Dementia Differential Diagnosis and Management in the Age of Biomarkers

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Objectives:
1. Recognize the biochemical, neuro-anatomical, and genetics signatures associated with AD, DLB, FTD, and VCI.
2. Make a differential diagnosis of dementia based on history, neurobehavioral and neurological exam, laboratory and structural imaging.
3. Select appropriate patients for biomarker and newer FDA-approved diagnostic tests for dementia: Fluorodeoxyglucose (FDG) PET, Florbetapir (Amyvid) PET, CSF abeta and phospho-tau levels.
4. Review the current status of treatment and management of dementias.

Natural History of Alzheimer Disease

Malignant phase
- Neuritic plaques, tangles, neuron loss
- Death
- Loss of independence
- "AD"
- Diagnosed
- Clinical symptoms appear
- "AD" Diagnosed
- Loss of independence
- Death

Diffuse plaques
- Genetically/environmental risk factors
- -APOE-4
+ Education
- Promoting factors
- Age

Preclinical phase
- MCI = mild cognitive impairment

Screening Tests: Mini-Mental State Exam Modified MMSE (3MS Test) www.usc.edu/memory

Mild Cognitive Impairment (MCI)
Clinical Dementia Rating CDR = 0.5

- Impairment in memory or other cognitive function greater than expected for normal aging.
- No significant impairment of activities of daily living
- Variable likelihood of progression to dementia
  - 8-11% per year for amnestic MCI
  - Lower rates for non-amnestic MCI
  - Compared to 1-2% in the general population

Screening Test: Montreal Cognitive Assessment (www.mocatest.org)

Causes of Senile Dementia
Cardiovascular Health Study (n=707)

Low 5.5% (including PD, CTE, endocrine, SNP, CNS mass, CNS infection)
AD 64%
Vascular dementia 12.3%
AD + VaD 17.3%

Work up: History, Neuro and Vascular Exam, Structural Neuroromaging (MRI or CT), TSH, B12 (Methylmalonic acid), PTA.
Many asymptomatic elderly persons have early AD pathology.


"Amnestic" MCI means there is significant impairment in memory; it does not necessarily mean a hippocampal type of memory impairment that does not respond to cueing.


Site-Directed Spin Labeling Shows Parallel Structure Common Among Many Fibrils

Courtesy: Ralph Langen, Ph.D., Zilkha Neurogenetics Institute, USC

Neurofibrillary Tangles

Senile Plaques

Topographical Distribution of AD Lesions

MRI Progressive atrophy of Hippocampii in AD (Scheltens et al. 1992)

Braak & Braak Staging for Lewy Bodies

Dementia with Lewy Bodies
Stage 4: Mesocortical
Stage 5-6 Neocortical


Stage 5-6 Neocortical


Frontotemporal Lobar Degeneration (FTLD)


Braak & Braak Staging for Lewy Bodies

Dementia with Lewy Bodies
Stage 4: Mesocortical
Stage 5-6 Neocortical


Types of Cerebrovascular disease

- Atherosclerosis – large feeding vessels
- Arteriolosclerosis – small penetrating arterioles
- Amyloid angiopathy – meningeal, cortical and capillaries (associated with apoE4)
- CADASIL (cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy).

Boxer, Alzheimer Dis Assoc Disord. 2005 Oct-Dec;19 Suppl 1:S3-6

Behavioral Variant

Language Variant

Primary Progressive Aphasia

Semantic Type

Agrammatic (non-fluent) type

Silent infarcts were found in 24% of elderly persons.

Large and Small Vessel Disease (SIVD, SVD)

Silent infarcts were found in 24% of elderly persons.

Subcortical Vascular Dementia

PRE-FRONTAL-SUBCORTICAL CIRCUITS

Prefrontal cortex
Head of Caudate
Globus pallidus
Anterior & Dorsomedial Thalamus

Anterior centrum semiovale
Anterior limb internal capsule

Capsular genu
Cognitive Profiles in Dementing Disorders

1. Alzheimer disease (AD) – Episodic Memory Plus
2. Vascular cognitive impairment – Location of large and small vessel disease.
3. Dementia with Lewy bodies (DLB) – Attention & Executive control
4. Behavioral variant frontotemporal dementia (FTLD) – Emotional salience network
5. Primary progressive aphasia (FTLD variant) – Language network

