Diagnosis and management of non-Alzheimer dementias

Melissa Yu, M.D.
Department of Neurology
AGENDA

- Introduction
- When to think of alternate diagnoses
- Other forms of dementia
- Other reasons for confusion and memory loss

If not referenced on the slide, MRI imaging all taken from:
INTRODUCTION

Figure 1. Common Forms of Dementia

DEMENTIA

An “umbrella” term used to describe a range of symptoms associated with cognitive impairment.

ALZHEIMER’S 50%-75%
VASCULAR 20%-30%
LEWY BODIES 10%-25%
FRONTOTEMPORAL 10%-15%

MIXED DEMENTIA = ≥1 NEUROPATHOLOGY - PREVALENCE UNKNOWN
Why is this important?

- Patients and families benefit from having accurate diagnoses
- Prognosis and symptoms may be different
- Treatment likely different
- Additional therapy needed for other associated symptoms
- Reversible causes could be found
Alzheimer’s Disease is likely if:

- Slowly progressive, insidious course
- Memory loss as first and most prominent symptom
- Activities of daily living are impaired
- Age >65
- Patient has anosognosia
- Physical examination is normal
- Hippocampal/biparietal atrophy on MRI

http://mathuramg.com/projects/AD.html
Something else may be going on if:

- Initial symptoms are not memory related
- Sudden onset
- Fluctuating course
- Abnormal physical exam
- Rapid decline
- Prominent personality or mood changes
- Early language dysfunction
- Hallucinations early
- Age <65
MILD COGNITIVE IMPAIRMENT

- Amnestic or Non-amnestic type
- Deficit in one of four main cognitive domains:
  - Recent memory
  - Language
  - Visual spatial ability
  - Executive function
- Able to maintain independent life
- Can represent “prodromal” Alzheimer’s Disease
- No specific treatment
- 10-15% of aMCI patients will convert to Alzheimer’s disease each year
VASCULAR DEMENTIA

- Second most common form of primary dementia
- 20-30% of patients with AD also have vascular dementia
- Sudden or stepwise onset
- Executive dysfunction, language dysfunction, visual-spatial reasoning issues
- Delayed memory often intact
Vascular dementia progresses in different ways

- Stroke with static cognitive dysfunction
- Stroke followed by progressive cognitive dysfunction
- Multiple strokes over time
- Incipient dementia with stroke causing worsening
- Stroke followed by recovery followed by cognitive dysfunction
- Subclinical changes on MRI (white matter disease) causing ischemia-related cognitive dysfunction
Subtypes of vascular dementia

- Multi-infarct dementia
- Strategic infarct
  - MCA or PCA territory
  - Carotid occlusion
  - Watershed infarcts
  - Lacunar infarct in thalamus or internal capsule
- Small vessel disease
  - Amyloid angiopathy
- Mixed dementia (with Alzheimer’s or Lewy Body disease)
Overlap with Alzheimer’s Disease
Management of vascular dementia

- Screening for vascular risk factors
  - Carotid disease
  - Atrial fibrillation
  - Hyperlipidemia, tobacco use, diabetes
  - Hypertension
  - Hyperhomocysteinemia

- Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)

- Memantine

- Treat neuropsychiatric symptoms as they arise
Dementia with Lewy Bodies

- 10-25% of cases of dementia
- May not have memory loss as first symptom
- Impaired attention, executive function, visual spatial function
- Changes in thinking and reasoning
- FLUCTUATIONS
- HALLUCINATIONS
- PARKINSONISM

https://www.emedicinehealth.com/image-gallery/lewy_body_dementia_picture/images.htm
Dementia with Lewy Bodies

- MRI may be normal or may show generalized atrophy
- May have nearly intact MMSE
- Associated symptoms:
  - Dysautonomia
  - Sleep disorders
  - Neuroleptic sensitivity
  - Decreased sense of smell
  - Auditory or tactile hallucinations
  - Delusions
Treatment of Dementia with Lewy Bodies

