

## Diagnosis and Management of Dementia

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19<sup>th</sup> 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)**

American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). American Psychiatric Association, Arlington, VA 2013

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## Mild-Major Neurocognitive Disorders

### Mild Neurocognitive Disorders

- 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 **1-2 standard deviations below norms** (3<sup>rd</sup>-16<sup>th</sup> percentile)

### 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** (3<sup>rd</sup> percentile or below)

American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). American Psychiatric Association, Arlington, VA 2013

## Neurocognitive Disorders Causes

- Alzheimer's Disease
- Frontotemporal Dementia
- Dementia with Lewy Bodies
- Vascular Cognitive Impairment
- Mixed Dementia

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## 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")

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## Neurocognitive Disorders Reversible Causes

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

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## Neurocognitive Disorders Recommended Testing

<p><b>Routine</b></p> <ul style="list-style-type: none"> <li>• Metabolic panel</li> <li>• Complete blood count</li> <li>• Vitamin B12 level*</li> <li>• Thyroid function studies*</li> <li>• CT/MRI*</li> <li>• Syphilis serology</li> </ul>	<p><b>Optional</b></p> <ul style="list-style-type: none"> <li>• Sedimentation rate</li> <li>• Chest x-ray</li> <li>• Electrocardiogram</li> <li>• Urinalysis</li> <li>• Drug levels</li> <li>• HIV testing</li> <li>• Lyme serology</li> <li>• 24-urine for heavy metal</li> <li>• Electroencephalogram</li> <li>• Cerebrospinal fluid</li> <li>• PET/SPECT</li> <li>• Autoimmune encephalitis panels</li> </ul>
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\*Suggested by the American Academy of Neurology

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## 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 set-up
- Recently won championship at his local golf club

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## Vignette I

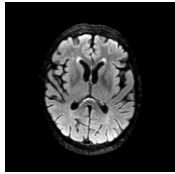
- Well controlled HTN
- Masters degree, retired in early 70s
- Remote smoking history, 1-2 alcohol beverages per day
- Father and maternal grandmother late onset AD
- Normal neurological exam
- Normal Vitamin B 12 and TSH

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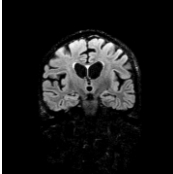
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## Brain MRI

Axial FLAIR



Coronal FLAIR



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**RBANS 2017 and 2018**

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**Vignette 1**

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

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**Vignette 1**

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

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**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

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**RBANS 2019-2021**

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**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 amnesic deficits
- Normal neurological exam
- Atrophy of temporal lobes and hippocampus
- Absence of significant vascular disease on imaging

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## 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

The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease. Mohrhan GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koschitzki WJ, Mairly J, Mayo R, Mitsch RC, Morris JC, Rossor MN, Schatzberg S, Carrillo MC, Thies B, Weintraub S, Phelps CH. Alzheimer's Dement. 2011 May;7(3):263-9. Epub 2011 Apr 21.

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## 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)

Jack CR, Bennett DA, Blennow K et al. NIA-AA research framework: towards a biological definition of Alzheimer's Disease. Alzheimer's Dement 2018;14:535-62

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## NIA-AA Research Framework

A-T-(N)-	Normal AD biomarkers
A+T-(N)-	Alzheimer's pathological change
A+T+(N)-	Alzheimer's Disease
A+T+(N)+	Alzheimer's Disease
A+T-(N)+	Alzheimer's and suspected non-Alzheimer's pathological changes
A-T+(N)-	Non-Alzheimer's pathologic change
A-T-(N)+	Non-Alzheimer's pathologic change
A-T+(N)+	Non-Alzheimer's pathologic change

Jack CR Jr, Bennett DA, Blennow K et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's Disease. Alzheimer's Dement 2018;14:535-562

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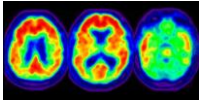
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## Markers of Amyloid-Accumulation

**CSF**

Decrease of CSF A $\beta$  1-42: evidence for A $\beta$  polymerization and deposition in the brain as fibrillar plaques

**Amyloid-PET imaging**



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## Markers of Amyloid-Accumulation

Plasma-Based Testing

- No FDA approved tests for plasma A $\beta$ -42/40
- Multiple tests in clinical trials
- Currently one test commercially available in US:
  - not FDA approved or covered by insurance
  - analyzes concentration of A $\beta$  42/40 and apolipoprotein E isoforms

Janelidze S, Tuunainen CE, Zetterberg H, Alafuzi IA, Sarasa L, Eichenlaub U, Blennow K, Ovod V, Verberk IMW, Toba K, Nakamura A, Bateman RL, Blennow K, Hansson O. Head-to-Head Comparison of 8 Plasma Amyloid  $\beta$  42/40 Assays in Alzheimer Disease. JAMA Neurol. 2021 Sep 20;62(13):180.

