Alzheimer’s Disease

Improving Clinical Diagnosis

“Jewels”
- Amyloid Plaques
- Neurofibrillary Tangles
- Lewy Bodies

Tools
- Neuroimaging
- Fluid Biomarkers
- Clinical Assessments

Rules
- Diagnostic Criteria
- Differential Diagnosis
## Early Concepts of Dementia

<table>
<thead>
<tr>
<th>Era</th>
<th>Perspective</th>
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<tbody>
<tr>
<td>Plato, 350 BC</td>
<td>Cognitive decline is an inevitable consequence of aging due to the weakness of the brain</td>
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<tr>
<td>Cicero, 50 BC</td>
<td>A consequence of weak will. An active mental life could prevent or postpone cognitive decline</td>
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<tr>
<td>Galen, 200 AD</td>
<td>Psychic and cognitive abilities are localized to the brain</td>
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<tr>
<td>Willis, 1650</td>
<td>Developmental disability separate from acquired dementia; specific etiologies for dementia, including head injury, aging, and stroke</td>
</tr>
<tr>
<td>19th Century</td>
<td>Psychiatric and neurologic conditions were distinguishable; cortical atrophy recognized; vascular calcification prominent; Kraepelin “dementia praecox”; “general paresis” (neurosyphilis) in &gt; 10%; arteriosclerotic brain atrophy is predominant cause of senile dementia</td>
</tr>
</tbody>
</table>

### Causes of dementia
- Sequelae of delivery
- Head injuries
- Menstrual disorders
- Severe weather conditions
- Progression of age (20%)
- Mania
- Syphilis and mercury abuse
- Dietary excess
- Wine abuse
- Masturbation
- Unhappy love
- Political upheavals
- Unfulfilled ambitions
- Poverty
- Domestic problems

Assal 2019
Alzheimer 1906

New histological stains – cortex

51 yo woman with confusion and psychosis
- Presenile dementia
- Prominent plaques and tangles
- vs Senile dementia: arteriosclerosis
- Distinction persisted for 50 years

1960s: Blessed, Tomlinson, Roth
- In older adults (mean age 78), cognition and function during life associated with cortical neuritic plaque density at post-mortem
Clinical Diagnostic Criteria
NINCDS-ADRDA, 1984

Probable AD

- Dementia, objective testing
- Two or more cognitive domains
- Progressive worsening
- No disturbance of consciousness
- Onset between age 40 and 90
- Absence of other CNS or systemic etiology
- Supportive factors
  - Progressive decline in characteristic domains
  - Impaired ADLs and “patterns of behavior”
  - Family history
  - CT: atrophy
  - May be depression, psychosis, emotional outbursts
  - No focal neuro signs, seizures, or gait change early

Possible AD

- Variations in the onset, presentation, or clinical course
- Another systemic or CNS disorder that may be driving the dementia
- Single cognitive deficit

Definite AD

- Clinical criteria for Probable AD
- Histopathologic evidence

McKhann 1984
AD Clinical Diagnosis

PubMed Citations, By Decade

<table>
<thead>
<tr>
<th>Decade</th>
<th>Citations</th>
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<tbody>
<tr>
<td>1950-60</td>
<td>24</td>
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<tr>
<td>1961-70</td>
<td>53</td>
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<td>1971-80</td>
<td>193</td>
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<td>1981-90</td>
<td>2838</td>
</tr>
<tr>
<td>1991-2000</td>
<td>9219</td>
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<td>2001-2010</td>
<td>17404</td>
</tr>
<tr>
<td>2011-</td>
<td>23912</td>
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</table>

Pub Med; Sept 24, 2019
Key Advances
Improving Clinical Diagnosis

1. Longitudinal studies of symptoms and biology
   Mild Cognitive Impairment

2. Neuropathology and relationship with clinical symptoms

3. *In vivo* biomarkers for AD proteins

4. Refined clinical diagnostic criteria

5. What isn’t Alzheimer’s disease

6. Role of distinct cognitive and non-cognitive symptoms
Alzheimer’s Pathology Isn’t Alone

Comorbid Pathology in 1153 Patients With AD Neuropathology

- **Mixed cases are very common in the brain**
  - 43% of cases with AD pathology had at least 3 different pathologies

