Diagnosis and Management of Dementia

Susanne Seeger, MD
Department of Neurology
University of Wisconsin
School of Medicine and Public Health

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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

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 (3rd-16th 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 (3rd 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

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, hypercalcemia, 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
- Urinalysis
- Drug levels
- HIV testing
- Lyme serology
- 24-urine for heavy metal
- Electroencephalogram
- Cerebrospinal fluid
- PET/SPECT
- Autoimmune encephalitis panels

*Suggested by the American Academy of Neurology

Vignette I

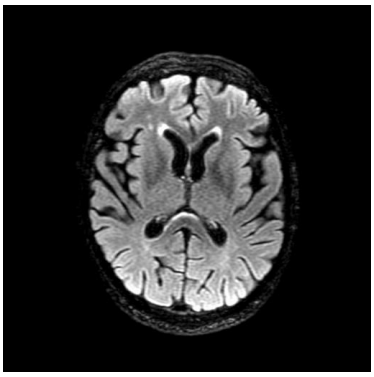
- 75 y/o gentleman seen in September 2018 for second opinion regarding diagnosis of dementia
- Failed clock draw during routine physical in 2017
- Abnormal neuropsychological testing in 2017, diagnosed with dementia
- Independent in IADLS and ADLs
- Recently bought new smartphone, no trouble with set-up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

Vignette I

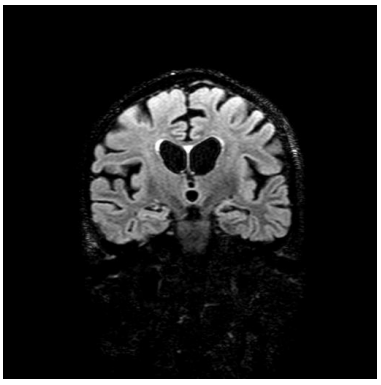
- Well controlled HTN
- Masters degree, retired in early 70s
- Remote smoking history, 1-2 alcohol beverages per day
- Father and maternal grandmother late onset AD
- Normal neurological exam
- Normal Vitamin B 12 and TSH

Brain MRI

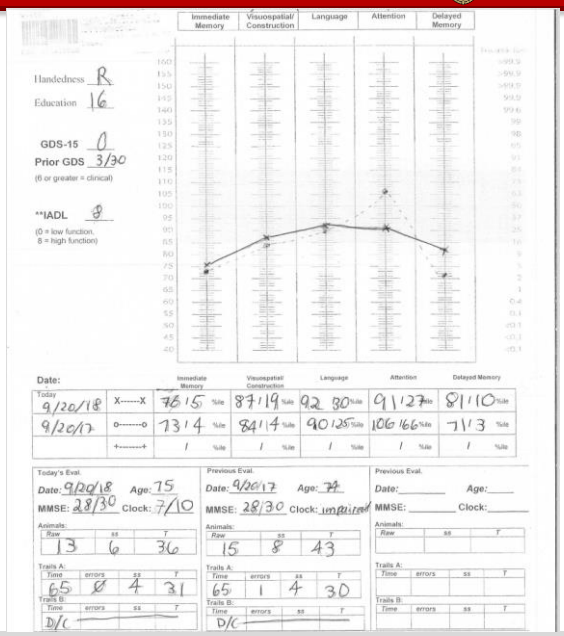
Axial FLAIR



Coronal FLAIR



RBANS 2017 and 2018



Vignette 1

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

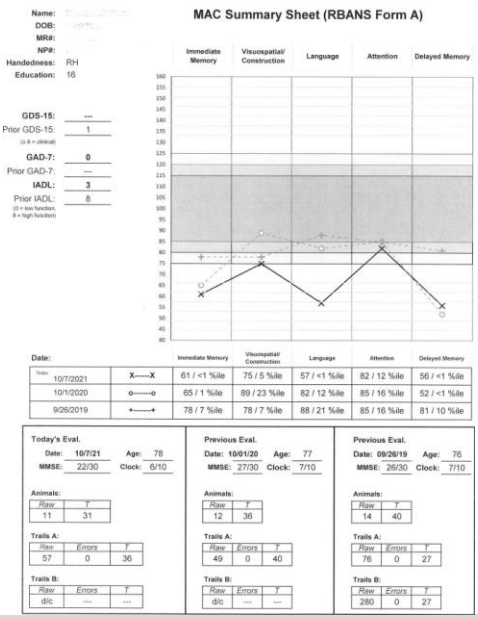
Vignette 1

- 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

RBANS 2019-2021



MAC Summary Sheet (RBANS Form A)

