Prevalence of dementia: aging — age most significant risk factor for Alzheimer disease (AD) and dementia in general; individuals ≥85 yr of age (in whom prevalence 50%) most rapidly growing segment of population; per current estimates, number of cases of AD and related dementias may triple by 2050; in India, China, Brazil, and Indonesia, cases of age-related disorders expected to increase >2-fold; data show that incidence decreasing slightly because of decreasing incidence of vascular diseases; study — identified patients with newly diagnosed dementia enrolled in largest health maintenance organization in Seattle; significant number of patients had different types of dementia, but only small proportion had AD alone (number of patients with mixed AD plus Lewy body dementia [LBD] or plus vascular dementia equal to number with AD alone); pure LBD or vascular dementia more common in younger patients

Case: 61-yr-old man with 3.5-yr history of progressive memory impairment; has word-finding difficulty, poor concentration, difficulty following directions, and managing his finances; still “functionally” able to drive; before retiring, worked as billing specialist; had 12 yr of education; family history includes probable dementia in father; physical examination (PE) within normal limits; Mini-Mental State Examination (MMSE) score 19; partially oriented; has trouble naming parts of objects; scored 0 of 3 on delayed recall, but improved with prompting; at 4 yr — unable to read, name president, or calculate; at 5 yr — still able to travel; may reverse clothing; skips parts of lawn while mowing, and unable to start new lawnmower; experiencing some anxiety; at 6 yr — unable to roll down car windows, find utensils while eating, or speak in full sentences; subsequently, had “hallucinations” (common in late stage, but actually delusions in most cases); died after ≈9 yr

Laboratory testing: within normal limits; speaker typically includes vitamin D level (link to AD unclear, but some evidence supports link between vitamin D and cognitive impairment in Parkinson disease [PD])

Imaging: magnetic resonance imaging (MRI) better for identifying vascular disease; neuroquantitative system allows for actual measurements of volumes (eg, hippocampus; beneficial in early cases); amyloid imaging used to increase diagnostic accuracy (more important for early-onset dementia); imaging of case patient — shows hippocampal atrophy; fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrates hypoperfusion of posterior parietal and posterior temporal regions, with slight frontal sparing of motor strip, and hypoperfusion of posterior cingulate

Other findings: on autopsy, some loss of brain weight noted; immunostaining showed dramatic frontocortical amyloid deposition and significant tau antibody staining; neuritic plaques (confirmed positive for amyloid) and neurofibrillary tangles present; diagnosis AD

Alzheimer Disease

Presentation: short-term memory loss most common presenting symptom; immediate memory also affected; language variants (eg, logopenic [difficulty repeating or retrieving word]) and visual variants (eg, inability to find objects in visual field) also seen; other symptoms — executive dysfunction; apathy; reactive irritability; psychosis early in disease suggests LBD; most patients with dementia have delusions late in disease

Bedside testing: MMSE — standard for many years (now considered costly); widely understood; tests broad spectrum of neuropsychological functions but provides insufficient testing of short-term memory (STM); Mini-Cog — 3-item test (immediate recall, clock drawing, and delayed recall); sensitivity and specificity similar to those of MMSE for detecting cognitive impairment; brief format lacks detail for non-AD dementias; Montreal Cognitive Assessment (MoCA) — free; available in multiple languages; compared with other tests, includes more executive testing and more difficult STM task; other testing — proverb interpretation; computer-assisted programs acceptable if used consistently and validated

Interpretation: clock drawing — several scoring schemes available; MoCA — speaker looks for pattern rather than score; for AD, look for delayed recall not significantly helped by category assists or hints; more variability and less benefit from hints observed in patients with AD; later in disease, disorientation common, so testing of orientation helpful; visuospatial and clock construction problems common; proverb interpretation more helpful for frontotemporal dementia (FTD); patients with LBD and PD dementia (PDD) have difficulty with executive functioning and visuospatial skills but perform well on delayed recall; letter fluency associated with frontal pathways, while animal fluency associated with temporal pathways; poor performance on animal fluency suggests medial temporal or temporal lobe disorder (eg, AD), while poor performance on letter fluency more suggestive of PD or LBD
Detailed neuropsychological testing: most useful in early stages and for atypical cases

