Outline

- New concepts in Alzheimer disease
- Biomarkers and *in vivo* diagnosis
- Future trends in Alzheimer disease
- When it isn’t Alzheimer disease
  - Other common dementias
  - Signs of non-Alzheimer dementia
Old Concepts

Traditional Diagnosis of AD

- Cognitive disorder
- Insidious onset, gradual progression
- Interferes with activities/relationships
- No other apparent cause
Old Concepts

Consequences of tradition

- AD considered a diagnosis of exclusion
  - Patient, caregiver, provider uncertainty
  - Confusion with other diagnoses
- Poor diagnostic specificity (max 85%)
- Limited progress
  - Symptom-driven trials
  - Failure of disease-modifying therapies
Current Concepts

Goals of newer criteria

- Utilize scientific advances, particularly biomarkers
- Diagnose Alzheimer disease/dementia earlier and more accurately
- Enable positive identification of Alzheimer disease/dementia
- Clarify the relationship between Alzheimer disease and Alzheimer dementia
Current Concepts

Alzheimer disease (biological)
- Plaques (amyloid) and tangles (phos-tau)
- Cell death and cerebral atrophy
- Determinative mutation

Alzheimer dementia (clinical)
- Overt manifestation of the disease
- Final stage of Alzheimer disease
Current Concepts

Risk factors > Protective factors

Pathological Alzheimer disease

Pathophysiological Alzheimer disease

Symptomatic Alzheimer disease

Alzheimer dementia
Current Concepts

- It is possible to have Alzheimer disease (biologically) without the typical signs of Alzheimer dementia.
- There may be syndromes that resemble Alzheimer dementia (clinically), but are not caused by Alzheimer disease.
Current Concepts

Some stage(s) of Alzheimer disease occur prior to dementia

**Mild cognitive impairment**
- Objective cognitive (memory) decline
- Generally preserved ADLs
- High risk of progression to dementia
  - Not all progress
  - Not always Alzheimer disease
Focus on Biomarkers

Why the emphasis on biomarkers?

- Detectable biological changes
  - Identify disease before clinical symptoms
  - Better chance of stopping disease
- Related to underlying pathophysiology
  - Increase specificity
  - Potentially increase sensitivity
  - Direct association with disease progression
Biomarkers: FDG PET

Frontotemporal Dementia

Alzheimer Disease

Sensitivity 90-95%
Specificity 60-75%

Coleman, Neuroimaging Clinic NA 2005
Patwardhan et al, Radiology 2004
Biomarker: Hippocampal Atrophy

NORMAL
- Mild generalized atrophy
- No mesial temporal atrophy

ALZHEIMER
- Moderate generalized atrophy
- Mesial temporal atrophy
- Sensitivity/specificity >85%
- Detectable in early stages
Biomarkers: Cerebrospinal Fluid

↓ beta-amyloid
↑ phos-tau

Sensitivity 92%
Specificity 89%

Sunderland et al, JAMA 2003
Biomarkers: Amyloid PET

- Correlates with microscopic pathology and CSF
- Detectable 10-15 years before cognitive changes
- Not specific for AD—amyloid deposition occurs in Lewy dementia, vascular dementia, NPH, probably others
## New Conceptualization

<table>
<thead>
<tr>
<th></th>
<th>Impaired memory</th>
<th>Biomarkers</th>
<th>Other requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presymptomatic</td>
<td>No</td>
<td>+</td>
<td>• AD mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No symptoms</td>
</tr>
<tr>
<td>Asymptomatic at risk</td>
<td>No</td>
<td>+</td>
<td>No symptoms</td>
</tr>
<tr>
<td>Mild Cognitive Impairment</td>
<td>±</td>
<td>±</td>
<td>Nonspecific biomarkers or symptoms</td>
</tr>
</tbody>
</table>

Dubois et al, *Lancet Neurology* 2010
New Conceptualization

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<tr>
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<th>Impaired memory</th>
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<tbody>
<tr>
<td>Typical Alzheimer disease</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Prodromal Alzheimer disease</td>
<td>+</td>
<td>+</td>
<td>• Symptoms present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dementia</td>
</tr>
<tr>
<td>Typical Alzheimer dementia</td>
<td>+</td>
<td>+</td>
<td>Dementia</td>
</tr>
</tbody>
</table>
Progress? Perhaps

25,000

Number of new Alzheimer disease publications since 2003
Current AD Treatments

Some effect on symptoms, but…

- Overall effect is small
- Do not stop progression of symptoms
- No effect on underlying disease

Disease modification needed

- Stop or reverse pathophysiology
- Pathology-related symptoms will follow
Amyloid Cascade

X=failed trial

XXX Aβ Peptide

Neuritic Plaque

APP

p-Tau

NFT

Cell Injury XX

Cell-to-cell Propagation

XX Inflammation

X Synaptic Dysfunction

Oxidation

X Transmitter Deficits

Cell Death/Atrophy

Cummins, 2011
Why Have Trials Failed?

Wrong drugs?

Wrong trial subjects?
  - Already symptomatic—too late
  - Some subjects probably do not have AD
    - No use of biomarkers
    - Minimal autopsy follow-up

Wrong hypothesis?
  - Amyloid pathology ≠ symptoms
  - Phospho-tau possibly a better target
The Future of AD Trials

- Trials at earlier disease stages
  - Mutation carriers
  - Amyloid PET
  - Stop disease before brain damage occurs
- Increased use of biomarkers
  - Improve subject selection
  - Disease-based (rather than symptom-based) outcomes
Non-Alzheimer Dementias
Why Am I Bothering You?