Name:
DOB:
MR#:
NP#:
Handedness: RH
Education: 16

GDS-15: ---
Prior GDS-15: 1
GAD-7: 0
Prior GAD-7: ---
IADL: 3
Prior IADL: 8

Immediate Memory | Visuospatial/ Construction | Language | Attention | Delayed Memory

Date:		Immediate Memory	Visuospatial/ Construction	Language	Attention	Delayed Memory
Today 10/7/2021	X------X	61 / <1 %ile	75 / 5 %ile	57 / <1 %ile	82 / 12 %ile	56 / <1 %ile
10/1/2020	o------o	65 / 1 %ile	89 / 23 %ile	82 / 12 %ile	85 / 16 %ile	52 / <1 %ile
9/26/2019	+------+	78 / 7 %ile	78 / 7 %ile	88 / 21 %ile	85 / 16 %ile	81 / 10 %ile

Today's Eval. Date: 10/7/21 Age: 78 MMSE: 22/30 Clock: 6/10

Animals:

Raw	T
11	31

Trails A:

Raw	Errors	T
57	0	36

Trails B:

Raw	Errors	T
d/c	---	---

Previous Eval. Date: 10/01/20 Age: 77 MMSE: 27/30 Clock: 7/10

Animals:

Raw	T
12	36

Trails A:

Raw	Errors	T
49	0	40

Trails B:

Raw	Errors	T
d/c	---	---

Previous Eval. Date: 09/26/19 Age: 76 MMSE: 26/30 Clock: 7/10

Animals:

Raw	T
14	40

Trails A:

Raw	Errors	T
76	0	27

Trails B:

Raw	Errors	T
280	0	27

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

The diagnosis of dementia due to Alzheimer's disease: recommendations from the **National Institute on Aging-Alzheimer's Association workgroups** on diagnostic guidelines for Alzheimer's disease. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH Alzheimer's Dement. 2011 May;7(3):263-9. Epub 2011 Apr 21.

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

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

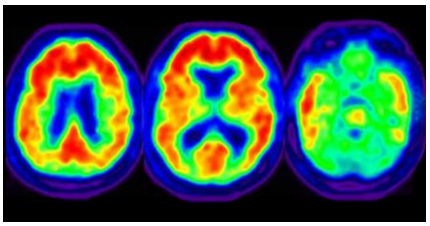
Jack CR Jr, Bennett DA, Blennow K et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's Disease. Alzheimer's Dement 2018;14:535-562

Markers of Amyloid-Accumulation

CSF

Decrease of **CSF Aβ 1-42**: evidence for Aβ polymerization and deposition in the brain as fibrillar plaques

Amyloid-PET Imaging



Markers of Amyloid-Accumulation

Plasma-Based Testing

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

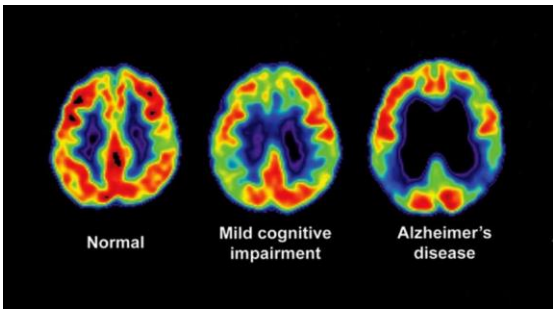
Janelidze S, Teunissen CE, Zetterberg H, Allué JA, Sarasa L, Eichenlaub U, Bittner T, Ovod V, Verberk IMW, Toba K, Nakamura A, Bateman RJ, Blennow K, Hansson O. Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease. JAMA Neurol. 2021 Sep 20:e213180.

