Dementing Disorders in the Elderly

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Disclosures

• NIH
• Dominantly Inherited Alzheimer Network Therapeutic Trial Unit
• UpToDate
Diagnosis
Clinical

• Earliest, most salient feature
• Temporal progression
• Focal symptoms (Domains)
  – Cognitive
  – Behavioral
  – Motor

Diagnostic

• Imaging
• Neuropsychological Testing
• Serum/CSF
• Polysomnogram
CLINICAL FEATURES
Pathology (aging vs. dementia)

Not significantly impaired [n=189]

Demented [n=183]

Micro/lacunae infarcts

AD/Microinfarcts

Distribution of neuropathologic lesions: HAAS

- AD lesions
- Micro/lac
- Cort LB
- HS
- AD+HS
- AD/HS/ML
- AD/MLI
- AD/CLB
- Other
- Large inf
- None

White 07
Brain Network Degeneration

Seeley 09
Clinical Features

AD
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Probable (still probable)</strong></td>
<td></td>
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<tr>
<td>Progressive memory + 1 other domain</td>
<td><strong>Amnestic</strong> vs Nonamnestic presentation + 1 other domain (Language/Visualspatial/Executive)</td>
</tr>
<tr>
<td>Absence of systemic or neurological disorders that in and of themselves could account for the cognitive deficits</td>
<td>Absence of substantial concomitant CVD (includes isolated imaging findings), core symptoms of DLB, bvFTD, PPA (SD/PNFA)</td>
</tr>
<tr>
<td><strong>Supported by or Increased level of certainty</strong></td>
<td></td>
</tr>
<tr>
<td>Family history of similar disorder (especially with neuropathology)</td>
<td>Carrier of causative AD genetic mutation</td>
</tr>
<tr>
<td><strong>Possible AD</strong></td>
<td></td>
</tr>
<tr>
<td>presence of additional factor that can cause dementia but <strong>not</strong> considered the cause; ‘single, progressive, severe deficit identified in the absence of other identifiable causes’- Currently MCI</td>
<td>Etiologically mixed presentation (core symptoms +: stroke, features of DLB, evidence of another neurological disorder or medical comorbidity/medication possibly contributing)</td>
</tr>
<tr>
<td><strong>Laboratory Tests or Biomarkers (probable AD w evidence of AD pathology)</strong>*</td>
<td></td>
</tr>
<tr>
<td>LP, EEG, CT brain</td>
<td>Amyloid markers (csf Aβ$_{42}$, PET ligands); Downstream neuronal markers (CSF tau, FDG PET, MRI imaging)</td>
</tr>
<tr>
<td>- <strong>3 categories: clearly +, clearly -, indeterminate.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Possible AD w evidence of AD pathology</strong></td>
<td></td>
</tr>
<tr>
<td>N.A.</td>
<td>Clinical criteria for non-AD + biomarker evidence or neuropathological criteria (requires + both AD biomarkers)‡</td>
</tr>
<tr>
<td><strong>Unlikely AD</strong></td>
<td></td>
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<tr>
<td>Sudden onset, focal symptoms, early seizures or gait disorders</td>
<td>Evidence of support for alternative diagnosis which rarely overlaps with AD (HD, HIV dementia); possible AD but both biomarkers negative</td>
</tr>
</tbody>
</table>
Summary

• Dementia diagnosis is better defined in new NIA-AA guideline (behavioral changes considered a domain)
• Specificity? (+/- biomarkers)
• Clinically updated to reflect a better sense of other dementia syndromes and multiple causes in single subject
• Introduces biomarkers currently of greatest focus to large audience
Focal Variants of AD*

• Language variant- Logopenic aphasia
  – Non fluent speech pattern (word retrieval problems)
  – Frequent phonemic paraphasic errors
  – Spared single work comprehension
  – IMPAIRED REPETITION OF SENTENCES/PHRASES

• Visuo-Perceptive- Posterior Cortical Atrophy

*Memory impairment less at early stage
Posterior Variant AD

PCA

LPA

EO-AD
Clinical features

AD VS. VAD
Clinical features

• Subcortical Cognitive Phenotype (SLOWING)
  – Bradyphrenia
  – Bradykinesia
  – ‘subcortical’ memory disorder
  – Memory pattern- improves with recognition/prompts

• Gait Disorders!

