Diagnosis and Management of Dementia

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19th Annual Update in Alzheimer’s Disease and Related Dementias
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Disclosure Statement
I have no relevant financial relationships with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity

Objectives
• Review diagnostic criteria for mild cognitive impairment (MCI) and dementia
• Review diagnostic criteria for Alzheimer’s Disease (AD)
• Discuss clinical features suggesting non-AD dementia
• Discuss select cases of non-AD dementia

DSM-5 Criteria for Major Neurocognitive Disorder (Dementia)
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:
   - Learning and memory
   - Language
   - Executive Function
   - Complex attention
   - Perceptual motor function
   - Social Cognition
B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively during the context of delirium
D. The cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)


Mild-Major Neurocognitive Disorders

Mild Neurocognitive Disorder
- Evidence of modest cognitive decline from a previous higher level of performance in one or more cognitive domains
- Cognitive deficits do not interfere with independence in everyday activities
- Greater effort and compensatory strategies are needed
- Neuropsychological testing 3-2 standard deviations below norms (7th-16th percentiles)


Major Neurocognitive Disorders
- Evidence of significant cognitive decline from a previous higher level of performance in one or more cognitive domains
- Cognitive deficits do interfere with independence in everyday activities
- Requiring assistance in IADL
- Neuropsychological testing typically 2 or more standard deviations below norms (2nd percentile or below)

Neurocognitive Disorders Causes
• Alzheimer’s Disease
• Frontotemporal Dementia
• Dementia with Lewy Bodies
• Vascular Cognitive Impairment
• Mixed Dementia

Neurocognitive Disorders

Other Causes

- Traumatic brain injury (TBI)
- Chronic traumatic encephalopathy (CTE)
- Movement disorders
- Normal Pressure Hydrocephalus (NPH)
- Substance abuse
- HIV infection
- Neurosyphilis
- Prion Disease
- Post-COVID 19 neurocognitive disorders (“Long-Haul COVID”)

Neurocognitive Disorders

Reversible Causes

- Depression (“pseudo-dementia”)
- Metabolic or endocrine disorders: renal and hepatic insufficiency, hypercalcaemia, hypothyroidism etc.
- Vitamin deficiencies (B12, B1, etc.)
- Severe anemia
- Medication effects (anticholinergics, pain medications, sedatives)
- Autoimmune Encephalitis
- Others

Neurocognitive Disorders

Recommended Testing

Routine

- Metabolic panel
- Complete blood count
- Vitamin B12 level
- Thyroid function studies
- CT/MRI
- Syphilis serology

Optional

- Sedimentation rate
- Chest x-ray
- Electrocardiogram
- Urea
- Drug levels
- MRI
- Lyme serology
- 24-hour urine for heavy metal
- Electroencephalogram
- Gender-specific
- VSG/PET
- Autoimmune encephalitis panels

* Suggested by the American Academy of Neurology

Vignette I

- 75 y/o gentleman seen in September 2018 for second opinion regarding diagnosis of dementia
- Failed clock draw during routine physical in 2017
- Abnormal neuropsychological testing in 2017, diagnosed with dementia
- Independent in IADLS and ADLS
- Recently bought new smartphone, no trouble with setup
- Recently won championship at his local golf club

Vignette I

- Well controlled HTN
- Masters degree, retired in early 70s
- Remote smoking history, 1-2 alcohol beverages per day
- Father and maternal grandmother late onset AD
- Normal neurological exam
- Normal Vitamin B 12 and TSH

Brain MRI

Axial FLAIR

Coronal FLAIR
Vignette 1

• Return visit 2019
  • No change in functional status
  • No longer playing golf competitively

Vignette 1

• Return visit 2020
  • Further functional decline
  • Social isolation due to COVID-19
  • Forgetful for events, conversation
  • Struggling with electronics

Vignette 1

• Return visit 2021
  • More forgetful
  • Needs help or supervision with most IADLs
  • Difficulties with reading comprehension
  • No longer able to use smartphone
  • Can’t keep score or keep track of ball positions when playing golf
  • No longer driving
  • No behavioral manifestations

Vignette 1

Major Neurocognitive Disorder (Dementia) due to Alzheimer’s Disease

• Age of onset >65
• Family history of Alzheimer’s Disease
• Gradual functional decline
• Early, prominent decline in memory
• Neuropsychological profile with prominent amnestic deficits
• Normal neurological exam
• Atrophy of temporal lobes and hippocampus
• Absence of significant vascular disease on imaging
Probable AD Dementia
National Institute on Aging-Alzheimer’s Association, 2011