Markers of Fibrillary Tau

CSF

Elevated phosphorylated-tau and total tau

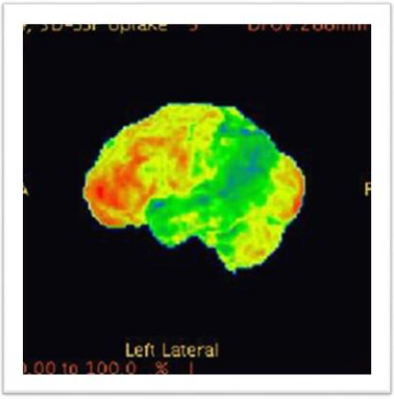
Tau-PET Imaging



Markers of Neuronal Injury or Neuro-Degeneration

FDG-PET

Bilateral temporo-parietal hypometabolism

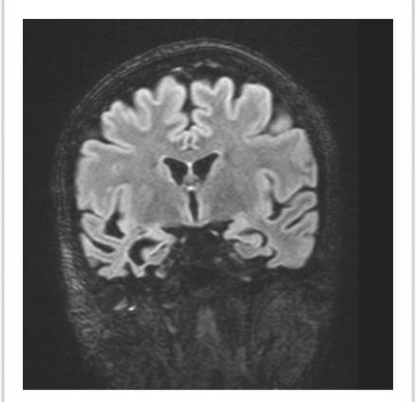


Markers of Neuronal Injury or Neuro-Degeneration

Structural Imaging

Progressive **cortical atrophy**:

hippocampus, entorhinal cortex but also heteromodal cortices: posterior cingulate, precuneus, lateral parietal, temporal and frontal regions



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)

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

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 β-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

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

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

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

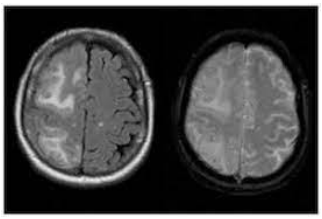
- Baseline MRI within 1 year prior to treatment
- MRI at any time with new symptoms
- MRI prior to 5th dose
- MRI prior to 7th dose
- MRI prior to 12th dose

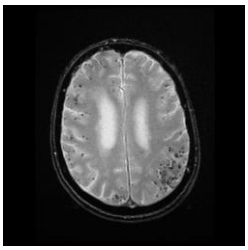
Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021;8(4):398-410.

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





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

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

- Kelley, Boeve, Josephs, 2008. Kelley B.J., Boeve B.F., and Josephs K.A.: Young-onset dementia: demographic and etiologic characteristics of 235 patients. Arch. Neurol. 2008; 65: pp. 1502-1508
- Hendriks S, Peetoom K, Bakker C, van der Flier WM, Papma JM, Koopmans R, Verhey FRJ, etal. Global Prevalence of Young-Onset Dementia: A Systematic Review and Meta-analysis. JAMA Neurol. 2021 Sep 1;78(9):1080-1090.

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

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

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

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

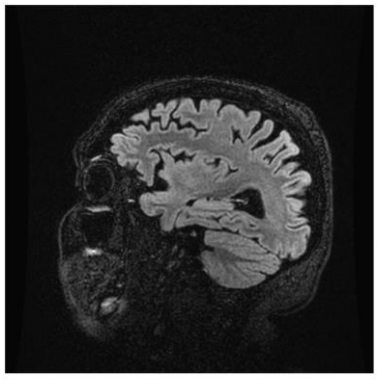
- Visuospatial/construction: average
- Delayed Memory: average
- Immediate Memory: low average
- Attention: low average
- **Language: mildly impaired**

Additional Language and Executive Function Assessment

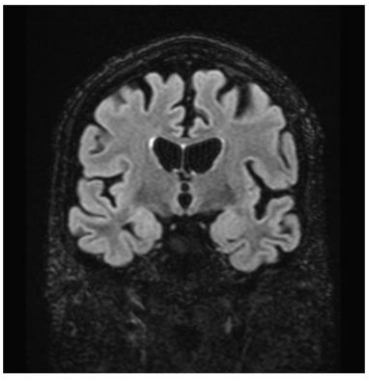
- **Comprehension: impaired**
- **Confrontational naming: borderline impaired**
- **Novel problem solving skills: impaired**
- **Perseverative responses**
- **Impulsive test taking**