- Behavioral strategies to modify environment important
- Educate on diagnosis, associated symptoms, prognosis
- Cholinesterase inhibitors can help with cognitive symptoms and hallucinations
- Mixed data on memantine
  - Some patients have worsening of delusions and hallucinations
- Be careful with neuroleptics
- REM Behavior symptoms may respond to melatonin, low dose clonazepam
- SSRIs useful for mood symptoms
- Mixed response to carbidopa/levodopa
Frontotemporal dementia
Behavioral variant frontotemporal dementia

- Early personality changes
- Younger (40s – 60s)
- Compulsive behaviors
- Memory often intact at first
- Executive dysfunction and inattention
- Most patients lack insight into deficit
- May have frontal reflexes on examination (snout, grasp, palmomental)
- 15-20% also develop motor neuron disease (ALS)
Primary progressive aphasia

- Fluent and non-fluent presentations
- Deficit remains only in speech for an extended period of time
- Mean age of onset is 58
- Other cognitive domains become involved as disease progresses
- MRI may show focal atrophy

https://radiopaedia.org/articles/progressive-non-fluent-aphasia-1
Treatment of Frontotemporal dementia

- Patients may get worse with cholinesterase inhibitors
- SSRIs may be helpful for behavioral symptoms
- Trazodone sometimes helpful for anger and aggression
- Use atypical antipsychotics with caution
- Watch for development of motor neuron symptoms (fasciculations, dysphagia, weakness, dysarthria)
- Watch for signs of gait disturbance and parkinsonism
- Counsel family on safety, driving
- Speech therapy
What else could it be?
Cognitive problems AND gait issues....
Head trauma
Progressive supranuclear palsy (PSP)

- Poor mobility and falls
- Parkinsonism
- Visual problems
- Growling or forced speech
- Pseudobulbar affect
- Cognitive problems
- Average age of onset 65
MRI findings in PSP
Normal pressure hydrocephalus

- Due to impaired absorption of CSF
- Can be secondary to meningitis or subarachnoid hemorrhage
- Dementia
- Gait disturbance
- Urinary incontinence
Distinguishing NPH from cortical atrophy
Alcohol related cognitive impairment

- **Wernicke’s Encephalopathy:** Ataxia, ophthalmoplegia, confusion
  - Thiamine replacement
  - Can also occur after GI surgery, particularly *bariatric surgery*

- **Korsakoff’s Syndrome:** retrograde and anterograde amnesia
  - can follow an episode of Wernicke’s encephalopathy
  - Attention and social behavior are relatively preserved

- **General cognitive dysfunction:** 50-70% of alcohol abusers have deficits on neuropsych testing
  - Varied symptoms
  - Can see atrophy on imaging, including hippocampal atrophy
Alcohol related cognitive impairment
Rapidly progressive or sudden onset....
Creutzfeldt-Jakob disease (CJD)

- 5th to 7th decade of life
- Rapidly progressive
- Subacute dementia, myoclonus, parkinsonism
- MRI changes
- EEG with triphasic waves
- No known treatment
CJD. A. FLAIR with hyperintensity in caudate head and putamen as well as occipital cortex. B/C. Restricted diffusion in right caudate, putamen and occipital cortex. D/E: restricted diffusion in right frontoparietal cortex
Autoimmune and paraneoplastic encephalitis

- Acute to subacute onset
- Personality changes
- Cognitive dysfunction
- Seizures
- Often associated with cancer – lung, breast, ovarian teratoma, testicular
- Treated with removal of the tumor, steroids, IVIG, plasmapheresis

https://www.rarediseasereview.org/publications/2017/2/9/oojx5ip8cd58paslejwgf3hmi9m3nl
Younger patients...
Sleep apnea

- Can occur with dementia
- Causes problem with retrieval
- Intact maintenance, recognition
- Decreased working memory, inattention
- Normal short term memory
- Can co-exist with REM behavior disorder
Psychiatric illness

- Depression
- Post traumatic stress disorder
- Anxiety
- Fluctuating symptoms, inattention
- Often intact neuropsychological testing or frontal-mediated symptoms
HIV associated neurocognitive disorders (HAND)