• Pseudobulbar affect
Vascular Associated Cognitive Disorders

Probable VaD

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
   a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
   b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).
2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaD

There is cognitive impairment and imaging evidence of cerebrovascular disease but

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and the cognitive impairment.
2. There is insufficient information for the diagnosis of VaD (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD.
4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
   a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
   b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, PS1 mutation); or
   c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
Neuropsychological Evaluation

- Slowing
- Memory less impaired in comparison to AD, particularly with sub-cortical vascular dementia
- However, pathological studies have questioned the true distinction of neuropsychological profile.
Clinical features

AD VS. DLB
AD vs. DLB

• Look for
  – Autonomic symptoms
  – Sleep disorders
  – Fluctuations (hour to hour, not day to day)
  – Subcortical Cognitive Phenotype
  – Hallucinations early in the course of the disease
## Diagnostic Features

<table>
<thead>
<tr>
<th>Features</th>
<th>Specific Symptoms</th>
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<tbody>
<tr>
<td>Central feature</td>
<td>Dementia</td>
</tr>
<tr>
<td>Core features</td>
<td>Parkinsonism, fluctuations in attention, recurrent visual hallucinations</td>
</tr>
<tr>
<td>Suggestive features</td>
<td>REM-sleep behavior disorder, severe sensitivity to typical psychotics</td>
</tr>
<tr>
<td>Supportive features</td>
<td>transient episodes of loss of consciousness, significant day time somnolence, delusions, apathy, repeated falls, orthostatic hypotension</td>
</tr>
</tbody>
</table>
• Cognitive Impairment
  – Episodic memory loss (*minimal early*)
  – Executive dysfunction
  – Non-specific aphasia (*minimal early*)
  – Visual spatial impairment
  – Visuoperceptual impairment
  – Fluctuations
  – Bradyphrenia
  – Topographagosisia (buildings, directions and maps)
• **Motor Dysfunction**
  – *Stooped posture, shuffling gait, reduced Arm swing*
  – *Hypomimia (masking)*
  – *Hypophonia (soft voice)*
  – *Resting tremor (less frequent than in PD)*
  – *Bradykinesia (common)*
  – *Cogwheel rigidity (common)*
  – *Postural instability with occasional falling*
  – *Myoclonic jerks (can occur early)*
Others

- REM sleep behavior disorder (RBD)
- Blackouts or syncope with falls
- Nausea
- Neuroleptic sensitivity
- Restless leg syndrome
- Periodic limb movements during sleep
- Orthostatic hypotension
- Impotence
- Constipation
- Urinary incontinence
REM Sleep Behavior Disorder (RBD)

• Highly Specific to alpha-synuclein associated disorders (PD, DLB, MSA)
  - autopsy cases 94% associated with synucleinopathy
• May precede the cognitive symptoms in up to 50% of cases with a mean of 10 years
Sleep Evaluation

- Sleep as a symptom of neurodegenerative disorder
  - Amyloid (AD)
    - Altered sleep patterns in those with amyloid but cognitively normal
  - Synuclein (DLB/PDD)
    - REM associated sleep behavior disorder (RBD)
- Sleep as a contributor to cognitive disorders
  - Obstructive Sleep Apnea
Neuropsychological Evaluation

• Dictated by where the pathology is
  – **Cortical Lewy bodies**
    • Global impairment – difficult to differentiate from AD
  – **Limbic predominant Lewy bodies**
    • Greater Visual spatial impairment
      – (severely impaired clock drawing/3 D Cube/ Pentagons)
Clinical features

AD VS FTLD
Behavior and Language disorders

- Currently classified into 2 groups:
  - Behavioral variant
  - Language variant (2 types)
    - Semantic dementia
    - Agrammatic/ Non fluent aphasia
Diagnostic Criteria* for Behavioral Variant FTD

