Diagnosis and Treatment of Dementia

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Someday, I aspire to disclosures...

A few off-label drug uses, marked by:
Outline

- When is screening happening?
  - Clinic screening tools
- Memory Clinic Diagnostics
- Expected progression
- Pharmacologic Therapies
- Non-pharmacologic Therapies
When are clinicians screening?

- Annual Wellness Visit (required)
  - Health report
- Patient reports problems (sens 45-55%, spec 75-85%)
- Family reports problems (sens ~95%, spec ~85%)
- Clinician suspicion
- All patients >80 (NIA, USPSTF)
Normal aging

- “Occasional” and “Temporary” memory lapses
- Decline with normal aging:
  - Processing speed
  - Rapid novel problem solving
  - Delayed recall
- Stable:
  - Vocabulary
  - Fund of information
Cognitive ability changes

- “Crystallized ability” stays the same
  - Information/skills gained from experience
- “Fluid intelligence” declines
  - Flexible reasoning and novel problem-solving
- Decreased learning efficiency (takes longer/more repetition)
- “Tip-of-the-tongue” phenomenon (word-finding)
- Slowed reactions (both mental and physical)
Dementia Types:

- Alzheimer’s disease ~55% of all dementia
- Vascular dementia ~10-15% of all dementia
- Lewy body dementia ~20% of all dementia
- Frontotemporal Dementia
- Parkinson’s disease
- Parkinson’s plus syndromes
- Normal Pressure hydrocephalus
- Traumatic Brain Injury
- Cerebral Amyloid Angiopathy
- Rarer: HIV, Toxin-induced (Alcohol, Wilson’s, etc), CJD, CADASIL, Corticobasilar, Huntington’s, PTLD, autoimmune
Before Memory Clinic

- Some sort of screening test
- More story:
  - Slope of decline
  - Meds to stop
  - Comorbidities to address
- Neuro Exam
- Tests:
  - TSH, B vitamins, Vit D, CMP, CBC
  - Head Imaging
MiniCog

- 3-word recall
- Clock Draw Test
- Score: 1 pt/word, 1 pt clock numbers, 1 pt clock hands
  - <3 = dementia
- Sensitivity/specifity ~75-85%
- PPV 0.34, NPV 0.98
- Highly validated
- No education/language bias (studied!)
- 3-5 minutes
MMSE

- Score: >24 = normal, add 1 point if <12 years education
- Proprietary ($1-5/test)
- Oldest (1975), most studied
- Sensitivity ~70%, Specificity ~85-89%
- PPV ~0.6, NPV ~0.9
- Takes ~10 min
SLUMS

- Score: >25 or 27 = normal, >20 or 21 = MCI
- Free!
- Takes ~10 min
- Sensitivity/Specificity >90
- Less well-studied
  - Mostly at VA
MoCA

- Score: >26 = normal, 18-25 = MCI, add 1 pt for ≤ 12 yrs education
- Better screen for MCI
  - MMSE sens 17%, MoCA sens 83%
- Sensitivity ~95%, Specificity ~50%
- Moving towards being proprietary
- More executive function: more types of dementia
- Takes ~15 min
- More versions: many languages, visually impaired, low education
  - Requires more training (has a user manual)
What are we testing?

Areas of cognition:
- Immediate memory
- Delayed memory
- Attention
- Visuospatial/construction
- Language
- Executive function
Memory Clinic?

- Scoring well, but a clear clinical problem
- Atypical symptoms (not “just Alzheimer’s”)
- Complicated comorbidities
- Patient/family disagrees
WAI Memory Clinics

A comprehensive, team approach to dementia diagnosis, treatment, and support for the patient and caregiver.

- Supports the PCP
- Empowers the patient and caregiver
- Reduces crisis visits
- Decreases caregiver burnout
Inter-Professional Model

**Medical Evaluation**

- Differential diagnostic algorithm

**Cognitive Testing**

- Battery of key cognitive domains

**Family Informant Assay**

- Analysis of hx, burden, ADL/IADL etc.

