Emerging Challenges in Primary Care: 2017

Differential Diagnosis of Four Common Dementias
Faculty

- Thomas Weiss, MD
  Researcher and Principle Investigator in Psychiatry
  Radiant Research
  San Antonio, TX
Disclosures

• Thomas Weiss, MD serves on the speakers bureau for Allergan.
Learning Objectives

• Understand the importance of obtaining history from both patient and collateral informant, in differentiating dementia syndromes.

• Recognize the value of the physical exam, especially the neurological, in the differential diagnosis of dementia.

• Review existing pharmacological and non-pharmacological treatment options for the four common dementia syndromes.
Introduction

Four clinical dementia syndromes account for 90% of all cases after excluding ‘reversible’ causes of cognitive impairment.

Alzheimer’s Disease (AD)
Vascular Dementia (VaD)
Dementia with Lewy Body (DLB)
Frontotemporal Dementia (FTD)
Major Neurocognitive Disorder

1. Evidence of significant cognitive decline from a previous level of performance in one or more domains.

2. The cognitive deficits interfere with independence in everyday activities.

3. The cognitive deficits do not occur exclusively in the context of a delirium.

4. The cognitive deficits are not better explained by another mental disorder.
Major Neurocognitive Disorder

SPECIFY:

1. Without behavioral disturbances.

2. With behavioral disturbances: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance such as psychosis, mood disturbance, agitation, or apathy.
Major Neurocognitive Disorder

SPECIFY:

1. Mild: difficulties limited to instrumental activities of daily living (IADLs).

2. Moderate: difficulties with basic activities of daily living (BADLs).

Major Neurocognitive Disorder

SPECIFY whether due to:

- Alzheimer’s disease
- Vascular disease
- Frontotemporal lobar degeneration
- Lewy body disease
- Traumatic brain injury
- HIV infection, prion disease
- Parkinson’s disease
- Huntington’s disease
Alzheimer’s Disease

A 70 y/o man presented with a 3 year history of progressive memory loss, primarily STM. He needed his daughter to remind him of appointments and ADLs. He had problems driving alone as he became confused with routes he had used for years. He could not manage his bills as usual. P.E. was unremarkable. MMSE 20/30.
Alzheimer’s Disease

- Most common dementia in adults >65.
- Multiple pathologic mechanisms.
- Course (diagnosis to death) 8-12 years.
- Memory decline is the hallmark of AD.
- Insidious onset, progressive course and impairment in either language, recognition, praxis or executive function.
- Motor signs absent early in the course.
- Behavioral changes common in mid-late stages.
Alzheimer’s Disease Treatment

SAFETY ISSUES: SUPERVISION

• Navigational issues.
• Driving.
• Firearm security.
• Fall hazards.
• Financial, healthcare, and legal directives completed or if limited capacity, proxies designated.
Alzheimer’s Dementia Treatment

Two different categories of FDA-approved medications for AD:

Acetylcholinesterase inhibitors (3):
(AChEIs): Donepezil, Rivastigmine, and Galantamine.

NMDA-antagonist/glutaminergic modulator:
Memantine.

Combination therapy memantine-donepezil (Namzaric) appears optimal.

Exercise for Dementia Prevention

Physical exercise/fitness improves

- Cardiovascular health which increases
- Neurotropic factors that protect and maintain
- Brain health that stabilizes or enhances
- Cognitive performance.

Exercise shown to increase BDNF 4X.

Increased neurotrophic factors: IGF-1, NGF, BDNF.

Vascular Dementia

A 65 y/o man with hypertension, DM, and CAD developed sudden left hemiparesis and dysarthria 6 months ago. Three months later, his wife noticed he could not name his only two grandchildren and could not remember to take medication. He could not operate a remote control nor cook meals as usual. On exam, there was a slight pronator drift and hyperreflexia.
Vascular Dementia

- Multiple Clinical Syndromes of VaD:
  - multi-infarct, single infarct, lacunar state, genetic forms, and hypoxic encephalopathy.

- Multiple Pathologic Mechanisms.

- Focal deficits and motor signs common.