- **Clinicians aren’t always seeing AD pathology**
  - More than one-third of those with “pure AD” at autopsy were thought to have a non-AD diagnosis during life

- **Clinicians often see “AD” when other pathologies are present**
  - ~80% of those with a clinical diagnosis of AD have mixed pathologies (70%) or no AD pathology (~10%)
Biomarkers for Alzheimer’s Disease

- AD biomarker changes occur at least 15 years before memory is compromised.
PET Imaging - Amyloid and Tau

Amyloid Imaging – Clinical

- Persistent or progressive unexplained MCI
- Possible AD: atypical course or mixed etiologies
- Early-onset progressive dementia

Assuming:
- Dementia expert involved
- Cognitive deficit present
- Expected to increase dx certainty or change management

An Outcome Study:
N=11,409 with MCI or dementia
60% with change in med rx or safety/planning
25% with dx change from AD to non-AD

Johnson 2013
Rabinovici 2019
Cholinergic Receptor Binding in AD and MCI

Lower binding in MCI and AD
- Medial thalamus
- Medial temporal cortex (hipp, amyg, parahipp)
- Anterior cingulate
- Insula

- In healthy older adults, cholinergic binding is strongly inversely correlated with age

Richter 2018, Brain

Clinical and cortical activation (fMRI) response to AChEI treatment in MCI depends on local acetylcholinesterase enzyme activity (MP4A-PET imaging)

Sultzer 2017
Fluid Biomarkers

**Cerebrospinal Fluid**
- Low β-amyloid 42 may precede amyloid seen on PET imaging
- Variable lab assays
- Elevated P-tau and tau levels
- Synaptic markers: neurogranin

**Blood Plasma**
- Small proportion of brain proteins in plasma
- High concentration of usual blood proteins
- β-amyloid 42, tau
- Neurofilament light protein
## More Comprehensive Diagnostic Criteria

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Normal Cognition</strong></td>
<td>-</td>
<td>x</td>
</tr>
<tr>
<td>Preclinical AD</td>
<td>Stage 1: Amyloid +</td>
<td>Asymptomatic at risk for AD (CSF amyloid + tau, PET amyloid)</td>
</tr>
<tr>
<td>Stage 2: Amyloid + and injury (Tau, FDG-PET, hippoc or med parietal atrophy)</td>
<td></td>
<td>Presymptomatic AD, if genetic carrier</td>
</tr>
<tr>
<td><strong>Subtle Cognitive Decline</strong></td>
<td>+</td>
<td>Preclinical AD, Stage 3</td>
</tr>
<tr>
<td><strong>Mild Cognitive Deficit, Preserved ADLs</strong></td>
<td>-</td>
<td>MCI (one or more domains: memory, executive, language, visuospatial, attention)</td>
</tr>
<tr>
<td>Preclinical AD</td>
<td>Stage 1: Amyloid +</td>
<td>Prodromal Alzheimer’s disease</td>
</tr>
<tr>
<td>Stage 2: Amyloid + and injury (Tau, FDG-PET, hippoc or med parietal atrophy)</td>
<td></td>
<td>Memory +/- other domain</td>
</tr>
<tr>
<td>High likelihood: Amyloid + and injury +</td>
<td></td>
<td>Otherwise: Atypical AD</td>
</tr>
<tr>
<td>Intermediate likelihood: Amyloid or injury +; other n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninformative: either +; other -</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Significant Cognitive Deficit, With Functional Impairment</strong></td>
<td>-</td>
<td>Probable AD dementia</td>
</tr>
<tr>
<td>At least two domains: memory, reasoning, visuospatial, language, personality/behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible AD dementia – atypical course or mixed etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>Probable or possible AD dementia</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>- With AD pathology</td>
<td></td>
<td>Memory +/- other domain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otherwise: Atypical AD</td>
</tr>
</tbody>
</table>
“Alzheimer’s Disease”

“When I use a word,” Humpty Dumpty said, in rather a scornful tone, “it means just what I choose it to mean – neither more nor less.”