**Speaker’s protocol:** genetic testing not ordered unless indicated by family history; apolipoprotein E (risk factor) unquestionably beneficial; presenilin-1 and amyloid precursor protein testing in patients with young-onset dementia and strong family history; blood testing typical starting point; neuropsychological testing in early stage of disease; brain imaging (magnetic resonance imaging [MRI] with volumetrics); if dementia strongly suspected, biomarkers may be obtained to strengthen diagnosis of AD (through examination of cerebrospinal fluid [CSF] for β-amyloid [Aβ] and phospho-tau [P-tau], or amyloid imaging)

**Interpretation of CSF:** Aβ low (because amyloid proteins incorporated into plaques in brain) and tau (specifically P-tau) usually high in AD; extremely high tau levels seen in prion disease and Creutzfeldt-Jakob disease; tau and Aβ levels normal in FTD; in LBD and PDD, Aβ low and P-tau levels normal or low; in AD, Aβ level should be < 400 pg/mL, with concomitant increase in P-tau (≥ 60 pg/mL); polystyrene tubes not recommended because polystyrene binds amyloid, resulting in artificially low amyloid level

**Interpretation of FDG-PET:** parietal and posterior cingulate hypometabolism classic findings in AD

**Indications for biomarker testing:** not recommended for normal individuals because of poor predictive value, but useful in patients with mild cognitive impairment (MCI); in patients with MCI who have abnormality on testing or imaging, likelihood of dementia in 5 yr = 80% (if normal, likelihood = 20%)

**Frontotemporal Dementia**

Case: 62-yr-old homemaker, with 8th-grade education had 2-yr history of personality changes and “memory loss”; no longer performed housework (apathy) and purchased items she did not need; eating more; laughed inappropriately at times; made statements that “people trying to dupe her”; PE — flat affect and poor awareness of cognitive changes; slow deliberate gait; cognitive testing — oriented; recalled names of presidents; and poor awareness of cognitive changes; slow deliberate gait; complained of feeling tired and hungry; required prompting; memory deficit noted on MMSE; at 4 yr — incontinent; screaming suddenly; showed delayed recall of 3 of 4 items at 5 min; died after 14 yr of symptoms

**Imaging:** often most important testing for FTD; often shows more atrophy than expected; look for asymmetry; **FDG-PET** — typical findings frontal hypometabolism and relatively preserved parietal or posterior cingulate metabolism

**Signs and symptoms:** in early stage, executive dysfunction and behavioral changes; minimal memory loss; apathy and poor insight; cortical dysfunction, particularly involving language; behavioral disturbances (speaker prescribes antipsychotic agent [eg, quetiapine] if unmanageable); cholinesterase inhibitors may activate behavioral disturbances, but may be beneficial for patients with language variants (helps with word finding); behavioral and aphasic main variants

**Variant:** logopenic variant usually AD; nonfluent variant indicative of corticobasal pathology; semantic variant usually transactive response DNA-binding protein of 43 kDa (TDP-43)-related pathology; motor neuron disease and FTD — both linked with C9orf72 mutation; if both present, recommend genetic counseling and consider C9orf72 testing; progressive supranuclear palsy and corticobasal ganglionic degeneration (CBD) — presently considered “under FTD umbrella” because significant proportion of patients with CBD present with nonfluent aphasia

**Diagnosis:** MRI and FDG-PET useful; in temporal variant of FTD, frontal function relatively preserved, with anterior temporal degeneration (typical of semantic dementia); CSF usually normal; tau or P-tau level normal despite significant neuronal loss

