Diagnosis and Management of Alzheimer's Disease and Other Dementias

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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 MCI and dementia
- Review diagnostic criteria for Alzheimer's Disease (AD)
- Discuss clinical features suggesting non-AD dementia
- Disucss 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, CTE)
- Movement Disorders
- Normal Pressure Hydrocephalus (NPH)
- Substance abuse
- HIV infection
- Neurosyphilis
- Prion Disease
- Post-COVID 19 neurocognitive disorders (“Long-Haul COVID”, “Long-Tail COVID”)

Neurocognitive Disorders
Reversible Causes

- Depression (“pseudo-dementia”)
- Metabolic or endocrine disorders: hypothyroidism, uremia, hepatic insufficiency, hypercalcemia etc.
- Vitamin deficiencies (B12, B1)
- Severe anemia
- Medication effects (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

- 78 y/o woman referred for forgetfulness
- Onset of symptoms 3 years prior with increasing forgetfulness
- Independent until 6 months ago

Vignette I

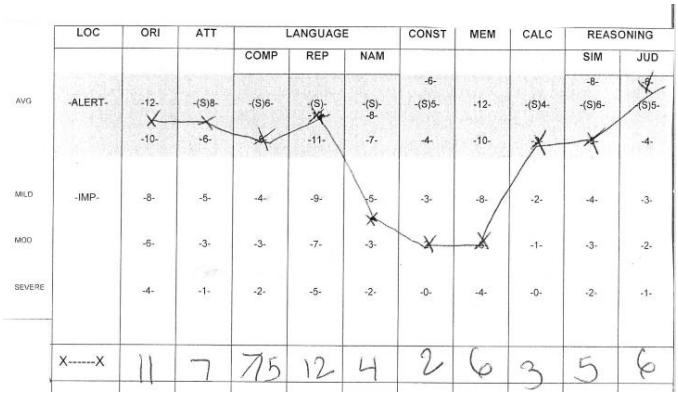
- Household in disarray
- Not managing medications or finances
- Forgetting appointments
- Resisting outside help

Vignette I

- One sister with advanced AD
- Normal general physical and neurological exam
- Normal TSH, Vitamin B12

Neuropsychological Testing

- MMSE 20/30
- Clock Draw 6/10
- Animal fluency 7 (impaired)



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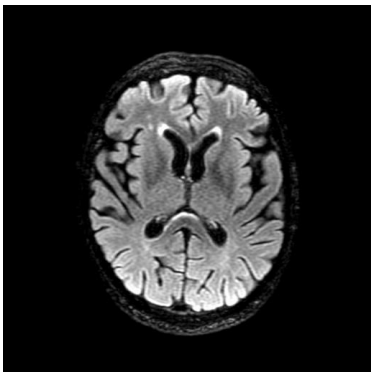
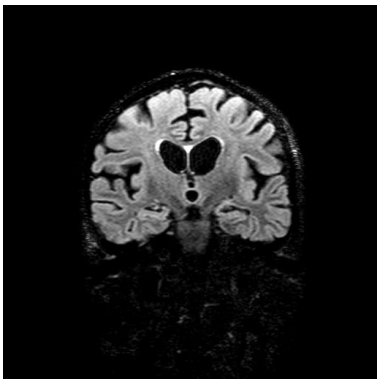
Brain MRI

Axial FLAIR



Coronal FLAIR



Vignette 1

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

- Age of onset >65
- FH of Alzheimer's Disease
- Gradual functional decline
- Early, prominent decline in memory
- Neuropsychological profile with prominent amnestic deficits
- Atrophy of temporal lobes and hippocampus
- Absence of significant vascular disease

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 Alzheimers 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)

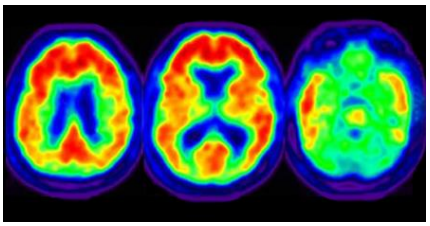
Jack CR, Bennett DA, Blennow K et al. NIA-AA research framework: towards a biological definition of Alzheimer's Disease. Alzheimers Dement 2018; 14:535-62