- Early, marked impairment of executive function.
<table>
<thead>
<tr>
<th><strong>Clinical</strong></th>
<th><strong>VaD</strong></th>
<th><strong>AD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>H/o ASCVD</td>
<td>TIAs, CVAs, HTN</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden or Gradual</td>
<td>Grad</td>
</tr>
<tr>
<td>Progression</td>
<td>Stepwise</td>
<td>Slow</td>
</tr>
<tr>
<td>Neuro Exam</td>
<td>Neuro Deficits</td>
<td>Wnl</td>
</tr>
<tr>
<td>Gait</td>
<td>Disturbed Early</td>
<td>Wnl</td>
</tr>
<tr>
<td>Memory</td>
<td>Mild Impairment</td>
<td>Mod</td>
</tr>
<tr>
<td>Executive Funct.</td>
<td>Early Marked</td>
<td>Later</td>
</tr>
<tr>
<td>Hachinski Score</td>
<td>&gt;7</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Imaging</td>
<td>Infarction or WM</td>
<td>HC Atrophy</td>
</tr>
</tbody>
</table>
Vascular Dementia Treatment

Must prevent future stroke/vascular disease:

• Aspirin
• Anticoagulants
• Exercise

Off label treatments for apathy:

• Antidepressants (sertraline, bupropion)
• Stimulants (methylphenidate)
Methylphenidate for Apathy in Alzheimer’s Disease

N=60 pts with AD – 30 per study arm.

6 week study.

Start 10 mg bid and titrate to 20 mg bid.

No side effect differences for psychosis, agitation, EKG changes, or blood pressure.

Weight loss and anxiety in treatment group approached significance.

Dementia with Lewy Bodies

A 72 y/o man with a 6 month history of cognitive impairment and visual hallucination presented to an ER after repeated falls. His wife felt he had been slow in thinking, speaking and performing his routine activities for a few months. On exam he had bilateral rigidity, parkinsonian gait, and masked face. No history of medication could be elicited.
Dementia with Lewy Bodies

• **Core clinical features**: fluctuating cognitive impairment, visual hallucinations, and parkinsonism.

• **Secondary features**: repeated falls, syncope, neuroleptic sensitivity, systematized delusions, hallucinations of other modalities, REM sleep disorder, and depression.
<table>
<thead>
<tr>
<th>Clinical</th>
<th>DLB</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Psychiatric Sxs.</td>
<td>Early/Likely</td>
<td>Late</td>
</tr>
<tr>
<td>Fluctuation MS</td>
<td>50-75%</td>
<td>If Delirious</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Memory Impairment</td>
<td>Semantic</td>
<td>Episodic</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Poor Early</td>
<td>Less Severe Early</td>
</tr>
<tr>
<td>Visual Hallucinations</td>
<td>Common Early</td>
<td>Rare Early</td>
</tr>
<tr>
<td>Autonomic Dysregulation</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neuroleptic Response</td>
<td>EPS;Aggrav.</td>
<td>Behavioral Response</td>
</tr>
<tr>
<td>Clinical</td>
<td>DLB</td>
<td>PDD</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Tremor</td>
<td>Less Common</td>
<td>Common</td>
</tr>
<tr>
<td>Motor Sxs.</td>
<td>Bilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Postural Instability</td>
<td>Common</td>
<td>Less Common</td>
</tr>
<tr>
<td>(Masked face)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism at Dementia dx</td>
<td>25-50%</td>
<td>100%</td>
</tr>
<tr>
<td>Response to L-dopa Cognitive Impair.</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Before Motor sxs</td>
<td>After Motor sxs. &gt;2 yrs</td>
</tr>
</tbody>
</table>
Lewy Body Dementia Treatment

- No disease-modifying drugs are available.
- Very few randomized, controlled clinical trials.
- Management is symptom focused.
- Targeting one symptom may make other symptoms worse.
- The clinician, patient, and family must co-prioritize symptomatic approach.
- Acetylcholinesterase inhibitors appear more helpful in LBD than SDAT.
VISUAL HALLUCINATIONS:

- Occurs early in disease course.
- Fully formed detailed 3D objects, people, or animals ("Lilliputian").
- MANAGEMENT:
  - Reduce dose of Parkinson’s medications.
  - Clozapine and Quetiapine helpful BUT side effects….
  - Pimavanserin (Nuplazid)
LEWY BODY DEMENTIA TREATMENT

PIMAVANSPANIN:

• FDA approved for treatment of hallucinations/delusions in Parkinson’s disease. Inverse agonist at 5-HT2A and 5-HT2C receptors.