Brain MRI

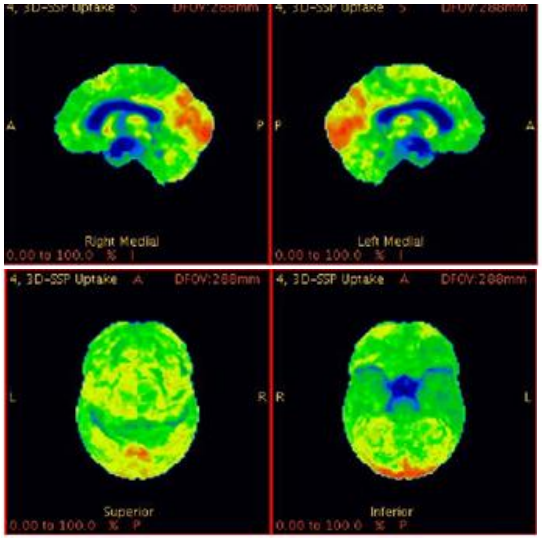
Sagittal T2 FLAIR Images



Coronal T2 FLAIR Images



FDG-PET

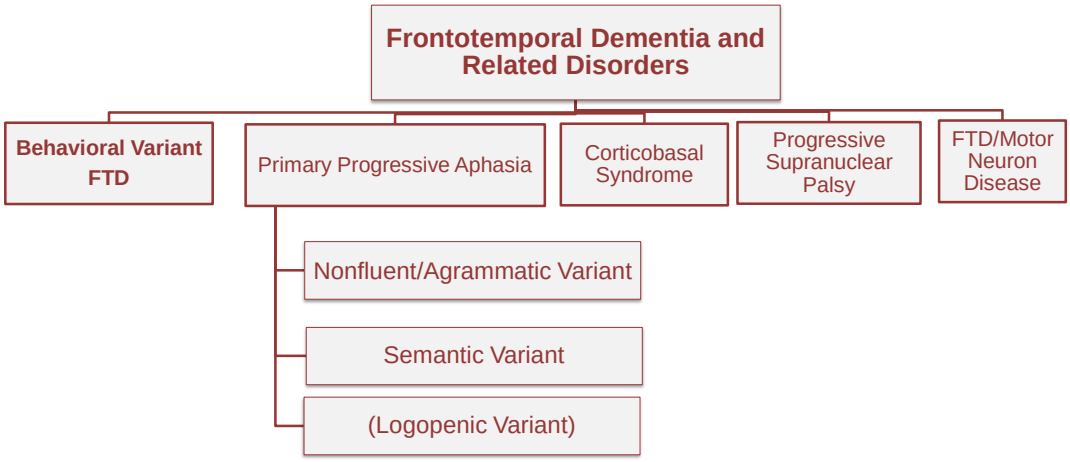


Behavioral Variant-FTD

Diagnostic Criteria

CLINICAL SYMPTOMS	NEUROPSYCHIATRIC FINDINGS	NEUROIMAGING
• 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	• F. Executive and/or generation deficits with relative sparing of episodic memory and visuospatial functions •If 3/6: **POSSIBLE bv FTD**	•Frontal and/or anterior temporal atrophy on MRI or CT, or • Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT •If >3/6 and above neuroimaging features: •**PROBABLE bv FTD**

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

Vignette II

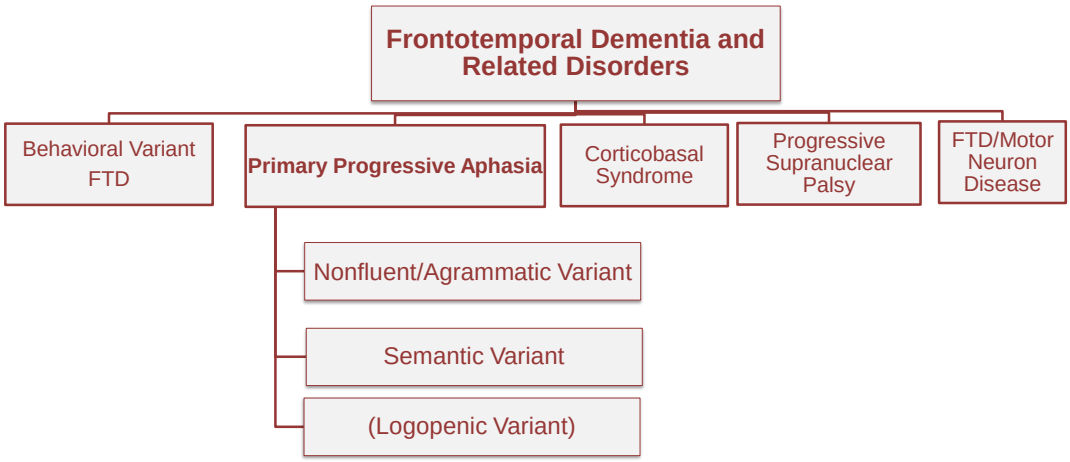
- Increasing dysphagia and weight loss
- Tongue and global muscle atrophy with fasciculations
- Motor neuron disease confirmed on EMG
- Rapid decline over the course of several months
- Deceased within 3 years of diagnosis

