Dementia & Alzheimer disease
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LEARNING OBJECTIVES

- Define dementia and how it differs from mild cognitive impairment (MCI).
- Distinguish the early symptoms of Alzheimer disease (AD) from 3 other common causes of dementia.
- Describe some simple tools that are useful for making the clinical diagnosis of dementia.
- Review medications that should be avoided in any older patient who complains of memory loss.
- Discuss drugs that are useful in managing cognition, sleep, and behavior in patients with dementia.
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Disclosures: None
Dementia: a definition

- **Dementia** is not one specific disease, but a group of thinking disorders that are severe enough to **interfere with daily function**.

- In dementia, there is a **decline in general cognitive ability**, compared to the patient’s previous level of cognitive function.

- In dementia, there are signs of **memory loss** and loss of at least one other cognitive ability (language, visuospatial, executive, etc).
Dementia: a wide range of symptoms

- Memory loss...most common early complaint
- Executive changes....poor organizational skills
- Behavioral changes....more irritability, more apathy, poor judgement, less motivation
- Language changes ......word finding problems
- Visuospatal problems ..... visual agnosia
- Physiologic changes.... sleep disturbances
- Distortion of reality....visual hallucinations
Dementia: classical phenotypes

- Alzheimer disease (AD)
- Vascular dementia (VaD)
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia (FTD)
- Parkinson disease with dementia (PDD)
- Wernicke-Korsakoff syndrome (WKS)
- Huntington disease (HD)
- Progressive supranuclear palsy (PSP)
Mild Cognitive Impairment (MCI)

- MCI = Transition state from normal aging to dementia.
- MCI patients do NOT meet criteria for dementia, even though they have cognitive complaints and memory loss on bedside tests of memory function. They usually perform their jobs and function reasonably well at home (normal IADLs).
- Amnestic MCI = Patients have memory complaints, but most bedside cognitive tests scores are normal. Many aMCI pts have pre-symptomatic AD (conversion rate = 15% per year).
- Non-amnestic MCI = Patients may c/o visuospatial problems more than memory problems (pre-DLB, for example). Others may have apathy or loss of judgement (pre-FTD, for example).

Visit #1: tools for dementia diagnosis

- Ask caregiver & pt about IADLs (balancing checkbook, driving car, preparing meals, etc).

- Assess pt’s cognitive function, using a 30-question screening test (MMSE, MoCA).

- Ask caregiver & pt about behavioral changes (12-item NPI, neuropsychiatric inventory).
Lawton & Brody IADL Scale

- Getting to places beyond walking distance (driving)
- Using the telephone
- Grocery shopping
- Preparing meals
- Doing housework
- Doing laundry
- Taking medications
- Managing money

Each item = 2 (needs no help); 1 (needs some help), or 0 (unable).

A normal IADL score is \( \geq 13/16 \) on this IADL scale.

Mini-mental State Exam (MMSE)

- Orientation to time and place: 10 pts
- Registration: 3 pts
- Attention/calculation: 5 pts
- Short-term memory: 3 pts
- Language function: 8 pts
- Visuospatial function: 1 pt

A normal MMSE score is = or >24/30 pts.

Montreal Cognitive Assessment (MoCA)

- Executive functions........................................4 pts
- Orientation to time & place.......................... 6 pts
- Attention, concentration.............................. 6 pts
- Short-term memory...................................... 5 pts
- Language function...................................... 5 pts
- Visuospatial function.................................. 4 pts

A normal MoCA score is = or >26/30 pts

Neuropsychiatric Inventory (NPI)

- Delusional ideas
- Hallucinations
- Agitation
- Depression
- Anxiety
- Elation/euphoria
- Apathy/loss of interests
- Disinhibition
- Irritability/lability
- Motor disturbance/pacing
- Nighttime behaviors
- Appetite/weight change

Visit #1: tools for dementia diagnosis

Perform the **neurological examination:**

a) Look for focal signs of stroke (VaD)

b) Look for signs of parkinsonism, such as tremor, rigidity, and bradykinesia (PDD, PSP)

c) Look for cerebellar ataxia (WKS, MSA)

d) Look for frontal gait disorders (VaD, NPH)

e) Look for signs of Huntington disease, such as chorea and a hyperkinetic gait disorder
Clinical Dementia Rating Scale (CDR)

- 0.5 = Very mild dementia (i.e. MCI)
- 1.0 = Mild dementia
- 2.0 = Moderate dementia
- 3.0 = Severe dementia

When to stop driving: What is the evidence?

- When Clinical Dementia Rating (CDR) score is 1.0 (mild dementia) or greater (level A).
- When caregiver says pt is unsafe (level B).
- When pt has had a Hx of crashes (level C).
- When MMSE score is 24 or less (level C).
- Evidence of impulsive personality (level C).

Disclosures:

1) I write reviews for MedLink Neurology about memory loss & sleep and dementia.

2) I serve (unpaid) on the editorial board for the journal *Neurology*.