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

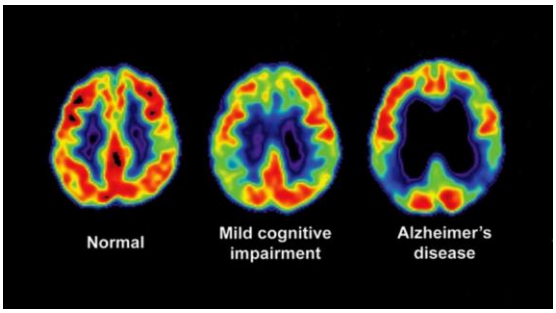


Markers of Fibrillary Tau

CSF

Elevated P- tau and total tau

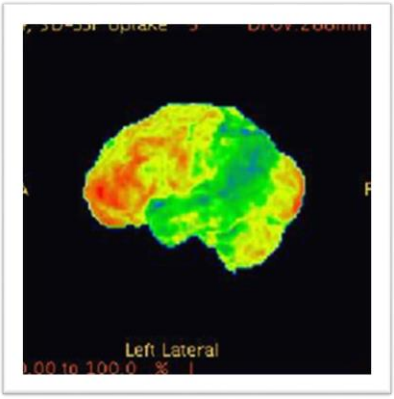
Tau-PET Imaging



Markers of Neuronal Injury or Neuro-Degeneration

FDG-PET

Bilateral temporo-parietal hypometabolism

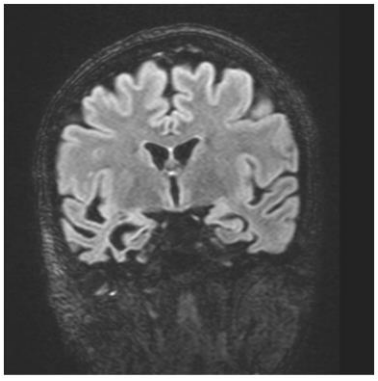


Markers of Neuronal Injury or Neuro-Degeneration

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
- Citalopram for depression/agitation
- Trazodone for sleep
- Avoid: neuroleptics, benzodiazepines, antihistamines

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

Early Onset Alzheimer's Disease

- Onset <65 years of age
- 5-6% of all Alzheimer's Disease
- Genetic predisposition: 10% autosomal dominant familial AD (PSEN1, PSEN 2, APP)
- Aggressive disease course with rapid progression

Early Onset Alzheimer's Disease

- **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
- Greater psychosocial needs

When to be **Bashful** about AD?

- Behavioral Changes: prominent and early
- Age <65
- Seizures/Speech Impairment: prominent and early
- 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 FTD/MND, died age 57 (autopsy confirmed)
- Sister alive age 62; mental illness with hoarding behavior
- Normal general physical and neurological exam
- Normal TSH, Vitamin B 12

Neuropsychological Testing

RBANS

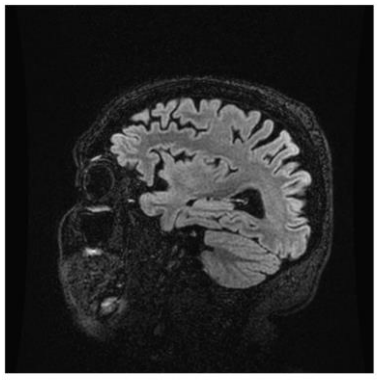
- Visuospatial/construction: average
- Delayed Memory: average
- Immediate Memory: low average
- Attention: low average
- Language: mildly impaired

Additional Language and Executive Function Assessment

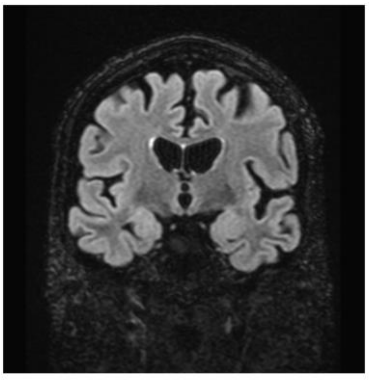
- Comprehension: impaired
- Confrontational naming: borderline impaired
- Novel problem solving skills: impaired
- Perseverative responses
- Impulsive test taking