**Impact - Clinicians**

- Earlier diagnosis
- Improved coordination of care
- Improved management of co-morbidities
- Improved connection of families to resources
- Improved support to PCP

**Impact - Patient Care**

- Quality diagnostic process
- Optimization of patient, family, population outcomes

**Inter-professional Practice**

- Integrate skill sets
- Share knowledge
- Organize planning
Memory Clinic Team

Geriatric Family Specialist:
✓ Caregiver informant collection
✓ Functional screens
✓ Family burden
✓ Ongoing patient and caregiver support and resources

Neuropsychology:
✓ Administer/analyze cognitive evaluations
  i.e. Cognistat/RBANS
✓ Offer cognitive therapies recommendations

Physician:
✓ Specialized dementia training
✓ Comprehensive assessment
  Lab review
  Medical exam
  Poly-pharmacy
  Imaging

Team:
Provides recommendations and management plan back to PCP
Comprehensive History

- Symptoms at onset
- Time course and pattern of cognitive decline
- Past and present function at higher level tasks
- Safety concerns
- Other associated symptoms
  - depression, tremor, frequent falls, visual hallucinations, stroke and/or transient ischemic attack symptoms, ataxia, urinary incontinence, agitation, personality changes, etc...
Past Medical/Surgical History

- Vascular risk factors/history of vascular disease
- Coronary artery bypass surgery
- Other major central nervous system (CNS) event (e.g., TBI with LoC)
- Hearing and/or vision loss
- Obstructive sleep apnea
- Alcohol or other substance abuse
- Depression, anxiety, posttraumatic stress disorder, or other psychiatric illness
- Other neurologic disease (Parkinson’s, ALS, seizure)
- History of malignancy with or without prior treatment with chemotherapy
Pertinent History

- All medications and supplements
- Correlation of dose change/initiation with cognitive symptoms
- Family, friends, and other social support
- Use of community resources
- Educational and Work history
- Military history (including exposure to combat or blast injuries)
- Hobbies and other daily activities
- Family history of vascular, neurologic or psychiatric disorders
Physical Exam

- General appearance & Mental status
  - behavior, attitude, mood, affect, insight, judgment, thought content, thought process, speech, language
- Cranial nerves
- Motor function and integration
  - strength, tone, cogwheeling
- Sensory function
- Coordination
- Deep tendon reflexes
- Gait & balance
<table>
<thead>
<tr>
<th>TYPE OF DEMENTIA</th>
<th>ALZHEIMER DISEASE</th>
<th>VASCULAR DEMENTIA</th>
<th>DEMENTIA WITH LEWY BODIES</th>
<th>FRONTAL TEMPORAL DEMENTIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Course</td>
<td>Insidious onset and gradually progressive</td>
<td>Acute onset of cognitive impairment with some stabilization (if only one vascular event) and/or stepwise deterioration (if multiple infarcts)</td>
<td>Progressive cognitive decline with fluctuating cognition, attention, and alertness</td>
<td>Insidious onset and gradually progressive</td>
</tr>
<tr>
<td>Cognitive Symptoms</td>
<td>Memory is the most commonly affected cognitive domain. May also have impairments in executive function, language, and/or visuospatial skills.</td>
<td>Various cognitive domains may be affected depending on the location of the clinical stroke(s) and/or severe subcortical cerebrovascular disease</td>
<td>Cognitive symptoms may fluctuate. May have prominent impairment in visuospatial ability, attention, and/or executive function.</td>
<td>Will have early behavioral disinhibition and apathy (frontal lobe predominance) or early prominent language abnormalities (temporal lobe predominance).</td>
</tr>
<tr>
<td>Other Associated Symptoms/Signs</td>
<td>Some patients may have agitation and/or behavioral changes. Should have evidence of relevant cerebrovascular disease by brain imaging</td>
<td>May or may not have focal neurologic signs on examination.</td>
<td>May have recurrent well-formed visual hallucinations (usually people or animals), parkinsonism (including tremor, rigidity, and postural instability), recurrent falls and syncope, rapid eye movement (REM) sleep behavior disorder, neuroleptic sensitivity, and/or delusions.</td>
<td>Deficits are chiefly noted in executive tasks with relative sparing of memory and visuospatial skills.</td>
</tr>
</tbody>
</table>