Alzheimer’s Disease
NINCDS-ADRDA Research Diagnostic Criteria

- **Definite AD**
  - Characteristic clinical findings and widespread neurofibrillary tangles and neuritic plaques on neuropathology
- **Probable AD**
  - No alternative disorder present
  - Prominent amnesic memory loss
- **Possible AD**
  - Contributing medical condition present
  - Single non-memory cognitive function affected
- **Unlikely AD**
  - Acute onset, focal signs, seizures, gait disturbance
  - Non-amnesic memory loss

Clinical Criteria for DLB
(McKeith et al., Neurology 1996; 47: 1113)

- **Dementia** (Memory disorder need not be prominent)
- **Two of the following = probable; one = possible**
  - Fluctuating cognition, attention, and alertness
  - Recurrent visual hallucinations (well-formed, detailed)
  - Spontaneous motor features of parkinsonism

Behavioral Neurology Approach
Which cognitive domain is predominantly impacted?

- **Basic attention** - Delirium (systemic condition)
- **Amnesic type of memory loss** (Good attention, Poor response to cueing)
  - If yes, possible or probable AD
- **Executive Yes, No, DK**
  - If yes, depression?
  - If yes, vascular (MRI or CT)
  - If yes, DLB? (EP37 Visual hallucinations, RBS)
- **Other**
  - Language (Primary progressive aphasia)
  - Behavior & personality (bvFTD)
  - Cortical blindness (posterior cortical atrophy)
  - Apraxia (corticobasal ganglionic degeneration)
Montreal Cognitive Assessment (MoCA)

Developed to improve detection of MCI

5 word recall + Executive function


MoCA is more sensitive than MMSE for detection of MCI

MMSE has lower ceiling effect

When MMSE =30
MoCa may be 18-30


Basic Attention – Acute Reticular Activating System
Working memory Executive function - prefrontal cortex

Basic Attention: Digit span forward; selective attention

Affected disproportionately in delirium; search for toxic metabolic disturbance, consider EEG.

Working Memory: Serial 7 subtraction;
Difference between forward and backward digit span (normally=2)

Executive function: disproportionately affected in SIVD and DLB.

Secondary Memory – Episodic memory
Medial temporal (Hippocampus)
Diencephalic memory system

Lesions of Medial temporal - diencephalic memory system (e.g., Alzheimer, herpes simplex, Wernicke Korsakoff, limbic encephalitis) are associated with rapid forgetting and do not improve much with cueing or recognition format.

TRAILS TEST AND CLOCK DRAWING
Executive Function

Language
Dominant perisylvian frontal temporal cortices

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Correlation between Trails B and driving

Alzheimer disease usually associated with framing of repetition (e.g., transcortical anomic or sensory aphasia)

Note: exception is logopenic form of PPA

In AD, category fluency (animals, vegetables) is usually worse than phonemic fluency (F-A-S).

In SIVD and FTD, category and phonemic fluency are equally impaired.
Left Fronto-temporal lobar degeneration syndromes
Primary Progressive Aphasia (PPA)

Agrammatic – Inf Front
Logopenic

FTD -tau
Alzheimer -tau

Semantic – Anter Temp FTD - TDP43

Northwestern Anagram Test (NAT)

Active: The boy
Passive: It is the girl who pulling the is
Subject Who: It is the girl
Who: who pulling is boy the
Object Who: is by boy who pulling being the
Subject Cleft: It is the boy
Object Cleft: It is the girl

Analysis for VCI:
Location, Size, Number of Infarcts

Pure VCI
• Disruption of cognitive network
• Strategic location
  – Anterior limb or genu of internal capsule
  – Dorsomedial and anterior nuclei of thalamus
  – Angular gyrus
  – Frontal white matter
• Confluent white matter hyperintensities

Mixed AD/VCI
• Presence of significant memory impairment, especially with poor response to cueing/recognition
  Possible AD

2011 NIA-AA Diagnostic Criteria
Alzheimer & Dementia; 2011; 7: 279-6; 263-269.

Shift in emphasis to Biomarkers:
Atrophy, Glucose metabolism, beta-amyloid and tau (CSF and PET).

Alzheimer’s Disease
2011 NIA-AA Research Criteria with Biomarkers

• Definite AD
  – Characteristic clinical findings and widespread neurofibrillary tangles and neuritic plaques on neuropathology
• Probable AD
  – Prominent amnestic memory loss (language or visual spatial variants allowed)
  – Biomarker positive
• Possible AD
  – Other etiologies (e.g., infarcts) present
  – Biomarker uncertain
• Unlikely AD
  – Biomarker negative

Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset in Dominantly Inherited Alzheimer Disease (DIAN)

Quantification of Hippocampal Atrophy for clinical diagnosis

Not yet approved by FDA for clinical diagnosis.