3) I serve as an unpaid Consultant for the FDA (for the design of AD trials).
Visit #2: discuss labs and mimics

- R/O **subacute toxic-metabolic delirium** (renal failure, liver failure, drug interactions, thyroid dysfunction, B12 deficiency, etc).....**review lab work
- R/O **hydrocephalus, tumor, .... ** review MRI
- R/O **pseudo-dementia** ....GDS if pt is depressed.
- R/O **post-ictal confusion** ....EEG if pt had seizures.
- R/O **encephalitis or meningitis** (CNS herpes, tuberculous meningitis, cryptococcal meningitis)....LP is needed if either of these (or CJD) is suspected.
Dementia: 4 common phenotypes

- Alzheimer disease (AD)
- Vascular dementia (VaD)
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia (FTD)
Alzheimer disease: the basics

- This is the **most common type** of dementia.
- **Onset** = insidious with gradual decline over time.
- **MRI** = no signs of stroke, tumor, etc.
- **Neuro exam** = no signs of parkinsonism, stroke, chorea, ataxia, or other gait disorder.
- **Key feature** = memory loss with anterograde amnesia early on (retrograde amnesia later).

Alzheimer: early IADL/behavioral changes

- “He gets lost when driving on his usual routes”.

- “I have to finish her sentences for her...she can’t think of the right words to say”.

- “She makes mistakes with familiar recipes (she recently left baking soda out of a cake recipe...the cake never rose)”.

- “He does not recognize me as being his wife (he sometimes refuses to sleep with me at night)”.

Alzheimer disease: MRI changes

a) No dementia

b) Mild dementia with mild medial temporal atrophy (red arrows)

c) Moderate dementia

d) Severe dementia with marked temporal lobe atrophy (red arrows)
Alzheimer disease: histopathology

- Intracellular Neurofibrillary Tangles (tau)
- Extracellular Plaques (β-amyloid)
Alzheimer disease: management

- **Family support**... explain diagnosis early on & encourage pt to assign **power of attorney** to a family member (i.e. the main communicator). Encourage family to attend a **support group**.

- **Mediterranean diet** (fruits, vegetables, nuts, fish, oils).
- **Daily exercise** (walking, work-out on a bicycle, etc).

- **Rx...cholinesterase inhibitors** (donepezil, galantamine, rivastigmine) for mild, moderate and severe disease and... **NMDA inhibitor** (memantine) for moderate-severe disease.

- * **AVOID ANTICHOLINERGIC/ANTIHISTAMINE DRUGS!!** *

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Anticholinergic /antihistamine drugs to avoid in any older patient with memory complaints

- Amitriptyline
- Benztropine
- Chlorpromazine
- Diphenhydramine
- Doxepin
- Hydroxyzine
- Meclizine
- Oxybutynin
- Tolterodine
- Trihexiphenidyl

Dementia: classic clinical phenotypes

- Alzheimer disease (AD)
- Vascular dementia (VaD)
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia (FTD)
Vascular dementia: the basics

- This is **2nd most common** cause of dementia.
- **Onset = acute or subacute** (it comes with or soon after a TIA, or a stroke).
- MRI shows one or more of these findings:
  a) extensive subcortical white matter changes,
  b) a single large stroke, or
  c) multiple small strokes, such as in CADASIL.
- **VaD pts have fewer memory complaints**, more inattention, more loss of executive abilities, and slower verbal processing (vs AD pts).
65 yo W with HTN & HLD was given the Dx of VaD in 2014 (she became acutely confused when driving, and this MRI showed grade 2/4 subcortical white matter changes).

She scored 18/30 on the MMSE in 2015 in the OU Physicians office (she experienced mild improvement with donepezil).

NPI = 3/12...depression, anxiety and irritability (she responded to an SSRI).
Single infarct dementia: MRI changes

58 yo M truckdriver developed VaD after an RMCA infarct (RICA & RMCA were occluded). He had smoked 3 PPD x 30 yrs and had high LDL cholesterol levels.

IADLs = He was unable to drive, or balance his checkbook.

MMSE = 22/30….poor attention (-5), and 1 pt each was lost for recall, copying, and writing.

NPI = 4/12…depression, anxiety, irritability, and disinhibition (he responded well to an SSRI)
CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MRI changes

58 yo W former teacher had had multiple strokes in spite of Rx with ASA, anticoagulants, etc.

FHx was positive for strokes & dementia (she & two brothers tested positive for the Notch 3 gene mutation on chrom 19).

On neuro exam in 2011, she had pseudobulbar affect, mild aphasia, dementia, dysarthria, hyperreflexia, & mild right hemiparesis.
VaD: early behavioral changes

- "She doesn’t pay attention anymore” (65 yo lady with subcortical VaD).

- "He flies off the handle at every little thing” (58 yo man with single-infarct VaD).

- "She cries at the drop of a hat” (58 yo lady with CADASIL).
Vascular dementia: management

- **Family support**...explain Dx; advise POA, support grp.

- **Mediterranean diet**...fruits, veg, nuts, fish, oils, etc.

- **Daily exercise**....walking, going to the gym, PT, OT.