Hazzard’s Geriatric Medicine and Gerontology, 7e > Dementia Including Alzheimer Disease
Differential Diagnosis

- Depression/anxiety
- Substance abuse
- Delirium
  - cannot dx dementia within 6 months of hospitalization
- Thyroid dysfunction
- Vitamin deficiencies
- Medication side effects
  - anti-cholinergics, benzodiazepines, anti-psychotics, transplant meds, etc
- Sleep apnea/chronic hypercapnia and hypoxia
- Uremia/Hepatic Encephalopathy
- Infection: HIV, Syphilis, Lyme
- Seizure disorder
- Environmental toxicity (heavy metals)
- Progressive multifocal leukoencephalopathy
- Brain tumors
- Paraneoplastic syndromes
- Post-operative cognitive dysfunction
- Chronic encephalitis
- Chronic traumatic encephalopathy (CTE)
Imaging

- CT head: rule out vascular disease, tumor
- MRI: Lacunar infarcts, CAA, infection/inflammation, paraneoplastic, tumor
- PET-CT glucose
  - Alzheimer’s vs FTD
Imaging

- Amyloid PET scans
  - Approved for equivocal cases

- Tau PET scans
  - Still in research

70-year old woman with cognitive decline (pre-MCI)

MRI  Plaques  Tangles

Courtesy: Sterling Johnson, PhD
Diagnostic Testing: Lumbar Puncture

- CSF Aβ1-42 (Aβ1-42:40 ratio), T-tau, P-tau Thr181 & Thr231
  - All 3 abnormal = valid for early/pro-dromal AD
  - All 3 normal = rules out AD

- Combine with imaging to ↑ accuracy in indeterminate cases
CSF Biomarkers

One type of Amyloid,
Two types of tau

CSF β-amyloid levels

CSF tau levels

Spinal Fluid Levels

Time

Healthy Memory
Mild Cognitive Impairment
Alzheimer’s disease
Summary

- Comprehensive Interprofessional Evaluation
- Extensive history from multiple sources
- Comprehensive neurocognitive testing
- Increasing use of advanced imaging and biomarkers
Treatment

- Progression
- Pharmacologic
- Non-pharmacologic
- BPSD addressed elsewhere
Alzheimer’s Progression

- FAST stages
- Behavioral Changes
FAST Stages:

1. Normal adult
2. Normal adult with mild memory changes (normal older adult)
3. MCI
4. Mild dementia
5. Moderate dementia
6. Moderately-severe dementia
   - Difficulties with ADLs, continence
7. Severe dementia
   - Complete motor loss, speech loss, hospice eligible at stage 7b
Behavior: Early Changes

- ↓ tolerance for chaos
- ↑ rigidity, possessiveness, self-focus
- ↓ sense of boundaries
- Social graces maintained
  - stressful for families (different person with strangers)
- Routines increasingly important
Mid changes:

- ↓ conversational retention (1/4 words lost)
- ↑ repetition, perseveration
- ↑ anxiety
- ↑ confabulation ("filling in the gaps")
- Circadian changes/sun-downing
- No reasoning with them
- Gait becomes small/shuffling
- ↓ fine motor skills
Mid-late changes:

- Tunnel vision:
  - Cannot recognize time/space/whole object or person
- Lack of danger sense/insight
- Repetition is soothing
- Hypersensitivity of hands, mouth, genitals – agitation with cares
- Focused on immediate needs: imposing, demanding
- Agitation with inability to describe needs
Late changes:

- Fine motor skills gone
- Picks up objects; cannot use them
- Mimics body actions; cannot follow directions
- Forgets familiar people/faces
- Cannot initiate; difficulty task-switching
- Reliant on emotional response for comfort, vocal tones
- Memory of basic bodily functions ↓
- ↑ startle reflex
- ↑ bed sores, loss of ambulation, complete ADL dependence
Agitation/Aggression in dementia