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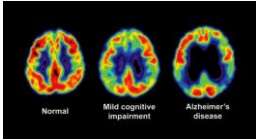
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## Markers of Fibrillary Tau

**CSF**

Elevated phosphorylated-tau and total tau

**Tau-PET Imaging**



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## Markers of Neuronal Injury or Neuro-Degeneration

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

Left Lateral

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## Markers of Neuronal Injury or Neuro-Degeneration

**Structural Imaging**  
Progressive cortical atrophy:  
**hippocampus**, entorhinal cortex but also heteromodal cortices: posterior cingulate, precuneus, lateral parietal, temporal and frontal regions

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## Alzheimer's Disease Pharmacological Treatment

<p><b>Cholinesterase Inhibitors</b></p> <ul style="list-style-type: none"> <li>• Donepezil (mild-moderate-severe AD)</li> <li>• Rivastigmine (mild-moderate AD)</li> <li>• Galantamine (mild- moderate AD)</li> </ul>	<p><b>NMDA receptor antagonist</b></p> <ul style="list-style-type: none"> <li>• Memantine (moderate-severe AD)</li> </ul>
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## Alzheimer's Disease 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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## Alzheimer's Disease Anti-Amyloid Therapies

- FDA approved aducanumab (Aduhelm) under an Accelerated Approval Program in June 2021
- Monoclonal antibody directed at the N-terminus of  $\beta$ -amyloid peptide
- Approval based on results of one 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

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## Alzheimer's Disease Aducanumab Appropriate Use Recommendations

- Age 50-85
- MCI or mild dementia due to AD
- MMSE 21-30/30 or MoCA 17-30/30
- Amyloid positivity (Amyloid PET or CSF)
- No other neurological disorders
- Absence of or stable cardiovascular, medical or psychiatric disease
- No anticoagulation; antiplatelets ok
- No macrohemorrhages
- <4 microhemorrhages
- No cortical or lacunar stroke >1.5 cm
- No or 1 area of superficial siderosis
- Absence of diffuse white matter disease

Cumingsi J, Aisen P, Apostolova LG, Afriz A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021;8(4):398-410.

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## Alzheimer's Disease

### Aducanumab Appropriate Use Recommendations: Dosing and Imaging

**Dosing**


- Monthly infusions
- 1mg/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 5<sup>th</sup> dose
- MRI prior to 7<sup>th</sup> dose
- MRI prior to 12<sup>th</sup> dose

Cummings J, Aisan P, Apostolova IG, ARI A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021;8(4):398-410.

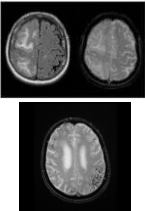
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## Alzheimer's Disease

### Aducanumab and ARIA

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



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## 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

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## Causes of Dementia <Age 65

MC Causes of Dementia Ages 17-45	MC Causes of Dementia Ages 30-65
Frontotemporal Dementia	Alzheimer's Disease
Huntington's Disease	Vascular Cognitive Impairment
Multiple Sclerosis	Frontotemporal Dementia
Autoimmune Encephalopathy	Alcohol Related Dementia
Neuropsychiatric Lupus	Dementia with Lewy Bodies
Mitochondrial Disease	Huntington's Disease
Storage Disease	Multiple Sclerosis
Prion Disease	Dementia due to Down Syndrome
Vasculitis	CBD/Prion Disease/Parkinson Dementia

• Galley, Boone, Josephs, 2008. Kelley B.J., Boone B.F., and Josephs K.A. Young-onset dementia: demographic and etiologic characteristics of 235 patients. Arch. Neurol. 2008; 65: pp. 1500-1508  
 • Pineda S, Puetzmann K, Bakker C, van der Flier WM, Pajonk JM, Koopmans R, Verhey FRJ, et al. Global Prevalence of Young-Onset Dementia: A Systematic Review and Meta-analysis. JAMA Neurol. 2021 Sep 1;78(9):1080-1090.