• FDA class effect black box warning for increased mortality.
REM Sleep Behavior Disorder: augmented muscle activity and dream content; typically precedes onset of dementia, hallucinations and Parkinsonism.

Remove sharp objects/potential weapons.

Place mattress on the floor.

Clonazepam and Melatonin are helpful.
Lewy Body Dementia Treatment

AUTONOMIC INSTABILITY:

- Increase salt in diet
- Compression stockings.
- Increase fluid intake.
- Decrease or D/C anti-psychotics.
- Minimize anti-cholinergics (GERD and OAB meds).
Frontotemporal Dementia

A 50 y/o woman presented with behavioral change over the course of two years. She was less responsible to her job and had less concentration to finish tasks. She began eating more and gained 20 lbs in 3 months. She told lies and dirty jokes, openly stole office supplies, and randomly picked up objects within reach and sight. Her personal hygiene deteriorated and she refused to bathe. PE positive only for palmomental and grasp reflexes. MMSE 29/30 but CDT poor.
Frontotemporal Dementia

- Prominent personality and behavior change early in course.
- Frequently misdiagnosed as late-onset psychiatric illness or personality disorder.
- P.E. may reveal primitive or frontal reflexes.
Frontotemporal Dementia
Behavioral Variant

1. Three or more of these behavioral symptoms:
   - Behavioral disinhibition.
   - Apathy or inertia.
   - Loss of sympathy or empathy.
   - Perseverative or compulsive behavior.
   - Hyperorality and dietary changes.

2. Decline in social cognition or executive function.

3. Relative sparing of learning and memory.
<table>
<thead>
<tr>
<th>Clinical</th>
<th>FTD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age @ Onset</strong></td>
<td>Rarely&gt;75</td>
<td>Increases with Age</td>
</tr>
<tr>
<td><strong>Early Behavioral Problems</strong></td>
<td>Common</td>
<td>Late/Unusual</td>
</tr>
<tr>
<td><strong>Socially Inappropriate</strong></td>
<td>Common Early</td>
<td>Late, Usually in Severe</td>
</tr>
<tr>
<td><strong>Memory Impairment</strong></td>
<td>Less Prominent Early</td>
<td>Early/profound</td>
</tr>
<tr>
<td><strong>Language Problems</strong></td>
<td>Isolated (PPA)</td>
<td>Usually w/Memory Impairment</td>
</tr>
<tr>
<td><strong>Visuospatial Defect</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Motor Signs</strong></td>
<td>More Common</td>
<td>Less Common</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td>Alexithymia, Irritability, Apathy, Anhedonia, Withdrawal</td>
<td>Sadness, Apathy, Guilt</td>
</tr>
<tr>
<td><strong>Psychotic Features</strong></td>
<td>Rare Persecutory; Usually Jealous/Religious/Bizarre</td>
<td>Mid to Late Stage: Persecutory or Misidentification</td>
</tr>
<tr>
<td><strong>Appetite; Diet</strong></td>
<td>Increased; Weight Gain CHO Craving</td>
<td>Less Common; Anorexia and Weight Loss</td>
</tr>
</tbody>
</table>
Frontotemporal Dementia Treatment

Multiple targets: Tau and PGRN (Progranulin)

Multiple investigational agents:

- Lithium
- Riluzole
- Chloroquine
- Amiodarone
- Methylene Blue

Boxer, AL et al. Alz and Dem 2013;9:176-188
Fig. 3.—Case 490. Orbitoclast in primary position parallel with the bony ridge of the nose.

Fig. 4.—Case 490. Orbitoclast in elevated position making deep frontal cut.

Fig. 5.—Case 490. Superimposed roentgenograms illustrating the range of movement of the orbitoclast within the frontal lobe.
Conclusions

• Failure to recognize dementia syndromes remains common.

• Different types of dementia require different approaches and management.

• Four common dementias should come to mind from history, examination, and simple cognitive testing.
Cure Sometimes
Relieve Often
Care Always