- 20-40% of people with dementia
- 33% in SNFs are on anti-psychotics (GAO)
- 14% overall on anti-psychotics
- >50% are on for >1 year
Pharmacologic Therapies

- Acetylcholinesterase Inhibitors
- Memantine
- Vitamin E

- 18-48% subjective improvements in cognition
- Most experience delay in progression
- Do not delay progression from MCI to dementia
AcetylCholinesterase Inhibitors

- Donepezil (Aricept)
- Rivastigmine (Exelon – patch better)
- Galantamine (Razadyne)

- Mild dementia and beyond
  - Lewy Body dementia can sometimes respond dramatically

- Side effects ~20%
  - Nausea, vomiting, bradycardia, vivid dreams, agitation
Memantine

- NMDA receptor antagonist
- FDA approved for moderate to severe dementia
- No evidence for use in mild dementia
- Adjunct with acetylcholinesterase inhibitor?
  - No evidence of superiority
- Theoretically more calming
- No difference between XR and short acting
Vitamin E

- VA trial: double-blind RCT 613 patients 2007-2012
  - Vitamin E 2000 IU daily, Memantine 20 mg daily, placebo

- Mild-moderate dementia, slower functional decline compared to other groups
  - Delay 19%, ~6 months compared to placebo

- Decreased caregiver burden compared to other groups

- Memantine and memantine + Vitamin E equivalent

- Side effect: increased bleeding, ?CV events (miniscule)
Exercise!

- Physical inactivity RF for cognitive decline
- ↑ BDNF and IGF1 pathways in brain
- ↑ Neurogenesis, especially in dentate gyrus, vasculature
- Can ↓ hippocampal loss in high-risk older people (APOE-4)

Front Hum Neurosci. 2016; 10: 626
Exercise During Dementia

- Am J Geriatric Psychiatry 2015:
  - Metanalysis 18 trials
  - Exercise benefit >> memory meds

- Aging Res Rev 2016:
  - Exercise improved cognition (SMD 0.42)
  - Aerobic better, high & low intensity both work
Treatment

- Supplements?
  - Many work great in mice!
    - Eg docosahexaenoic acid (DHA)
  - Prevogen?
    - No evidence it’s better than placebo

- Diet:
  - Mediterranean and “MIND” Diet
  - Data is on prevention, not treatment
Social Activity & Brain Games

- Cognitive stimulation for patient
- Some suggestion of improved mood, orientation, global functioning
- Decreases loneliness, improves outlook in early Alzheimer’s
- Respite for Caregiver
- Decreases depression and anxiety for both patients and caregivers
- Memory Cafés, Early Memory Loss Support Groups, Senior Centers

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3549347/
Music

- “Whole Brain Activity”
- Recognition of familiar tunes maintained across all stages of dementia
- Decreases anxiety, agitation
- Singing may increase recall of familiar people
- Effect can last hours to days after “treatment”

https://practicalneurology.com/articles/2017-june/music-and-dementia-an-overview
Caregiver Burden

- 60% report high stress levels
- Worse health: Spend 8% more per year on personal health care needs
- 18 billion hours unpaid care per year = $221 billion
- 70% have work-related difficulties because of caregiving
- Average lifetime income loss: ~150,000-$300,000
- >$33 billion in lost revenue to economy
- Can’t enjoy their relationship with loved one
Caregiver support

- Resources and Education:
  - Websites
  - Local ADRC and/or dementia specialists
- Respite
- Adult Day Centers/Senior Centers
- Automate as much as possible
- Technology (GPS trackers, Alarmed pill boxes, etc)
- Caregiver support groups
- Exercise!
Now you know...

- Memory clinic for complex cases
- Interprofessional evaluation
- Medications are few, somewhat useful
- Non-pharmacologic treatments equally important
Thanks!!

Acknowledgments

Wisconsin Alzheimer’s Institute
http://www.wai.wisc.edu/

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Wisconsin Alzheimer’s Disease Research Center (ADRC)
http://www.adrc.wisc.edu

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