MRI head

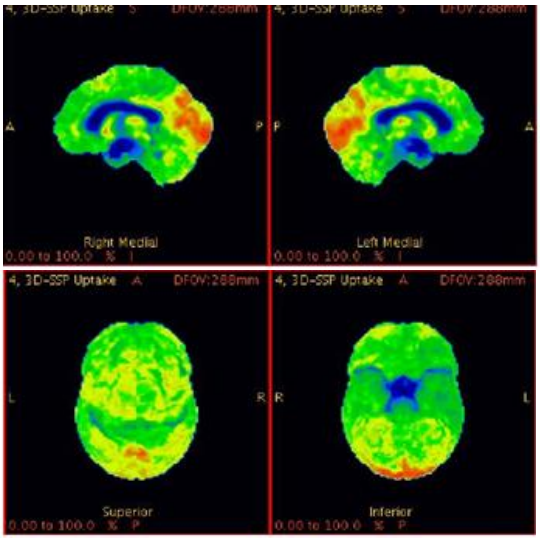
Sagittal T2 FLAIR Images



Coronal T2 FLAIR Images



FDG-PET

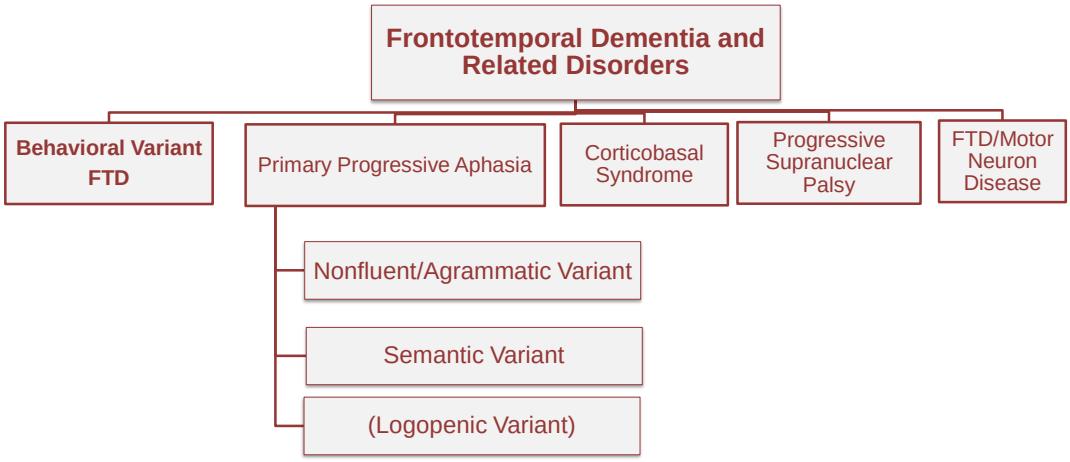


Behavioral Variant-FTD

Diagnostic Criteria

CLINICAL SYMPTOMS	NEUROPSYCHIATRIC FINDINGS	NEUROIMAGING
• A. Early behavioral disinhibition: socially inappropriate behavior, loss of manners or decorum, or impulsive, rash or careless action • 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

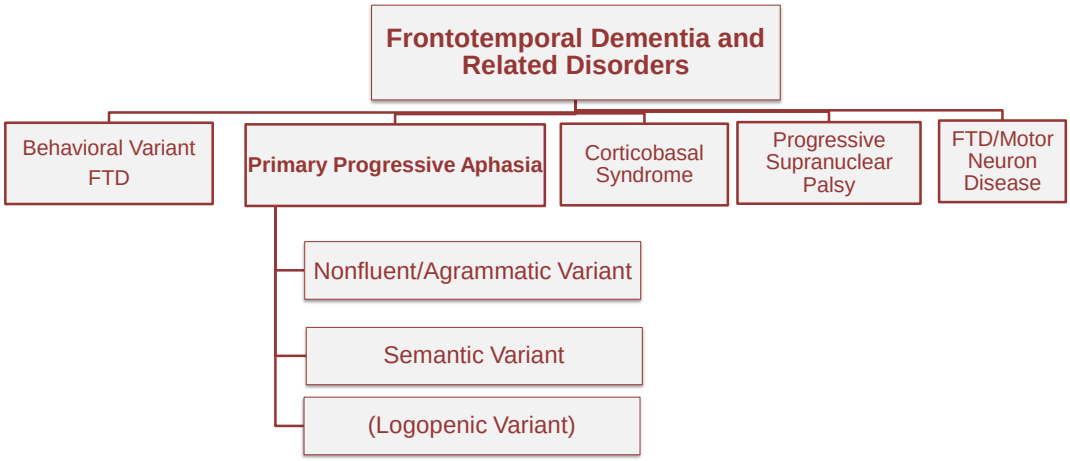
- Requires 24 hour supervision one year after diagnosis
- Nearly non-verbal
- Compulsive behaviors
- Restricted food preferences
- Increasing dysphagia and weight loss
- Tongue and global muscle atrophy with fasciculations
- Motor neuron disease confirmed on EMG
- Rapid decline over the course of several 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 Aphasias

	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 referred for 1 year h/o increasing forgetfulness
- Prominent difficulties with numbers and calculations
- Difficulties with time
- Driving “without difficulties”

Vignette III

- Fluctuations in functional status
- No behavioral changes
- 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

