Defining Types of Dementia

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Disclosures

I have no relevant disclosures.
The charge is to address four issues:
1. Diagnosis of different types of ADRD
2. Detection
3. Review the trajectory of each type of dementia
4. Racial and ethnic differences
5. Neurobiology of ADRD
6. Implications for risk factor associations
The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Dementia is diagnosed when there are cognitive or neuropsychiatric symptoms that:
1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder

Cognitive impairment is detected through a combination of:
1. History the patient and a knowledgeable informant and
2. An objective cognitive assessment

The cognitive or behavioral impairment involves two or more of the following domains
1. Impaired ability to acquire and remember new information
2. Impaired reasoning and handling of complex tasks, poor judgment
3. Impaired visuospatial abilities
4. Impaired language functions
5. Changes in personality, behavior, or comportment

Diagnosis of MCI
1. Cognitive concern reflecting a change in cognition reported by patient or informant or clinician.
2. Objective evidence of Impairment in one or more cognitive domains.
3. Preservation of independence in functional abilities
Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Meets criteria for dementia and has the following characteristics:

1. **Insidious onset** over months to years;
2. Clear-cut history of **worsening of cognition** by report or observation; and
3. The initial and most prominent cognitive deficits in one of the following: a. **Amnesia**; b. Non-amnestic presentations: Language, Visuospatial ability, Executive dysfunction

MCI due to AD Criteria is similar to AD except that it meets criteria for MCI rather than dementia.
Vascular Contributions to Cognitive Impairment and Dementia

Probable VaD
1. Cognitive impairment and imaging evidence of CVD, and
   1. Temporal relationship between a vascular event and onset of cognitive deficits, or
   2. Relationship between the severity and pattern of cognitive impairment and the presence of diffuse, subcortical CVD
2. No history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium


Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

<table>
<thead>
<tr>
<th>DISEASE*</th>
<th>Alzheimer’s disease (AD)</th>
<th>Cerebrovascular disease***</th>
<th>Lewy body disease</th>
<th>Frontotemporal dementia</th>
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<tbody>
<tr>
<td>PATHOLOGIC CHARACTERISTICS</td>
<td>Brain atrophy especially of the mesial temporal lobe; histologic hallmarks of neuritic plaques containing β amyloid and neurofibrillary tangles containing phosphorylated tau</td>
<td>Small, often cystic chronic infarcts (lacunar infarcts); multiple microinfarcts, or large infarcts including intracerebral hemorrhage; age of infarcts may be variable in the same person, including chronic and acute; cerebral vessel pathology such as atherosclerosis and arteriolosclerosis; white matter gliosis; focal brain atrophy</td>
<td>Brain atrophy, often generalized; intraneuronal Lewy body inclusions containing α synuclein, including in the neocortex (as opposed to inclusions restricted to the substantia nigra, as seen in Parkinson disease)</td>
<td>Focal brain atrophy affecting frontal and/or anterior temporal lobes, histologic hallmarks of phosphorylated Transactive response DNA-binding Protein 43 (TDP-43), microtubule-associated protein tau (MAPT), or fused-in-sarcoma (FUS) protein</td>
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<td>ONSET AND COURSE</td>
<td>Slow onset and gradual progression over months or years</td>
<td>Temporal relation between acute vascular event (stroke) and onset of cognitive impairment, within minutes or days; stepwise course</td>
<td>Slow onset and gradual progression over months or years; fluctuations in levels of alertness and cognition</td>
<td>Slow onset and gradual progression over months or years</td>
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<td>HISTORY, EXAM, AND COGNITIVE FEATURES IN THE EARLY STAGE*</td>
<td>History: presenting symptoms is typically short-term memory loss</td>
<td>History: vascular risk factors (e.g., hypertension, diabetes) or prior stroke or other vascular events (myocardial infarction)</td>
<td>History: Rapid Eye Movement (REM) Behavior Disorder (RBD) for years preceding the cognitive impairment; visual and other hallucinations</td>
<td>History: marked changes in behaviors such as in personality (e.g., disinhibition, apathy)</td>
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<td>Exam and/or cognitive testing: episodic memory impairment accompanied by other subtle cognitive deficits, such as visuospatial problems and anoma</td>
<td>Exam: focal neurologic deficits consistent with stroke such as unilateral weakness and hyperreflexia, Babinski sign</td>
<td>Exam and/or cognitive testing: marked visuospatial problems with relative preservation of memory; parkinsonism, especially with bradykinesia and rigidity, but also stooped posture and slow and shuffling gait</td>
<td>Exam and/or cognitive testing documenting disinhibition and inappropriate behaviors; in language variant, impaired fluency in speech, semantic paraphasias; other significant executive or language problems, with relative preservation of memory</td>
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Cochrane Review Summary: Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations

Community Studies

MMSE* at cut point 24 (indicating normal); 15 studies
sensitivity 0.85
specificity 0.90
dementia prevalence 7.4%

MMSE at cut point 25; 10 studies
sensitivity 0.87
specificity 0.82
dementia prevalence 8.4%

When adjusted for education; 7 studies (2 high risk of bias)
specificity was 0.70
sensitivity 0.97
dementia prevalence 13.8%