**Lewy Body Dementia**

Case: 69-yr-old man with 6-yr history of progressive dementia; first symptoms “out of character” behavior and irritability; 1 yr later, started having visual hallucinations, abrupt falls, hyperomnia, fluctuations over days, and acting out of dreams; 1 yr later, unable to drive but could perform activities of daily living independently; neuropsychologic testing showed good results on MMSE, poor copying, and visuospatial dysfunction; on neurologic examination, patient had clear signs of parkinsonism but without classic resting tremor; decline notable after 8 yr, with patient eating “junk food” and having continued visual hallucinations; diagnosis LBD

**Imaging:** **FDG-PET** — classic hypometabolism in occipital region (occipital lobe hypometabolic in normal and AD patients); scan not highly sensitive (false-negative rate high); **dopamine transporter scan** (DaTscan) — abnormal (normal in AD; most often abnormal in PDD); subset of patients respond to dopaminergic therapy

**Autopsy findings:** normal brain weight (minimal cortical involvement and atrophy); depigmentation of substantia nigra; evidence of neuronal loss or “tombstones” (macrophages with pigment); staining for α-synuclein reveals LB pathology (neuronal inclusions in amygdala and hippocampus; neurites with abnormal aggregated α-synuclein; dense area of neuritic pathology in hippocampus)

**Signs and symptoms:** executive dysfunction more prominent than memory loss (processing speed affected); insight often intact, so depression common; visuospatial dysfunction; early visual hallucinations strongly correlated with LB pathology (if patient bothered by hallucinations, manage with antipsychotic medications [eg, quetiapine, pimavanserin])

**Rapid eye movement sleep behavior disorder (RBD):** strongly associated with LB pathology; “acting out of dreams” typical (requires reliable informant); refer for sleep study (concotimand sleep disorder likely); excessive daytime sleepiness common

**Distinguishing PDD from LBD:** establish motor Parkinsonism; if dementia develops > 1 yr after response to treatment for PD seen, diagnose PDD; in patients with LBD, dementia precedes or occurs within first year of onset of motor Parkinsonism; as disease progresses, patients develop dementia, hallucinations, Parkinsonism, and RBD (in both PDD and LBD); patients who present with dementia have slightly different genetic profile than those who present with motor symptoms; at autopsy, ~ 30% of patients with PDD and 60% to 70% with LBD have coexistent AD

**Imaging:** on MRI, mild atrophy seen; occipital hypoperfusion seen on FDG-PET; DaTscan helpful when positive; visual variant of AD linked to LBD

**Questions and answers:** disorders linked to LBD — possibly Charles Bonnet syndrome; visual variant of AD strongly associated; **differentiating among language variants** — usually requires biomarkers; in semantic dementia, MRI shows left temporal lobe atrophy out of proportion with that in other parts of brain; biomarkers negative in AD; AD most common missed diagnosis in language-predominant cases; **therapies** — some of newest focus on eliminating amyloid and tau; trial showed that anti-amyloid compound beneficial in patients not on any AD therapy; immunotherapies for amyloid in 2 phase III trials (both showed some effect in MCI or early AD)

**Prion Disease**

Case: 80-yr-old, right-handed man had 3-mo history of gait instability, falls, and memory loss; gait instability preceded memory and speech difficulty; progressed from “scooter in my head” to falls and need for crutches, then to walker, and finally, wheelchair; symptoms noticeably worsened from week to week; patient experienced disorientation and difficulty managing daily affairs, and had to retire from work as pharmacist; examination — MMSE score 16, with some problems performing delayed recall task; had difficulty copying design and with naming; verbal output decreased and affect flattened; wheelchair-dependent; gait markedly unsteady; vertical gaze palsy noted

**Imaging:** cortical ribboning noted on diffusion-weighted imaging; biopsy findings — hematoxylin and eosin staining revealed
spongiform change in brain; diffuse prion staining; plaques classic finding; some variants associated with diffuse synaptic staining