• Criteria for dementia are met:
• Insidious onset over months to years
• Clear-cut history of worsening cognition in 2 cognitive areas
• The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
  a. Amnestic presentation
  b. Non-amnestic presentation:
     - Language presentation
     - Visuospatial presentation
     - Executive dysfunction

AD Biomarkers: ATN

• Markers of amyloid accumulation (A)
• Markers of fibrillary tau (T)
• Markers of neurodegeneration (N)
• Improved diagnostic accuracy in symptomatic patients
• Prediction of cognitive decline in MCI
• Helpful in the pre-symptomatic stages (research)

The NIA-AA Research Framework

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Markers of Amyloid-Accumulation

CSF
Decrease of CSF Aβ1-42: evidence for Aβ polymerization and deposition in the brain as fibrillar plaques

Markers of Fibrillary Tau

CSF
Elevated phosphorylated-tau and total tau

Markers of Neurodegeneration

CT
Decreased basal ganglia volume

Head-to-Head Comparison of Plasma Aβ42/40 and CSF Aβ42/40 in Alzheimer’s Disease. JAMA Neurol. 2021 Sep 20;78(17):1831-1839.


No FDA approved tests for plasma Aβ42/40
• Multiple tests in clinical trials
• Currently one test commercially available in US:
  - not FDA approved or covered by insurance
  - analyzes concentration of Aβ42/40 and apolipoprotein E isoforms

Markers of Neuronal Injury or Neuro-Degeneration

**FDG-PET**
- Bilateral temporo-parietal hypometabolism

**Markers of Neuronal Injury or Neuro-Degeneration**

**Structural Imaging**
- Progressions: cortical atrophy, hippocampus, entorhinal cortex, posterior cingulate, precuneus, lateral parietal, temporal and frontal regions

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- Progressions: cortical atrophy, hippocampus, entorhinal cortex, posterior cingulate, precuneus, lateral parietal, temporal and frontal regions

**Alzheimer's Disease**

**Pharmacological Treatment**
- **Cholinesterase Inhibitors**
  - Donepezil (mild-moderate-severe AD)
  - Rivastigmine (mild-moderate AD)
  - Galantamine (mild-moderate AD)
- **NMDA receptor antagonist**
  - Memantine (Moderate-severe AD)

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**Symptom Management**
- Focus on caregiver education and non-pharmacological treatment
- Lifestyle changes
- Citalopram, other SSRIs for depression/agitation
- Trazodone for sleep
- Avoid: neuroleptics, benzodiazepines, antihistamines

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**Anti-Amyloid Therapies**
- FDA approved aducanumab (Aduhelm) under an Accelerated Approval Program in June 2021
- Monoclonal antibody directed at the N-terminus of β-amyloid peptide
- Approval based on results of 2 large phase III clinical trials: EMERGE and ENGAGE
- Both trials initially halted due to futility
- Reanalysis of EMERGE: patients on high dose aducanumab showed less cognitive decline over 18 months compared to placebo
- FDA approval controversial
- CMS decision about coverage not expected before April 2022

**Aducanumab Appropriate Use Recommendations**
- Age 50-85
- MCI or mild dementia due to AD
- MMSE 21-30 or MoCA 17-30
- Amyloid positivity (Amyloid PET or CSF)
- No other neurological disorders
- Absence of or stable cardiovascular, medical or psychiatric disease
- No or 1 area of superficial siderosis
- Absence of diffuse white matter disease

Alzheimer’s Disease
Aducanumab Appropriate Use Recommendations: Dosing and Imaging

**Dosing**
- Monthly infusions
- 1 mg/kg: dose 1 and 2
- 3 mg/kg: dose 3 and 4
- 6 mg/kg: dose 5 and 6
- 10 mg/kg: dose 7 and after

**Imaging**
- Baseline MRI within 1 year prior to treatment
- MRI at any time with new symptoms
- MRI prior to 5th dose
- MRI prior to 7th dose
- MRI prior to 12th dose

Alzheimer’s Disease
Aducanumab and ARIA

- ARIA: Amyloid related imaging abnormalities
- Clinical symptoms: mental status changes, dizziness, nausea, visual changes, headache
- ARIA-E: brain edema, hypointensities on FLAIR imaging
- ARIA-H: hemorrhage: microhemorrhages and/or superficial siderosis on MRI
- More common and more severe in APOE carriers