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
Impaired Language Function	Single word comprehension Object Knowledge "What is…"	Agrammatic Effortful Halting	Single word retrieval in spontaneous speech Sentence repetition Phonological errors
Less Impaired or Unimpaired Language Function	Expressive speech Repetition Prosody	Single word comprehension Object Knowledge	Expressive speech Single word comprehension Grammar
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

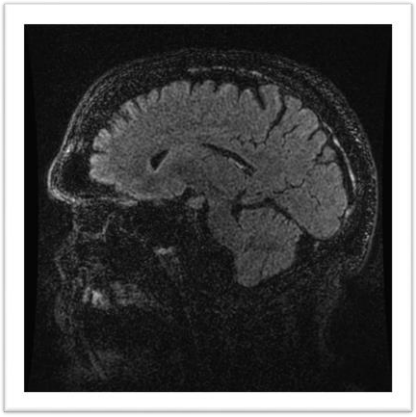
- Fluctuations in functional status
- Brief and non-threatening visual hallucinations
- Very active sleep, wife sleeps in different room

Vignette III

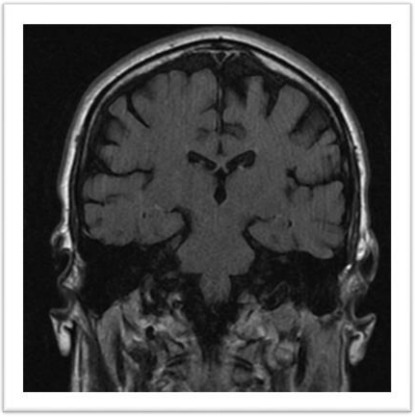
- Normal general exam
- Neurological exam: rigidity in both arms, bradykinesia
- Normal TSH, Vitamin B12

Brain MRI

Sagittal T2 FLAIR Images



Coronal T2 FLAIR Images



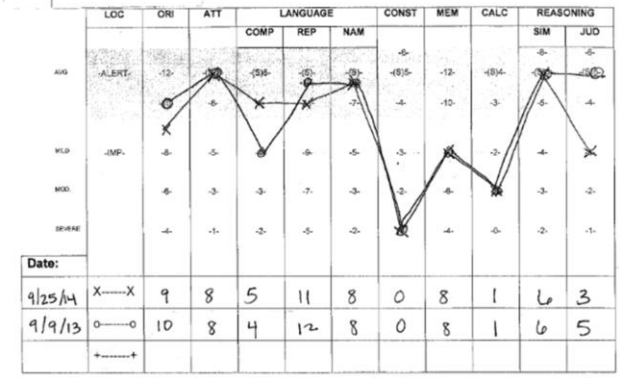
Vignette III

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

Neuropsychology MAC Battery Summary Sheet (NCSE)

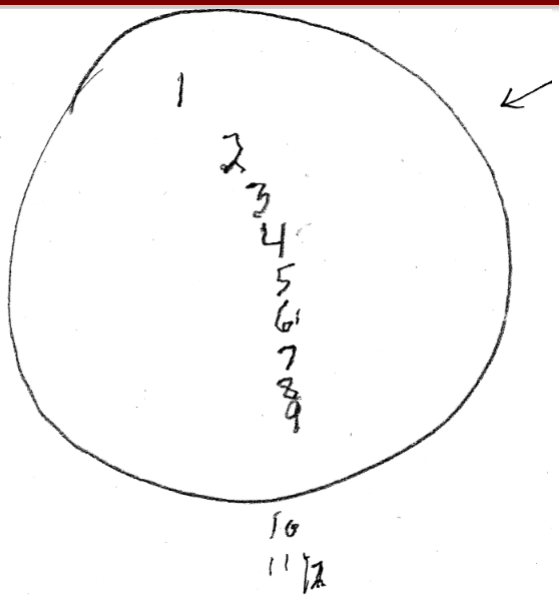
Handedness: L Education level: 18

COGNITIVE STATUS PROFILE

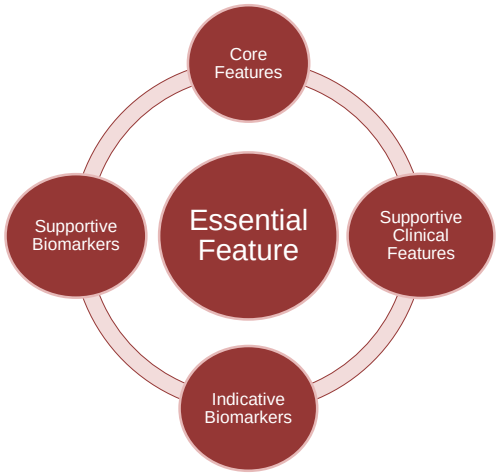


Date:											
9/25/14	X-----X	9	8	5	11	8	0	8	1	6	3
9/9/13	o-----o	10	8	4	12	8	0	8	1	6	5
	+-------+										