Humpty Dumpty, *Through the Looking Glass* (Lewis Carroll 1872)
### ATN Research Criteria

<table>
<thead>
<tr>
<th>Biomarker Profile</th>
<th>Cognitive stage</th>
<th>Cognitive stage</th>
<th>Cognitive stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitively Unimpaired</td>
<td>Mild Cognitive Impairment</td>
<td>Dementia</td>
</tr>
<tr>
<td>( A^+ T(N) )</td>
<td>normal AD biomarkers, cognitively unimpaired</td>
<td>normal AD biomarkers with MCI</td>
<td>normal AD biomarkers with dementia</td>
</tr>
<tr>
<td>( A^+ T(N) )</td>
<td>Preclinical Alzheimer’s pathologic change</td>
<td>Alzheimer’s pathologic change with MCI</td>
<td>Alzheimer’s pathologic change with dementia</td>
</tr>
<tr>
<td>( A^+ T(N) )</td>
<td>Preclinical Alzheimer’s disease</td>
<td>Alzheimer’s disease with MCI</td>
<td>Alzheimer’s disease with dementia</td>
</tr>
<tr>
<td>( A^+ T(N) )</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change, cognitively unimpaired</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change with MCI</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change with dementia</td>
</tr>
<tr>
<td>( A^+ T(N) )</td>
<td>non-Alzheimer’s pathologic change, cognitively unimpaired</td>
<td>non-Alzheimer’s pathologic change with MCI</td>
<td>non-Alzheimer’s pathologic change with dementia</td>
</tr>
</tbody>
</table>

A: CSF or PET imaging amyloid  
T: CSF p-tau, tau imaging  
N: MRI volume, FDG-PET, CSF total tau

Jack 2018

Alzheimer’s continuum

Suspected non-Alzheimer disease pathophysiology (SNAP)
What Isn’t Alzheimer’s Disease

• More refined clinical phenomenology and clinical diagnostic criteria

- Fronto-Temporal Dementia:
  - Behavioral Variant
  - PPA

- Dementia With Lewy Bodies

- Vascular Cognitive Impairment

- Normal Aging

International Consensus Criteria 2011

NINDS-AIREN 2014

DLB Consortium 2017
Profiles of Cognitive and Noncognitive Symptoms

- Amnestic memory deficit
  - vs. retrieval deficit with cue benefits

- Neuropsychiatric symptoms over the course of clinical AD
  - Fundamental expression of the degenerative process

- Depression is a risk factor for AD

- Apathy and anxiety can be early symptoms, before memory impairment
  - Shared biology?

Sultzer 2014
Anxiety Drives Amyloid Toxicity

- Prospective cohort, 333 healthy older adults
- Amyloid imaging
- Measures: Anxiety/depression, Neuropsych
- Anxiety moderated the effect of amyloid burden
  Larger effect in those with clinically meaningful symptoms
- No effect of depression
  Low scores
- Mechanism?
- Intervention opportunity?

Figure 1. Slopes of Change in Verbal Memory Composite Score by Amyloid-β (Aβ) and Anxiety Levels
Mild Behavioral Impairment

- Changes in behavior or personality, age ≥ 50
  - Decreased motivation
  - Affective dysregulation
  - Impulse dyscontrol
  - Social inappropriateness
  - Abnormal perception or thought
- Social or occupational consequences
- Not attributable to a psychiatric disorder
- No dementia; MCI can be concurrent

NPS-PIA
Alzheimer’s Association, 2015

Mild Behavioral Impairment Checklist (MBI-C)