- Virus enters the CSF during initial days of infection
- Cognitive symptoms can occur at time of seroconversion
- Processing speed issues, visual spatial deficits, difficulty with attention and concentration
- ART improves subcortical symptoms
- Increased risk if lower CD4 nadir, older age at seroconversion, duration of infection, prior AIDS-defining diagnosis
- Dementia typically occurs in untreated, advanced infection, CD4<200
- CNS viral escape syndrome
MRI in HIV
Menopause and cognition

- High concentration of estrogen receptors at several areas of the brain involved with cognition including the hippocampus and prefrontal cortex
  - Verbal memory and retrieval
  - Working memory
  - Executive function
  - Attention control

- Estradiol may be neuroprotective

- Estrogen can increase levels of neurotransmitters, enhancing neuronal growth and synapse formation

- Increased Alzheimer’s risk in women may be due to reduced estrogen, causing reduced neuroprotection
Menopause and cognition

- Estradiol increases synthesis of choline acetyltransferase in the brain
- One hypothesis is that loss of estradiol can lead to anticholinergic effects including loss of memory and attention, confused speech, ataxia, confusion, disorientation.
Menopause and cognition

- Kinmen Women-Health Investigation (KIWI) (Taiwan)
  - Significant reduction in verbal fluency in peri-menopausal women compared to pre-menopausal women

- Penn Ovarian Aging Study (POAS)
  - Immediate recall declined in post menopausal stage
  - Delayed verbal recall declined in early transition

- Other studies have shown no effect
Menopausal interventions and cognition – Hormone therapy

- Women’s Health Initiative Memory Study (age 65+)
  - 66% of women diagnosed with probable dementia in the treatment group
  - 34 percent in the placebo group (p=0.01)
  - Hazard ratio 2.05
  - Use of hormones associated with greater brain atrophy, particularly in women who already had cognitive deficits before initiating hormone therapy

- Kronos Early Estrogen Prevention Study (KEEPS) (avg age 52.6)
  - HT not associated with clear cognitive benefit but no harm found
  - Similar result in Women’s Health Initiative Memory Study of Younger Women

- Some evidence of cognitive benefit and reduced risk of Alzheimer’s disease if hormone replacement done in first 5 years of menopause
Medications that can cause cognitive dysfunction

- Benzodiazepines
- Psychotropics
- Opioids
- Antiepileptics
- Steroids
- Anticholinergics
- Antibiotics
Anticholinergics and other meds to avoid

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Example</th>
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<tbody>
<tr>
<td>Antihistamine</td>
<td>Hydroxyzine, diphenhydramine, OTC cold/allergy remedies</td>
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<td>Antispasmodic</td>
<td>Alverine, hyoscyamine</td>
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<td>Antidepressants</td>
<td>Fluoxetine, paroxetine, amitriptyline</td>
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<td>Benzodiazepines</td>
<td>Lorazepam, diazepam, alprazolam</td>
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<td>Opioids</td>
<td>Codeine, morphine, meperidine</td>
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<td>Antianthyrhythmic</td>
<td>Digoxin</td>
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<td>Diuretic</td>
<td>Furosemide, hydrochlorothiazide</td>
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<td>Antiparkinsonian</td>
<td>Carbidopa-Levodopa (Sinemet®), benzotropine</td>
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<tr>
<td>Antibiotics</td>
<td>Ciprofloxacin, metronidazole, cephalexin</td>
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<td>Bladder stabilizer</td>
<td>Oxybutynin, tolterodine</td>
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<td>H2 receptor Antagonists</td>
<td>Cimeclidine, ranitidine</td>
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<tr>
<td>Anti-inflammatory</td>
<td>Ibuprofen, naproxen, prednisone</td>
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<tr>
<td>Antiemetics</td>
<td>Diphenhydramine, medicine</td>
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<tr>
<td>Anticonvulsants</td>
<td>Dilantin, tegretol, valproic acid</td>
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<td>Alpha 1 Blockers</td>
<td>Tamsulosin, terazosin</td>
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<tr>
<td>Antihypertensives</td>
<td>Beta-blockers, alpha-antagonists, calcium channel blockers</td>
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<tr>
<td>Bronchodilator</td>
<td>Theophylline</td>
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THANK YOU!