Clinical presentation: sporadic — rapidly progressive; can occur in different sites in brain, so presentation variable; variant — not seen in United States, except in patients who have traveled to United Kingdom; onset at young age; often presents with psychiatric disturbances and painful dysesthesias; survival longer than in sporadic prion disease; control of beef supply has led to decrease in number of cases; familial — clinical course often atypical; different presentations possible; can have longer course

Creutzfeld-Jacob disease: diffusion-weighted MRI shows focal hyperintensity; tau levels in CSF significantly elevated; amyloid levels normal; P-tau levels not elevated

Prevalence: accounts for 70% to 80% of dementias, often in combination withvascular disease; may co-occur with AD, LBD, and other disorders; associated with white-matter changes (also seen in early-onset presenilin-1 mutation AD, hyperextension, and migraine); clear cortical or subcortical infarcts; MRI criteria — hyperintensities in >25% of white matter; multiple large-vessel infarcts; ≥2 basal ganglia and white matter lacunas

Suggested Readings


Acknowledgments

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<th>Activity</th>
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<tr>
<td>Review Educational Objectives on page 1</td>
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<td>Take pretest</td>
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<td>Listen to audio program</td>
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<td>Take posttest</td>
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1. Which of the following is the most significant risk factor for dementia?
   (A) Genetics (heredity)  
   (B) Smoking  
   (C) Alcohol use  
   (D) Age **

2. Which of the following is the most common presenting symptom of Alzheimer disease?
   (A) Apathy  
   (B) Disruptive agitation  
   (C) Short-term memory loss  
   (D) Poor insight **

3. ______ levels of β-amyloid and ______ levels of phospho-tau are expected findings on analysis of cerebrospinal fluid from patients with Alzheimer dementia.
   (A) Low; low  
   (B) Low; high  
   (C) High; low  
   (D) High; high **

4. Levels of β-amyloid and tau in the cerebrospinal fluid are expected to be normal in which of the following types of dementia?
   (A) Parkinson disease  
   (B) Lewy body disease  
   (C) Creutzfeld-Jakob disease  
   (D) Frontotemporal dementia **

5. Which of the following are expected findings on neuroimaging of patients with frontotemporal dementia?
   (A) Negligible atrophy  
   (B) Asymmetry  
   (C) Parietal hypometabolism  
   (D) Posterior cingulate hypermetabolism **

6. Which of the following types of dementia is most commonly associated with the C9orf72 mutation?
   (A) Alzheimer disease  
   (B) Frontotemporal dementia  
   (C) Lewy body disease  
   (D) Parkinson disease **

7. Abnormal results on dopamine transporter scan are expected in patients with which of the following types of dementia?
   1. Alzheimer disease  
   2. Lewy body disease  
   3. Frontotemporal dementia  
   4. Parkinson disease
   (A) 1,3  
   (B) 2,4  
   (C) 1,2,3  
   (D) 2,3,4 **

8. All the following autopsy findings are typical of patients who had Lewy body dementia, EXCEPT:
   (A) Decreased brain weight  
   (B) Depigmentation of substantia nigra  
   (C) Alpha-synuclein inclusions in amygdala and hippocampus  
   (D) Evidence of neuronal loss **

9. In patients with ______, dementia precedes or occurs within first year of motor symptoms; as disease progresses, patients with ______ develop hallucinations and rapid eye movement sleep behavior disorder.
   (A) Lewy body dementia (LBD); Parkinson dementia (PD)  
   (B) PD; LBD  
   (C) LBD; PD and LBD  
   (D) PD; PD and LBD **

10. Cortical ribboning on diffusion-weighted imaging and spongiform changes on hematoxylin and eosin staining of biopsied brain tissue are characteristic of:
    (A) Alzheimer disease  
    (B) Lewy body disease  
    (C) Parkinson disease  
    (D) Prion disease **

Answers to Audio Digest Internal Medicine Volume 64, Issue 11: 1-B, 2-C, 3-A, 4-C, 5-D, 6-D, 7-A, 8-C, 9-B, 10-C