Circle "Yes" only if the behavior has been present for at least 6 months (continuously, or on and off) and is a change from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: 1 = Mild (noticeable, but not a significant change); 2 = Moderate (significant, but not a dramatic change); 3 = Severe (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

<table>
<thead>
<tr>
<th>This domain describes motivation and drive</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person lost interest in friends, family, or home activities?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person lost motivation to act on her/his obligations or interests?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

This domain describes mood or anxiety symptoms

<table>
<thead>
<tr>
<th>This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person become agitated, aggressive, irritable, or temperamental?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has she/he become unreasonably or uncharacteristically argumentative?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become more impulsive, seeming to act without considering things?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

www.MBltest.org
So How Do These Advances Improve Diagnosis and Benefit Care?
Challenges To Detection and Accurate Diagnosis

- “Progressive cognitive difficulties are normal with age”
- Limited confidence among some primary care providers
- Few specialty memory clinics
- Assessment time and cost
- Therapeutic nihilism
- Denial, stigma, Public Health reports
Clinical Diagnosis - Basics 2019

- Screening in high-risk people and those with cognitive complaints or early symptoms
- Clinical history: specific symptoms, onset, course
- Medication review, substance misuse
- Neuro exam
  - Focal deficit
  - Tremor, rigidity, gait
- Psychiatric symptoms
  - Apathy
  - Depression
  - Anxiety
- Cognitive assessment
  - MMSE+, MOCA+, others
  - Memory/Learning and Executive skills
  - Neuropsychological testing in some cases
- Function and social assessment

- Labs
  - Chem, CBC, LFTs
  - B12, TSH, (Vitamin D)
  - If indicated: syphilis serology, HIV
- Neuroimaging
  - MRI
  - CT, if MRI challenges

➤ Added value – MRI findings
  - Hippocampal volume
  - Pattern of regional atrophy
  - Small-vessel cerebrovascular disease
  - Progression of atrophy over time
**Diagnostic Advances**

**Specific Circumstances**

<table>
<thead>
<tr>
<th>FDG-PET</th>
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<tbody>
<tr>
<td>DAT to exclude DLB</td>
</tr>
<tr>
<td>Amyloid PET</td>
</tr>
<tr>
<td>- If objective impairment, AD is a possible dx, but dx is uncertain after comprehensive assessment</td>
</tr>
<tr>
<td>- Knowledge of amyloid status would change dx or management</td>
</tr>
<tr>
<td>- Persistent unexplained MCI, or early onset of progressive dementia</td>
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<table>
<thead>
<tr>
<th>CSF biomarkers</th>
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</thead>
<tbody>
<tr>
<td>- Early onset or atypical dementia</td>
</tr>
<tr>
<td>- Persistent, progressive, unexplained MCI</td>
</tr>
<tr>
<td>- Consider reliability, ratios, and cutoffs</td>
</tr>
<tr>
<td>- Non-AD: prion, infectious, other rapidly progressive</td>
</tr>
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<tr>
<th>Plasma biomarkers</th>
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<tr>
<td>- Limited clinical value currently</td>
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<tr>
<th>Genetic testing</th>
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<tbody>
<tr>
<td>- Presenilin 1, 2, APP - Familial AD</td>
</tr>
<tr>
<td>- GRN, C9orf72 - Familial FTD</td>
</tr>
</tbody>
</table>
Summary and The Future
Improved Clinical Diagnosis

**Longitudinal symptoms and biology; MCI**

**Neuropathology heterogeneity**

**Biomarkers**

**Refined diagnostic criteria**

**What isn’t Alzheimer’s disease**

**Neuropsychiatric symptoms**

**Next Steps** -

- Embrace heterogeneity while refining distinct clinical syndromes
- Practical assessment in the community
- Biomarker advances
  - Plasma – e.g., NF-L or synaptic proteins
  - Clinical outcomes
- Early or preclinical diagnosis
  - Individualized risk score
- Optimal candidates for specific interventions