CSF Biomarker Signature in ADNI: Low Abeta, High Tau

Aβ (1-42)

Shaw LM. Ann Neurol 2009;65: 403-413

AAN Evidence based guideline: Diagnostic accuracy of 14,3,3 protein for CJD

sensitivity 92% (CI 89.8–93.6); specificity 80% (CI 77.4–83.0), positive likelihood ratio of 4.7; negative likelihood ratio of 0.10.

Muyqui T et al. Neurology 2012;79:1506–1506

For CSF 14,3,3 protein and total tau, send CSF to National Prion Disease Center (www.cjdSURveillance.com).

Deoxyglucose (FDG) PET in AD

Projected on a rendered MRI and shown in red are areas with low metabolism in a group of 28 patients with mild Alzheimer disease, compared with 28 healthy controls.

Masdeu J. Continuum 2008; 14: 144-163.

Neuro-quant


CSF Biomarkers in Alzheimer disease:

Total Tau, Phospho-tau, AB42

www.athenadiagnostics.com #177

AD vs non-demented: Positive likelihood ratio 8 to 17

Note: CSF must be sent in polypropylene tube (since abeta adheres to polystyrene and glass tubes).
FDG-PET is superior to baseline clinical evaluation and similar to an evaluation performed 4 years later.

If pre-test probability of AD = 70%,
+PET increases likelihood to 84%,
- PET decreases likelihood to 31%.

FDG-PET in Autopsy-Confirmed AD and FTLD

Control

AD

FTLD

Imaging AD Amyloid during life with Pittsburgh Compound B (PIB)

In vivo PET Amyloid imaging in aging and dementia using $^{18}$C Pittsburgh Imaging B (PIB) compound.

$^{18}$Florbetapir (Amyvid) PET
(approved by FDA in 4/2012)

- A positive scan does not establish the diagnosis of AD or any other disorder.
- Safety and efficacy of Amyvid has not been established for predicting the development of dementia or any other condition or for monitoring responses to therapies.

**AD Guidelines**

- Active screening
- Evaluation for reversible causes
- Referral to patient/caregiver education programs
- Consider specialty referral
- Active monitoring and support of caregiver’s physical and emotional health


**Commonalities Among AD Guidelines**

- Active case finding and treatment for behavioral disturbances
- Consider acetylcholinesterase inhibitor treatment
- Facilitated communication among clinicians within health care system and community
- Active surveillance and tracking of patient outcomes


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**Current FDA approved Treatment Options for AD – Cholinesterase Inhibitor (CI) and NMDA receptor antagonist**

<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Generic</th>
<th>Target (Action)</th>
<th>Dosing</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aricept (tablets and orally disintegrating tablets)</td>
<td>Donepezil</td>
<td>AChE (inhibition)</td>
<td>5, 10 mg q.d.</td>
<td>Mild AD, Moderate AD, Severe AD</td>
</tr>
<tr>
<td>Exelon</td>
<td>Rivastigmine</td>
<td>AChE (inhibition), BuChE (inhibition)</td>
<td>1.5, 3, 4.5, 6 mg b.i.d. (with food)</td>
<td>Mild AD, Moderate AD, Mild/Mod PDD</td>
</tr>
<tr>
<td>Exelon Patch</td>
<td>Rivastigmine</td>
<td>AChE (inhibition), BuChE (inhibition)</td>
<td>4.6 (5 cm²), 9.5 (10 cm²) mg/d</td>
<td>Mild AD, Moderate AD, Mild/Mod PDD</td>
</tr>
<tr>
<td>Razadyne ER</td>
<td>Galantamine</td>
<td>AChE (inhibition), nAChR (modulation)</td>
<td>8, 16, 24 mg q.d. (with food)</td>
<td>Mild AD, Moderate AD</td>
</tr>
<tr>
<td>Namenda (tablets and oral solution)</td>
<td>Memantine</td>
<td>NMDA Receptor (antagonism)</td>
<td>5, 10 mg b.i.d.</td>
<td>Moderate AD, Severe AD</td>
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**Patient and Family Education and Support**

- Integrate medical care and support
  - Alzheimer’s Association (800) 272-3900
  - www.alz.org
  - Caregiver Resource Center (800) 445-8106
- Discuss diagnosis and treatment
  - Report dementia diagnosis to local health office (CA law)
- Discuss progression
- Discuss end-of-life decisions