Alzheimer’s Disease
Aducanumab and ARIA

- 41% of trial participants with ARIA
- 26% of trial participants with symptomatic ARIA
- 6.2% of trial participants discontinued aducanumab due to ARIA
- May require interruption of treatment
- Treatment may resume after resolution of symptoms or improvement/stabilization of imaging

Causes of Dementia <Age 65
• 41% of trial participants with ARIA
• 26% of trial participants with symptomatic ARIA
• 6.2% of trial participants discontinued aducanumab due to ARIA
• May require interruption of treatment
• Treatment may resume after resolution of symptoms or improvement/stabilization of imaging

Early Onset Alzheimer’s Disease
Compared to Late Onset AD
• High percentage of non-amnestic phenotypes:
  - logopenic variant of PPA
  - posterior cortical atrophy
  - behavioral/dysexecutive variant
  - parietal syndromes (acalculia)
• Less radiographic involvement of hippocampus and temporal lobes
• Greater radiographic involvement of parietal lobe and temporoparietal junction

Causes of Dementia <Age 65
- Frontotemporal Dementia
- Huntington’s Disease
- Multiple Sclerosis
- Autoimmune Encephalopathy
- Neuropsychiatric Lupus
- Mitochondrial Disease
- Storage Disease
- Prion Disease
- Vascular

Early Onset Alzheimer’s Disease
Onset <65 years of age
• 5-6% of all Alzheimer’s Disease
• Genetic predisposition: 10% autosomal dominant familial AD (PSEN 1, PSEN 2, APP)
• Aggressive disease course with rapid progression
• Significant psychosocial needs
When to be Bashful about AD?

- Behavioral Changes
- Age <65
- Seizures/Speech Impairment
- Hallucinations
- Football/Falls
- Unusual Signs:
  - abnormal neurological exam
  - signs of movement disorder
- Length: Stepwise or rapidly progressive disease course

Vignette II

- 53 y/o man with 2 year history of behavioral changes
- Decline in social skills
- No interest in interaction with coworkers, clients
- Lack of emotional response to wife and son
- Decline in computer skills
- No apparent speech or memory problems

Vignette II

- No interest in previous hobbies
- Compulsive use of washing machine
- Decline in personal hygiene
- No change in food preferences
- No disinhibition
- No apparent speech or memory problems

Vignette II

- Mother diagnosed with dementia age 62, died in 70’s
- Sister diagnosed with frontotemporal dementia with motor neuron disease (FTD/MND), died age 57
- Sister alive age 62, mental illness with hoarding behavior
- Normal general physical and neurological exam
- Normal TSH, Vitamin B 12

Neuropsychological Testing

- RBANS
  - Visuospatial/construction: average
  - Delayed Memory: average
  - Immediate Memory: low average
  - Attention: low average
  - Language: mildly impaired

- Additional Language and Executive Function Assessment
  - Comprehension: impaired
  - Confrontational naming: borderline impaired
  - Novel problem solving skills: impaired
  - Perseverative responses
  - Impulsive test taking

Brain MRI

- Sagittal T2 FLAIR Images
- Coronal T2 FLAIR Images
FDG-PET

Behavioral Variant-FTD Diagnostic Criteria

**CLINICAL SYMPTOMS**

- A. Early behavioral disinhibition: socially inappropriate behavior, loss of manners or decorum, or impulsive, rash or careless actions
- B. Early apathy or inertia
- C. Early loss of sympathy or empathy
- D. Early perseverative, stereotyped, or compulsive/ritualistic behavior
- E. Hyperorality and dietary changes

**NEUROPSYCHIATRIC FINDINGS**

- F. Executive and/or generation deficits with relative sparing of episodic memory and visuospatial functions

If 3/6: POSSIBLE bvFTD

If >3/6 and above neuroimaging features: PROBABLE bvFTD


Frontotemporal Dementia and Related Disorders

- Behavioral Variant FTD
- Primary Progressive Agraphia
- Corticobasal Syndrome
- Progressive Supranuclear Palsy
- Motor Neuron Disease

- Nonfluent/Agrammatic Variant
- Semantic Variant
- Logopenic Variant

Vignette II

- Requires 24 hour supervision one year after diagnosis
- Nearly non-verbal
- Compulsive behaviors
- Restricted food preferences

FTD with Motor Neuron Disease

- Symptoms of bvFTD may precede, follow or coincide with symptoms of motor neuron disease (ALS)
- Mutation of C9ORF72 gene is the most common genetic mutation in familial bvFTD and ALS
- Short survival of 2-3 years