- **Medications**....Rx needed for BP, lipid control and stroke prevention (VaD pts need a complete stroke workup). **Cholinesterase inhibitors** are useful in some VaD cases. **SSRIs or SNRIs** (depression, PBA).
Dementia: classic clinical phenotypes

- Alzheimer disease (AD)
- Vascular dementia (VaD)
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia (FTD)
Dementia w Lewy Bodies: the basics

- This is the 3rd most common dementia.
- Onset = acute, subacute, or insidious
- Besides dementia, there must be 2 of these 4:
  a) parkinsonism (rigidity, bradykinesia, or tremor)
  b) visual hallucinations
  c) fluctuating levels of alertness
  d) REM sleep behavior disorder
- Histopathology = Lewy bodies (alpha- synuclein)

20-30% of pts with clinical DLB have pure LB pathology (left), but most show the combined findings of both DLB and AD (right).

Meeus et al, Arch Neurol 2012; 69: 1113-1118
DLB: early behavioral changes

- "He gets lost walking in his own neighborhood".

- "He talks constantly about bicycles he sees in the trees".

- "It takes him twice as long to get dressed, and he shuffles when he walks."

- "He sleeps until 11am...then he goes back to sleep at 3pm in the afternoon!"
DLB: management

- **Family support**...Explain Dx; lawyer for POA, & support group.
- **Mediterranean diet**...fruits, veggies, oils, fish, nuts, etc.
- **Daily exercise**...walking, working out at gym, daycare, etc.

- **Cholinesterase inhibitors** can help with hallucinations, nighttime behaviors, and global cognitive function.
- **Memantine** can improve global cognitive function.
- **Atypical antipsychotic agents** may be needed for delusions and troublesome visual hallucinations.
- **Levodopa** (low doses) can improve signs of parkinsonism.
- **Clonazepam or melatonin** can improve REM sleep disorder.
In DLB, the cholinergic deficiency in the basal forebrain (nucleus basalis of Meynert) is even more severe than it is in most cases of AD.

This may explain why the cognitive response of DLB patients to cholinesterase inhibitors is often more dramatic (4-5 points on the MMSE) than that seen in AD patients (only 0-2 points on the MMSE).
Dementia: classic clinical phenotypes

- Alzheimer disease (AD)
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Frontotemporal dementia: the basics

- FTD is the 2nd most common pre-senile dementia.
- Onset is typically before the age of 65.
- Histopathology: tau inclusions in neurons.
- Three major subtypes:
  a) behavioral variant FTD (bvFTD)...most common
  b) primary progressive aphasia (PPA): 2-3 subtypes
  c) atypical parkinsonism with motor neuron disease (most rare; has the shortest course)

 Behavioral variant FTD: MRI changes

This 63 yo W had had a 3 yr Hx of a presenile dementia. It began with poor judgement + poor memory (she lit a fire in the fireplace without opening the flue x 3 repetitions).

CC: Apathy. She had no interest in leaving the house.


Rx: She responded to an SSRI….She eventually went to the movies with her husband.
bv dementia/PPA: MRI changes

This 68 yo W had had a 3 yr Hx of memory loss & behavioral changes.

Hx: She collected cans, laughed inappropriately, forgot to wash and forgot to eat (she had lost 15# in the last year).

Exam: She could not name simple objects (she did not know what they were used for). She could follow only 1-step commands. She could not repeat, “no ifs, ands or buts”.

T1 MRI - horizontal view
FTD: early behavioral changes

- "She started a big fire...nearly burned down the house...She forgot & did it again!"

- "She collected cans with a grocery cart...She also forgot to wash!"

- "He gave away some of our best furniture to the Good Will without even asking me!"
bvFTD: management

- **Family support**: explain Dx; assign POA & join support group.

- **Mediterranean diet**: fruits, veggies, oils, fish, nuts, etc.

- **Daily exercise**: walking, working out at gym, daycare, etc.

- **Medications**: FTD patients often become more agitated with cholinesterase inhibitors & memantine. They respond better to certain antidepressants like SSRIs or trazodone (for treating apathy, agitation, and sleep disturbances) and to low-dose atypical antipsychotic agents (for their delusional ideas).
PPA: management

- Speech and language therapy is as important for the caregiver of the primary progressive aphasia patient as for the patient himself.

- There are two main subtypes of PPA:
  a) **Progressive non-fluent aphasia**...where pts cannot find the right words to say.
  b) **Semantic dementia**...where pts do not understand the meaning of words.

Managing sleep in dementia patients

- Daytime physical activity....prevents insomnia.
- Daytime light exposure....prevents insomnia.
- Cholinesterase inhibitors help sleep behaviors.
- Melatonin....(2-10mg/d) can improve sleep time, sleep efficiency and prevent “sun-downing” in pts with dementia. It also helps REM sleep disorder in DLB and PDD pts.
- Clonazepam....also helps REM sleep disorder.
Dementia: Learning Objectives

- Define dementia and how it differs from mild cognitive impairment (MCI).
- Distinguish the early symptoms of Alzheimer disease (AD) from 3 other common causes of dementia.
- Describe some simple tools that are useful for making the diagnosis of dementia.
- Review medications that should be avoided in any older patient who complains of memory loss.
- Discuss drugs that are useful for managing cognition, sleep, and behavior in patients with dementia.
THE END

Questions?

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