinal fluid.**

**The Core CSF biomarkers for Alzheimer’s disease**

- **CSF T-tau**
  - 188 studies
  - 20,600 AD patients and controls
  - Effect size 2.48

- **CSF P-tau**
  - 116 studies
  - 14,300 AD patients and controls
  - Effect size 1.88

- **CSF Aβ42**
  - 168 studies
  - 19,600 AD patients and controls
  - Effect size 0.56

Core AD CSF biomarkers: highly clinically validated
Core AD CSF biomarkers: performance to identify prodromal AD

- The core AD CSF biomarkers show high diagnostic performance also in the MCI stage

- Large multicenter studies confirm high predictive value of the AD core biomarker profile for prodromal AD

Core AD CSF biomarkers: Performance compared with amyloid PET

- CSF pTau/Aβ42 and tTau/Aβ42 show very high concordance with amyloid PET

Study design: Electrocy assays for Aβ1-42, tTau and pTau BioFINDER (n=277) and ADNI (n=646)

Concordance with visual amyloid PET:
- CSF pTau/Aβ42
- OPA = 89.9% - 90.3%
- OPA = 89.2% - 89.9%
- Visual vs SUVR PET agreement
- OPA = 90%
- OPA = 90-91%

ADNI=Alzheimer’s Disease Neuroimaging Initiative; BioFINDER=Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably; OPA=overall percent agreement; PET=positron emission tomography; SUVR=standardized uptake value ratio.
A blood test now has CLIA certification

The first blood test for detection of amyloidosis in individuals with cognitive impairment is now available for clinical use

- PrecivityAD test from C2N Diagnostics (IPM5 plasma Aβ42/Aβ40 + APOE genotype + age)
- More AD blood tests will likely follow soon (e.g. pTau181, pTau217, NFl)

Patient journey

Adapted from the patient journey developed by Alzheimer’s Disease International (ADI), Alzheimer’s Europe and Roche [Oct 2019]
New Conceptual Framework for Assessment of Dementia Due to AD

Tier I Steps

1. Structured Questionnaires
   - Structured questionnaire (eg, AD8, IQCODE, AQ)
   - Examine ≥10 (high sensitivity [>95%]: LCRS addresses specificity)
   - High score = possible AD
   - Low score = indeterminate diagnosis

2. Aggregate Risk Analysis
   - Aggregate score >12 indicates higher probability of AD
   - Aggregate score ≤12
     - Consider more extensive testing (CSF testing, PET)

3. Bedside Cognitive Screening
   - MoCA, MMSE ≤24 indicates higher probability of impairment

4. Physical & Neurologic Exam
   - Neurological exam to screen for NPH, parkinsonism, focal symptoms, or history of CVAs

5. Lab Screening & Biomarkers
   - Non-focal exam, forgo CT/MRI screening
   - Focal exam or abnormal gait: obtain structural imaging
   - Lab testing, APOE genotyping, plasma tau or amyloid (PET) assay, B12, TSH

6. Apply IWG Criteria
   - Apply IWG Criteria for Subjects with Dementia
   - Patients who meet IWG criteria have a high probability of progression of AD symptoms

Tier II Steps

Exclude other common neurodegenerative conditions with validated questionnaires (LBCRS, FTD screening)

Evolving the patient journey post Covid-19

Advantages

- Reduce patient, caregiver, and clinician burden
- Reduce number of negative PET scans
- Reduce burden on specialist centers
- Reduce patient, caregiver, and clinician burden

Interventions to improve functioning, cognitive stimulation and rehabilitation
eg Verbal instructions, GPS, videos, smart phones, telephones

CSF, cerebrospinal fluid; CT, computerised tomography; FDG, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Conclusions

- The identification of MCI can be made with more confidence
- The prediction of conversion from MCI to AD can be made with greater accuracy
- AD is no longer a diagnosis of exclusion
- Technology is becoming available that greatly improves the diagnostic accuracy of AD