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## 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

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## Early Onset Alzheimer's Disease

### Compared to Late Onset AD

- High percentage of non-amnesic 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

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## 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

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## 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

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## 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

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## 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

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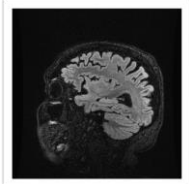
## Neuropsychological Testing

<p>RBANS</p> <ul style="list-style-type: none"> <li>• Visuospatial/construction: average</li> <li>• Delayed Memory: average</li> <li>• Immediate Memory: low average</li> <li>• Attention: low average</li> <li>• Language: mildly impaired</li> </ul>	<p>Additional Language and Executive Function Assessment</p> <ul style="list-style-type: none"> <li>• Comprehension: impaired</li> <li>• Confrontational naming: borderline impaired</li> <li>• Novel problem solving skills: impaired</li> <li>• Perseverative responses</li> <li>• Impulsive test taking</li> </ul>
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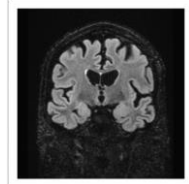
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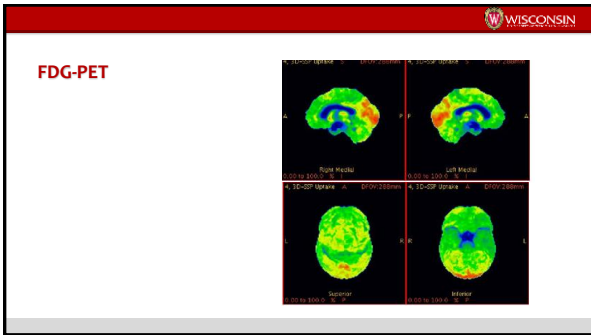
## Brain MRI

Sagittal T2 FLAIR Images



Coronal T2 FLAIR Images

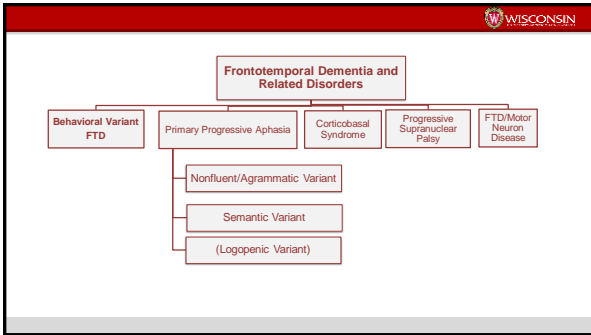




**Behavioral Variant-FTD**  
Diagnostic Criteria

CLINICAL SYMPTOMS	NEUROPSYCHIATRIC FINDINGS	NEUROIMAGING
<ul style="list-style-type: none"> <li>A. Early behavioral disinhibition: socially inappropriate behavior, loss of manners or decorum, or impulsive, rash or careless actions</li> <li>B. Early apathy or inertia</li> <li>C. Early loss of sympathy or empathy</li> <li>D. Early perseverative, stereotyped, or compulsive/ritualistic behavior</li> <li>E. Hyperorality and dietary changes</li> </ul>	<ul style="list-style-type: none"> <li>F. Executive and/or generation deficits with relative sparing of episodic memory and visuospatial functions</li> </ul>	<ul style="list-style-type: none"> <li>• Frontal and/or anterior temporal atrophy on MRI or CT, or</li> <li>• Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT</li> </ul>
	<ul style="list-style-type: none"> <li>• If 3/6: <b>POSSIBLE</b> bv FTD</li> </ul>	<ul style="list-style-type: none"> <li>• If &gt;3/6 and above neuroimaging features: <b>PROBABLE</b> bv FTD</li> </ul>

Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134(pt 9):2456-2477



**Vignette II**

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

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**Vignette II**

- 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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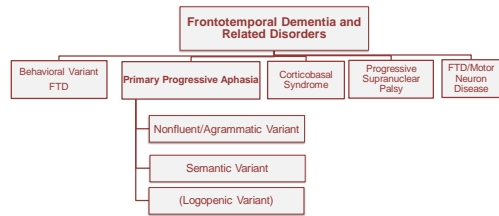
**FTD with Motor Neuron Disease**

- 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



## FTD Treatment

- Symptomatic and supportive treatment for patient and family
- SSRI's, trazodone
- Cholinesterase inhibitors ineffective
- Genetic Counseling



## Primary Progressive Aphasia

	Semantic Variant	Nonfluent/Agrammatic Variant	Logopenic Variant
<b>Impaired Language Function</b>	Single word comprehension Object Knowledge "What's..."	Agrammatic Effortful Halting	Single word retrieval in spontaneous speech Sentence repetition Phonological errors
<b>Less Impaired or Unimpaired Language Function</b>	Expressive speech Repetition Prosody	Single word comprehension Object Knowledge	Expressive speech Single word comprehension Grammar
<b>Underlying Pathology</b>	TDP-43 type C >80%	Tauopathy >80%	AD pathology >90%
<b>Earliest Radiographic Findings/Atrophy</b>	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

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## 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

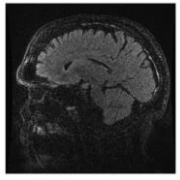
## Vignette III

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

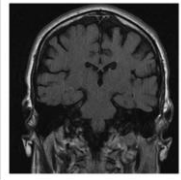
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## Brain MRI

Sagittal T2 FLAIR Images



Coronal T2 FLAIR Images



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## Vignette III

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

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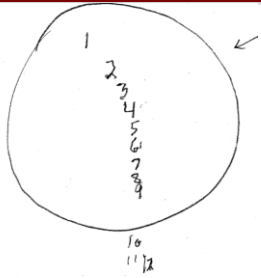
### Neuropsychology MAC Battery Summary Sheet (NCSE)

Handwritten: J.S., Education level: J.S.