MMSE is proprietary
11 screening tests were identified among 149 studies with 49,000+ participants. MMSE (n = 102) and included 10,000+ patients with dementia. Sensitivity and specificity were 0.81 and 0.89. Mini-Cog, 0.91 sensitivity and 0.86 specificity for dementia. Addenbrooke’s Cognitive Examination–Revised (ACE-R) 0.92 sensitivity and 0.89 specificity) for dementia. Montreal Cognitive Assessment (MoCA) 0.89 sensitivity and 0.75 specificity for MCI.
Prevalence of Cognitive Impairment without Dementia in the United States

Initial ADAMS sample selected from the parent Health and Retirement Study (n = 1770)

Assessed at initial visit (n = 856)

Targeted for follow-up (n = 333)
- Normal: 58
- Cognitive impairment without dementia: 241
- Dementia: 34

Not assessed at initial visit (n = 914):
- Deceased: 227
- Other reasons: 687

Completed follow-up (n = 252)
- Normal: 48
- Cognitive impairment without dementia: 180
- Dementia: 24

Not assessed at follow-up visit (n = 81):
- Deceased: 33
- Normal: 2
- Cognitive impairment without dementia: 26
- Dementia: 5
- Other reasons: 48
- Normal: 8
- Cognitive impairment without dementia: 35
- Dementia: 5

Alzheimer Disease in the US Population

Dementia prevalence age 71+ = 13.9%, 3.4 million individuals in the USA
In 2002 AD was 9.7% and 2.4 million individuals
Prodromal AD (CIND) 2 million
Other CIND 3.4 million
Dementia prevalence increased from 5.0% 71–79 years to 37.4% 90+

In 2000 4.5 million with AD age 65+
(half with mild dementia)


Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study
Conclusion:
“The diagnosis of AD in population studies is a complex process. When a diagnosis of AD excludes persons meeting criteria for vascular dementia, when not all persons with dementia are assigned an etiology, and when a diagnosis of dementia requires an informant report of functional limitations, the prevalence is substantially lower and the diagnosed cases most likely have a relatively higher level of impairment.”
Clinic AD patients: Younger persons decline faster

MMSE > 10

East Boston

Community AD participants:
Older persons decline faster

Cognitive decline in incident Alzheimer disease in a community population

**Community AD participants: Older persons decline faster**
Comparable effects in African American and white persons.

![Graph showing cognitive decline over study years](image)

Baseline level of each ability lower in Blacks
Decline in episodic and working memory not related to race
Decline in semantic memory, perceptual speed, and visuospatial ability was slower in Blacks
in semantic memory and perceptual speed the effect was stronger in older participants.

Adjusted for retest effects

A Cognitive Turning Point in Development of Clinical Alzheimer’s Disease Dementia and Mild Cognitive Impairment: A Biracial Population Study

Slope of cognitive decline after the change point is steeper among EAs than AAs.
The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort

Religious Orders Study and Rush Memory and Aging Project (ROSMAP)

No change in cognitive function until 7.5 years before dementia diagnosis.

Global cognitive measure declined 0.09-unit per year until 2.0 years before the diagnosis when it increased more than 4-fold to a mean loss of 0.37-unit per year.
Change in Cognitive Abilities in Older Latinos

Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies

Demographics
And Pathologic AD
And 7 other pathologies
And an indicator for unaccounted AD dementia cases

67.5% AD dementia cases attributable all eight neuropathologic indices

Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

Postmortem neurodegenerative markers and trajectories of decline in cognitive systems

Postmortem neurodegenerative markers and trajectories of decline in cognitive systems

Effect of common neuropathologies on progression of late life cognitive impairment

Causes and Patterns of Dementia: An Update in the Era of Redefining Alzheimer’s Disease

Conclusions

• Accepted criteria for the clinical diagnoses of common dementia syndromes are made by and for clinical specialists
  – Need to be adapted for use in community-based studies
• Alzheimer’s dementia is on a continuum
  – small differences in cut-points can result in very large differences in estimated prevalence
• Modest to large racial differences in level of performance but Blacks appear to decline more slowly
• Many brain pathologies in different combinations contribute to Alzheimer’s dementia
  – yet much of Alzheimer’s dementia remains unexplained
• Many brain pathologies contribute to loss of multiple cognitive domains making it impossible at this juncture to reliability distinguish different causes of dementia on a case by case basis
  – Blood biomarkers soon?
• In an era that now distinguishes AD from its clinical consequences, we need to rethink what it means to be a risk factor for AD
Preliminary Recommendations

- Need more data on regional, sex, racial, and ethnic differences in prevalence of cognitive impairment and dementia across the USA
  - I would not expend the effort at this time for differential diagnosis of ADRD
  - For political reasons I would diagnose Alzheimer’s dementia
- Need to develop simple and inexpensive approaches to diagnoses
  - This will be particularly challenging across race and ethnicity
- Need to monitor trends over time
  - Age-specific incidence and prevalence of dementia may be declining (not discussed)
  - Data not convincing for the relatively short time horizon addressed
  - given other long term health trends it is likely to be true – but not equally true across the USA or in all subgroups (e.g., increasing mortality rates among lower SES whites)
- Need to consider competing risk
- Generalizability and internal validity compete for resources and studies that maximize the former may not be the best place to accomplish risk factor associations beyond select social determinants