Date: 9/25/14 Age: 68	Date: 9/19/13 Age: 67	Date: _____ Age: ___
MMSE: 23/30 Clock: 4/10	MMSE: 23/30 Clock: 6/10	MMSE: Clock:



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)

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)

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)

Indicative Biomarkers

- Reduced dopamine transporter uptake in basal ganglia by SPECT or PET
- Abnormal (low uptake) ^{123} -iodine MIBG myocardial scintigraphy
- Polysomnographic confirmation of REM sleep without atonia

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)

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

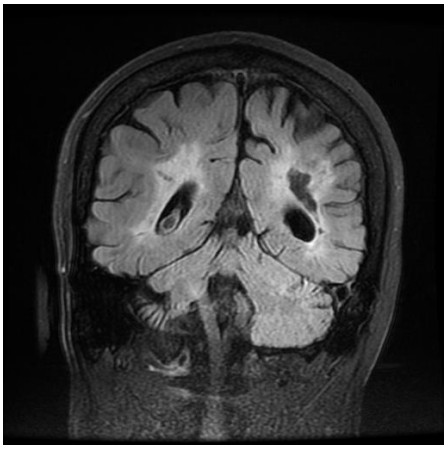
- PMH: “always healthy”, no medical care in 8 years
- 50 pack year h/o smoking
- Family history of stroke in father, uncle and 2 brothers

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

- Hachinski 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

Vascular Cognitive Impairment

Radiographic Findings

Predominant Cortical Vascular Disease	Predominant Subcortical Vascular Disease	Hypoperfusion
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	

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

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

Vignette V

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

Rapidly Progressive Dementia

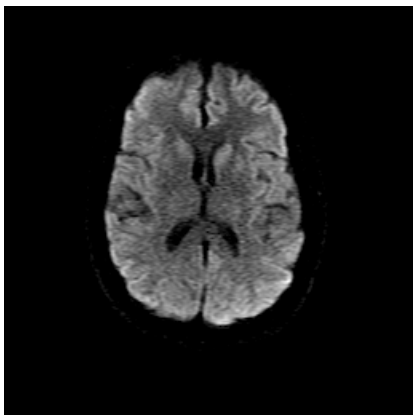
- Progression from normal cognition to dementia in less than 2 years BUT most progress over weeks to months
- Decline in MMSE by > 3 points/6 months
- Requires vigilance and careful evaluation
- Some causes are devastating
- Some causes are treatable

Rapidly Progressive Dementia

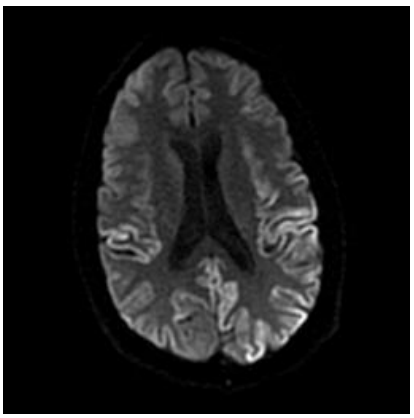
- Prion Disease: Creutzfeldt-Jakob Disease (CJD)
- Autoimmune/Paraneoplastic Encephalitis
- CNS/Systemic Infections
- Alzheimer's Disease and other neurodegenerative diseases
- Others

Vignette V

Brain MRI DWI on admission



Brain MRI DWI 6 days later



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
T-tau protein (CSF) **	10025 pg/ml	0 - 1149 pg/ml
14-3-3 protein (CSF) **	Positive	negative

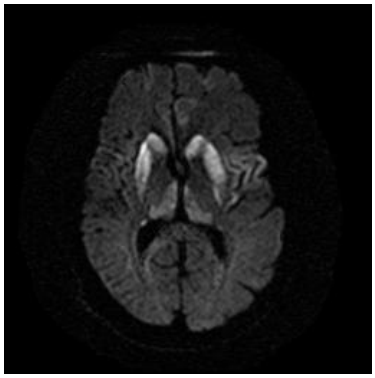
Vignette V

- 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: 1/1,000 000
- 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”



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

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

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