AGE	SEX	EDUC	COGNITIVE STATUS PROFILE													
			MMSE	ST	AN	LANG	REP	SPR	NUM	SPAT	RES	CALE	RECOGN			
65	M	12	24	10	10	10	10	10	10	10	10	10	10	10	10	10

Date: 4/25/13 Age: 65  
 MMSE: 24/30 Clock: 4/10  
 Date: 3/11/13 Age: 63  
 MMSE: 15/30 Clock: 6/10  
 Date: \_\_\_\_\_ Age: \_\_\_\_\_  
 MMSE: \_\_\_\_\_ Clock: \_\_\_\_\_

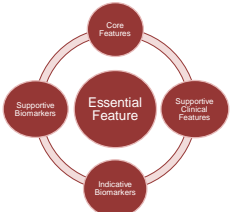
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## Dementia with Lewy Bodies



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)

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## 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

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”

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)

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## 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**

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)

## 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

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)

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## Neuropsychological Profile

	DLB/PDD	AD
Memory Impairment	++	+++
Visuospatial Impairment	+++	++
Hallucinations	+++	+
Delusions	++	++
Depression	+++	+
Apathy	+++	+

## 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
- SSRI's 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

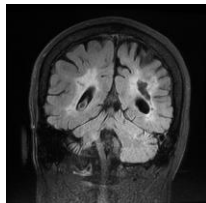
- PMH: "always healthy", no medical care in 8 years
- 50 pack year h/o smoking
- Family history of stroke in father, uncle and 2 brothers

## 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

## Brain MRI

Coronal T2 FLAIR Images




## 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

• Hochstetler V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006; 37:2220

• American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). American Psychiatric Association, Arlington, VA 2013




## 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

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## Vascular Cognitive Impairment

Radiographic Findings

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

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## Vascular Cognitive Impairment

Treatment

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


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## 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


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## Vignette V

- 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

- 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

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## Rapidly Progressive Dementia

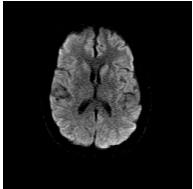
- Prion Disease: Creutzfeldt-Jakob Disease (CJD)
- Autoimmune/Paraneoplastic Encephalitis
- CNS/Systemic Infections
- Alzheimer's Disease and other neurodegenerative diseases
- Others

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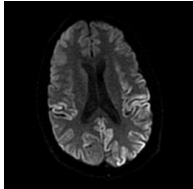
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## Vignette V

Brain MRI DWI on admission



Brain MRI DWI 6 days later



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## Vignette V

Estimated probability of prion disease in this patient: >98%

Test Name (specimen)	Result	Reference Range for Non-Prion Disease
RT-QuIC (CSF)*	Positive	negative

\*RT-QuIC identifies the disease-causing agent.

Test Name (specimen)	Result	Reference Range for Non-Prion Disease
Tau protein (CSF)**	10025 pg/ml	0-1349 pg/ml
14-3-3 protein (CSF)**	Positive	negative

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## Vignette V

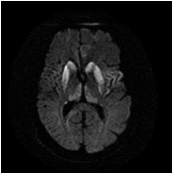
- Rapid decline with loss of speech, cortical blindness, myoclonus
- Periods of severe agitation alternating with sedation
- Deceased 2 weeks after admission
- Sporadic CJD autopsy confirmed

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## Creutzfeldt-Jakob-Disease

- Rare: 1/1,000,000
- 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"



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## Autoimmune Encephalitis

### Clues in the History

- (Sub)acute cognitive decline <3 months
- Viral prodrome
- Autonomic dysfunction
- Neuropsychiatric Symptoms

• Antibody Prevalence in Epilepsy and Encephalopathy: A Guide to predict the likelihood of neural antibody positivity. 2019 Mayo Foundation for Medical Education and Research.  
 • Graus F, Titulaer MS, Balu R et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016 Apr;15(4):391-404

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## 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 Mayo Foundation for Medical Education and Research.
- Graus F, Titulaer MS, Balu R et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016 Apr;15(4):391-404

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## 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

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