Possible FTD- ≥ 3 needed

• Early behavioral disinhibition
  ○ Socially inappropriate behavior
  ○ Loss of manors or decorum
  ○ Impulsive/rash, careless behaviors

• Early apathy or inertia

• Early Loss of sympathy or empathy

• Early perseverative, stereotyped or compulsive/ritualistic behavior

• Hyperorality and dietary changes

• Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions
  ○ Deficits in executive tasks (Trails B, generation tasks, errors)
  ○ Relative sparing of episodic memory
  ○ Relative sparing of visuospatial skills

* Based on 2009 revised criteria of the Int. Cons. Conf of bvFTD
Behavioral Core

- Apathy
- Disinhibition
- Irritability
- Poor insight
- Aberrant motor behaviors
- Poor social decorum
Behavioral Divergence

Apathetic Variant
- General loss of interest
- Withdrawal
- Blunted emotional response
- Decreased response to painful stimuli

Disinhibited Variant
- Restlessness/repetitive motor behaviors
- Hyperorality- increased interest in sweets
- Exaggerated sensory response
Neuropsychological Evaluation

• Deficits in executive tasks (Trails B, generation tasks (language fluency tasks, errors in tasks/ carelessness)
• *Relative* sparing of episodic memory
• *Relative* sparing of visuospatial skills
Disinhibition

Self appraisal

Atrophy

Empathy

Social Network

Decision Making
Clinical Features

OTHER (CURIOUS CONSIDERATIONS)
Somatoform Disorders in Degenerative Dementia

• Can be initial symptom
• May be rooted in trigger disease/disorder
  – Inability to revise cognitive state
• Somatic and hypocondriachal appear most common; rare conversion disorder
• Minimal existing literature on imaging correlates
• Right hemisphere > left hemisphere

Josephs 07; Devinsky & D’Esposito 04
Prevalence

- >1000 patients
  - 18% in Dementia Lewy Body
  - 7.0% in Parkinson’s disease
  - <2.0% (combined AD, FTD, MSA, PSP)
Related Signs and Symptoms

Symptoms

- Bladder fixation
  - Excessive toileting
- Bowel fixation
- Anorexia
- Food fads/restrictions
- Contamination fears
- Head pain

Co-morbidities?

- Obsessive-Compulsive disorders
- Anxiety disorder
- Delusions
DIAGNOSTIC APPROACH
Diagnostic Approach

MRI
VAD or AD?

A  PIB negative

B  PIB positive

Lee 2011
Cerebral Amyloid Angiopathy

Susceptibility weighted imaging (T2*/Gradient Echo)
CAA- Neuroimaging

CAA

Hypertension

## CAA and Anti-thrombotics

### Table 2
Multivariate analysis of predictors of recurrent lobar ICH in patients with CAA

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous lobar hemorrhage (other than index event)</td>
<td>4.80</td>
<td>1.4-15.6</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Microbleeds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.88</td>
<td>0.5-7.6</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>2-4</td>
<td>2.93</td>
<td>1.3-4.0</td>
<td>0.041</td>
</tr>
<tr>
<td>≥5</td>
<td>4.12</td>
<td>1.6-9.3</td>
<td>0.001</td>
</tr>
<tr>
<td>CT-WMH present (posterior)</td>
<td>4.72</td>
<td>1.44-15.47</td>
<td>0.010</td>
</tr>
<tr>
<td>Antiplatelet exposure after index event</td>
<td>3.95</td>
<td>1.6-8.3</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Abbreviations: CAA = cerebral amyloid angiopathy; CI = confidence interval; CT-WMH = CT-defined white matter hypodensity; HR = hazard ratio; ICH = intracerebral hemorrhage.

FTD

Frontal predominance
Diagnostic Approach

PET/SPECT
Role in Diagnosis

• Good test for discerning between dementia syndromes (particularly when MRI is relatively normal)
• What do you do with that info?
DLB- Cingulate Island Sign

Lim 09
Amyloid PET

http://www.amyvid.com/Pages/index.aspx
Diagnostic Approach

CSF
Normal Aging

AD

Depression

EtOH

B-12 Def

LBD

FTD

VaD

P-Tau

Aβ42