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- Increasing dysphagia and weight loss
- Tongue and global muscle atrophy with fasciculations
- Motor neuron disease confirmed on EMG
- Rapid decline over the course of several months
- Deceased within 3 years of diagnosis

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FTD Treatment

- Symptomatic and supportive treatment for patient and family
- SSRIs, trazodone
- Cholinesterase inhibitors ineffective
- Genetic Counseling

Frontotemporal Dementia and Related Disorders

Behavioral Variant
Primary Progressive Aphasia
Progressive Supranuclear Palsy
FTD/Motor Neuron Disease

- Nonfluent/Agrammatic Variant
- Semantic Variant
- (Logopenic Variant)

Primary Progressive Aphasia

<table>
<thead>
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<th>Semantic Variant</th>
<th>Nonfluent/Agrammatic Variant</th>
<th>Logopenic Variant</th>
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<tr>
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<tr>
<td>Single word comprehension</td>
<td>Object knowledge</td>
<td>“What is…”</td>
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<tr>
<td>Language speech fluency</td>
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<td>Prosody</td>
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<td>Object Knowledge</td>
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Underlying Pathology
- TDP-43 type C >80%
- Tauopathy >80%
- AD pathology >90%

Earliest Radiographic Findings/Atrophy
- Asymmetric (mostly left-sided) anterior and inferior temporal lobes
- Left inferior frontal lobe
- Insula
- Premotor cortex
- Left temporoparietal junction
- Left middle temporal gyrus
- Left angular gyrus
- Hippocampus
- Posterior cingulate
- Precuneus

Vignette III

- 67 year old retired high school science teacher with 1 year h/o increasing forgetfulness
- Prominent difficulties with numbers and calculations
- Difficulties with telling time
- Driving “without difficulties”

Vignette III

- Fluctuations in functional status
- Brief and non-threatening visual hallucinations
- Very active sleep, wife sleeps in different room

Vignette III

- Normal general exam
- Neurological exam: rigidity in both arms, bradykinesia
- Normal TSH, Vitamin B12
Brain MRI

Sagittal T2 FLAIR Images

Coronal T2 FLAIR Images

Vignette III

- Return visit one year later
- Further functional decline
- Several syncopal spells
- Persistent rigidity, bradykinesia

Essential Feature

- Dementia
  - not necessary in the early stages, but evident with progression
  - progressive cognitive decline
  - prominent deficits on tests of attention, executive function and visuospatial ability

Dementia with Lewy Bodies

Essential Feature

McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies. Fourth consensus report of the DLB consortium. Neurology 2017; 89(1)
Core Features

- Fluctuating cognition: pronounced variations in attention and alertness
- Recurrent visual hallucinations: well formed and detailed
- REM sleep behavior disorder: may precede disease onset by several years
- One or more spontaneous cardinal features of parkinsonism: “axial tendency”

Supportive Clinical Features

- Severe sensitivity to antipsychotic agents
- Postural instability
- Repeated falls
- Syncope or other transient episodes of unresponsiveness
- Severe autonomic dysfunction (constipation, orthostatic hypotension, urinary incontinence)
- Hypersomnia
- Hyposmia
- Hallucinations in nonvisual modalities
- Systematized delusions
- Apathy, anxiety, depression

Indicative Biomarkers

- Reduced dopamine transporter uptake in basal ganglia by SPECT or PET
- Abnormal (low uptake) 131I-iodine MIBG myocardial scintigraphy
- Polysomnographic confirmation of REM sleep without atonia

Supportive Biomarkers

- Relative preservation of medial temporal lobe structures on CT/MRI
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital lobe activity
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

Neuropsychological Profile

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<th>AD</th>
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<td>Visuospatial Impairment</td>
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<td>Hallucinations</td>
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<tr>
<td>Apathy</td>
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DLB vs PDD

- Dementia with Lewy Bodies: Cognitive impairment develops before or within 1 year of parkinsonian motor signs
- Parkinson’s Disease Dementia: Cognitive impairment develops in well established PD after more than 1 year
Treatment

- Avoid anticholinergic and neuroleptic drugs
- Carbidopa/levodopa: response variable
- Response to cholinesterase inhibitors more robust than in AD due to greater cholinergic deficit
- SSRIs for depression/anxiety
- Quetiapine or clozapine for psychotic symptoms (black box warning)
- Clonazepam or melatonin for REM sleep behavior disorder
- Fludrocortisone or midodrine for neurogenic hypotension