- Non-AD dementias can mimic AD
- Treatments may differ
- Types of symptoms differ
- Rates of symptom development differ
- To make you smart and powerful
Common Non-AD Dementias

Late onset (majority)
- Alzheimer disease (54%)
- Vascular (16%)
- Lewy body (16%)
- Other (14%)

86% of dementia Patients ≥ 60 yo

Kester et al, Neurol in Practice. 2009; 9
Schneider et al, Brain. 2012 Oct
Common Non-AD Dementias

Young onset
- Alzheimer disease (34%)
- Vascular (18%)
- FTLD (12%)
- Lewy body (7%)
- Alcohol (10%)
- Other (19%)

81% of dementia patients < 60 yo

Harvey et al, J Neurol Neurosurg Psychiatr. 2003; 74
Diagnostic Flow

1. Alzheimer or not? → NOT. Step 2
2. Lewy or vascular? → NEITHER. Step 3
3. FTLD? → NOT. Reconsider 1 and 2
4. Other
Diagnostic Flow

1. Alzheimer or not?  ➔ NOT. Step 2
2. Lewy or vascular?  ➔ NEITHER. Step 3
3. FTLD?  ➔ NOT. Reconsider 1 and 2
4. Other
# Alzheimer vs Non-Alzheimer

<table>
<thead>
<tr>
<th>COGNITION</th>
<th>Alzheimer</th>
<th>Non-Alzheimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>Often affected</td>
<td>FTLD, Lewy</td>
</tr>
<tr>
<td>Memory</td>
<td>Failure to store information</td>
<td>Failure to spontaneously retrieve</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td>Frontal dysfunction</td>
<td>Usually minimal early</td>
<td>Frequently involved</td>
</tr>
<tr>
<td>Mental speed</td>
<td>Usually normal early</td>
<td>Often slowed</td>
</tr>
<tr>
<td>Personality</td>
<td>Typically unchanged (irritability, depression)</td>
<td>Often apathetic, abulic</td>
</tr>
</tbody>
</table>
## Alzheimer vs Non-Alzheimer

<table>
<thead>
<tr>
<th>MOTOR</th>
<th>Alzheimer</th>
<th>Non-Alzheimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articulation</td>
<td>Normal</td>
<td>Often affected</td>
</tr>
<tr>
<td>Posture</td>
<td>Normal</td>
<td>Often stooped or extended</td>
</tr>
<tr>
<td>Coordination</td>
<td>Typically normal</td>
<td>Impaired</td>
</tr>
<tr>
<td>Adventitious movements</td>
<td>Usually none</td>
<td>Chorea, tremor, tics, dystonia, myoclonus</td>
</tr>
<tr>
<td>Motor speed</td>
<td>Normal</td>
<td>Slow</td>
</tr>
</tbody>
</table>
Alzheimer vs Non-Alzheimer

Mesial Temporal Atrophy

Hippocampus
Entorhinal
Perirhinal

Parieto-temporal Hypometabolism

MRI

FDG-PET
Alzheimer vs Non-Alzheimer

Other tests

- **CSF studies**
  - Elevated phospho-tau
  - Decreased beta-amyloid
- **Amyloid imaging**
  - Negative scan incompatible with AD
  - Positive scan *compatible but not definitive*
Diagnostic Flow

1. Alzheimer or not?
   → NOT. Step 2
2. Lewy or vascular?
   → NEITHER. Step 3
3. FTLD?
   → NOT. Reconsider 1 and 2
4. Other
Lewy Body vs Vascular Dementia

Characteristic of both

- “Parkinsonism”
  - Bradykinesia
  - Rigidity
  - Antipsychotic sensitivity (worse in DLB)
- Early gait abnormalities and falling
- Depression and/or apathy
Lewy Body vs Vascular Dementia

More characteristic of Lewy body
- Visual hallucinations
- Episodes of decreased consciousness
- REM behavior disorder—synucleinopathy
- Marked cognitive fluctuations

More characteristic of vascular
- Isolated deficits (large-vessel cortical)
- Focal motor signs
- Urinary symptoms
Lewy Body vs Vascular Dementia

Diagnostic testing

- MRI very sensitive for cerebrovascular disease
- Occipital and posterior parietal hypometabolism on FDG PET in Lewy (sensitivity 90%, specificity 80%)
- Dopamine transporter SPECT
  - Reflects death of dopaminergic cells
  - Abnormal in Lewy body (specificity 93.6%)
  - Also abnormal in related disorders (PD, MSA, PSP, CBD)

Papathanasiou et al, Parkinsonism Related Disord. 2012 Mar; 18(3)
Diagnostic Flow

1. Alzheimer or not? NOT. Step 2
2. Lewy or vascular? NEITHER. Step 3
3. FTLD? NOT. Reconsider 1 and 2
4. Other
FTLD Subtypes

Behavioral

- Personality change
- Decreased social awareness
- Ritualistic and rigid
- Emotional blunting
- Lack of insight
Progressive nonfluent aphasia

- Starts with anomia (word-finding, naming)
- Circumlocution
- Phonemic (sound) paraphasias
- Agrammatism
- Usually retained insight
- L>R frontal >temporal atrophy

Snowden et al, Brain. 2006; 129
FTLD Subtypes

Semantic dementia

- Impaired comprehension
- Normal fluency
- Semantic (concept) paraphasias
- Normal repetition
- Usually little insight
- L>R temporal atrophy

Boeve et al, Neurology. 2001; Oct 23
Summary

- Alzheimer disease is the most common cause of dementia
- Alzheimer, vascular, Lewy, and FTLD account for >80% of dementias
- There are distinguishing in vivo characteristics of these diseases
- Most cases of dementia can be diagnosed with confidence (i.e., neurologists aren’t that smart)
Cleveland Clinic

Every life deserves world class care.