Vignette IV

- 72 y/o gentleman with sudden onset of cognitive decline
- Sudden onset of forgetfulness 10 months prior
- Difficulties with names, checkbook, appointments
- Subtle personality changes
- Sudden right-sided weakness 5 months ago

Vignette IV

- PMH: “always healthy”, no medical care in 8 years
- 50 pack year h/o smoking
- Family history of stroke in father, uncle and 2 brothers

Vignette IV

- BP 167/98
- MoCA 22/30 (delayed memory, attention, executive function)
- Mild right sided weakness, difficulties with tandem gait
- Fasting glucose 187mg/dL, total cholesterol 285 mg/dL, creatinine 1.8 mg/dL

Vascular Cognitive Impairment

- Diagnostic Criteria:
  - AHA/ASA
  - Vas-Cog Society
  - DSM 5
- Cognitive impairment that is caused by or associated with vascular factors
- Brain injury or dysfunction caused by any cerebrovascular disease or cardiovascular disease

Coronal T2 FLAIR Images
Vascular Cognitive Impairment

Clinical Features

- Stepwise progression common but not required for diagnosis
- Prominent apathy and depression
- Prominent impairment in executive function and processing speed
- Impairments in other cortical domains
- Deficits related to location of stroke(s)
- Motor deficits with weakness, spasticity, hyperreflexia
- Urinary incontinence

Radiographic Findings

- Predominant Cortical Vascular Disease
  - Large Vessel Ischemic Stroke
  - Hemorrhagic Stroke
  - Multiple Microbleeds
    - (Amyloid Angiopathy)
  - Subarachnoid Hemorrhage
- Predominant Subcortical Vascular Disease
  - Multiple Lacunar Infarcts
  - Ischemic White Matter Disease
  - Dilated Perivascular Spaces
- Hyperperfusion
  - Hippocampal Sclerosis
  - Laminar Cortical Necrosis
  - Microinfarcts
  - Microhemorrhages

Treatment

- Focus on prevention of further strokes
- Increased risk for Alzheimer’s Disease
- Both conditions may coexist
- Trial of cholinesterase inhibitor justified

Vignette V

- 62 y/o gentleman with severe ataxia and behavioral changes
- Severe insomnia for 1 year
- Balance problems for 3 months
- Personality changes with irritability for 1 month
- Cognitive decline with impairment in IADLs for 1 month

Rapidly Progressive Dementia

- Progression from normal cognition to dementia in less than 2 years BUT most progress over weeks to months
- Decline in MMSE by > 3 points/6 months
- Requires vigilance and careful evaluation
- Some causes are devastating
- Some causes are treatable

- MMSE 16/30 (0/3 recall)
- Clock draw 4/10
- Animal Fluency 1
- Severe cerebellar dysfunction with aphasia, apraxia and visuospatial dysfunction

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Rapidly Progressive Dementia

- Prion Disease: Creutzfeldt-Jakob Disease (CJD)
- Autoimmune/Paraneoplastic Encephalitis
- CNS/Systemic Infections
- Alzheimer’s Disease and other neurodegenerative diseases
- Others

Vignette V

- Rapid decline with loss of speech, cortical blindness, myoclonus
- Periods of severe agitation alternating with sedation
- Deceased 2 weeks after admission
- Sporadic CJD autopsy confirmed

Creutzfeldt-Jakob Disease

- Rare: 1/3, 000, 000
- Prion Disease
- Rapidly progressive dementia
- Rapidly progressive ataxia
- Behavioral changes
- Myoclonus
- Diagnosis based on clinical findings, MRI, EEG and CSF studies
- No treatment

Axial DWI “high B value”

Autoimmune Encephalitis

- Subacute cognitive decline <3 months
- Viral prodrome
- Autonomic dysfunction
- Neuropsychiatric Symptoms

Autoimmune Encephalitis
Clues in the History

• Seizures, new onset status epilepticus (NORSE)
• History of autoimmunity: personal or family
• History of cancer

Antibody Prevalence in Epilepsy and Encephalopathy. A Guide to predict the likelihood of neural antibody positivity. 2019 Mays
Foundation for Medical Education and Research.


Autoimmune Encephalitis

• MRI may show signal changes predominantly in the temporal lobes
• EEG may be abnormal with some “classic” findings in select disorders
• Autoimmune/paraneoplastic markers in serum and/or CSF
• Treatment may reverse or improve the symptoms
• Steroids, IVIG, plasma exchange, other immunosuppressive treatment