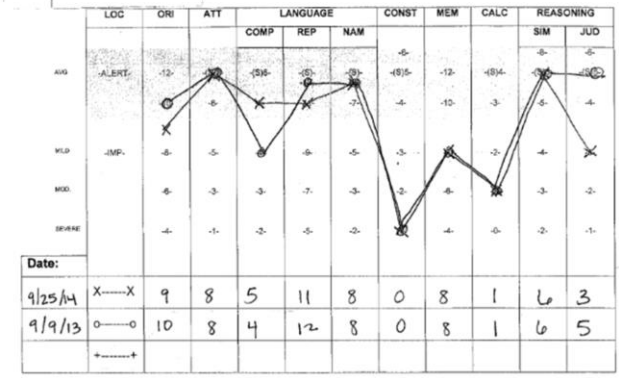
Vignette III

- 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



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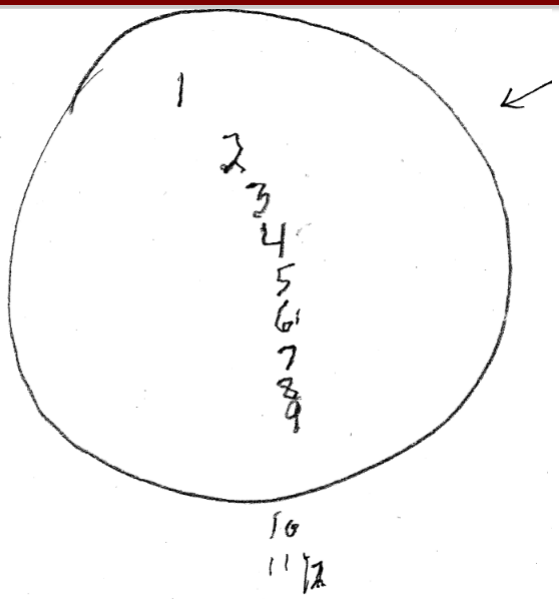
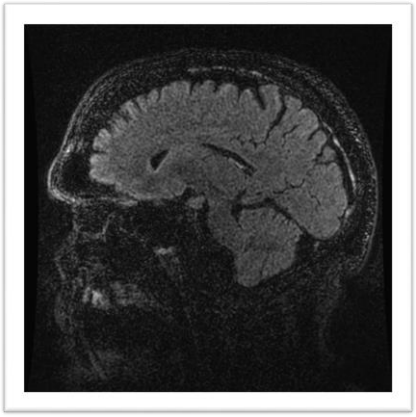
9/9/13	o-----o	10	8	4	12	8	0	8	1	6	5
	+-------+										

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:

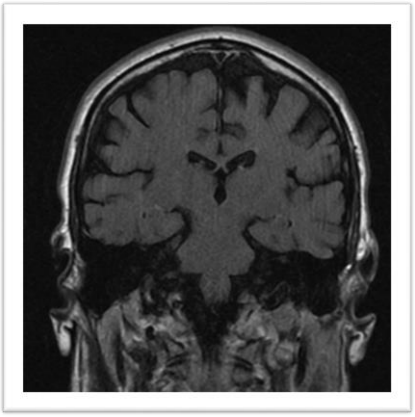


MRI head

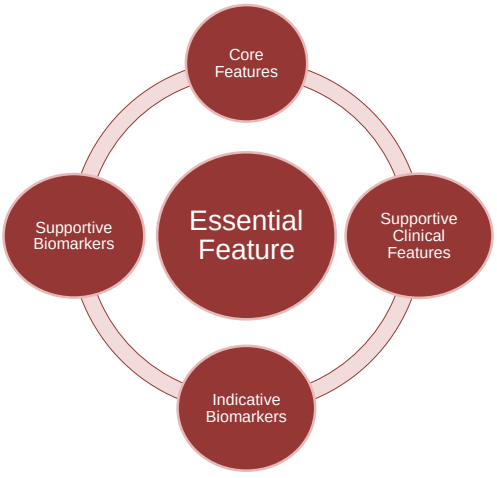
Sagittal T2 FLAIR Images



Coronal T2 FLAIR Images



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	Parkinson's Disease Dementia
Cognitive impairment develops **before or within 1 year** of parkinsonian motor signs	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 RBD
- Fludrocortisone or midodrine for neurogenic hypotension

Vignette IV

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

Vignette IV

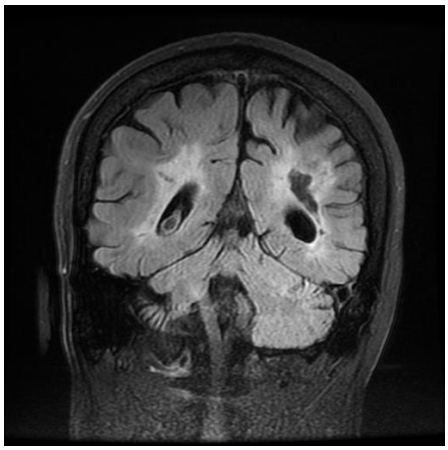
- PMH: “always healthy”, no medical care in 8 years
- 50 pack year h/o smoking
- Family history of stroke in father, uncle and 2 brothers

Vignette IV

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

MRI head

- Coronal T2FLAIR 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 is common but not required for diagnosis
- Prominent apathy and depression
- Prominent impairment in executive function and processing speed
- Involvement of other cortical domains often present
- 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
- Vascular disease increases the risk for Alzheimer's Disease
- Both conditions may coexist
- Trial of cholinesterase inhibitor may be justified

Vignette V

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

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

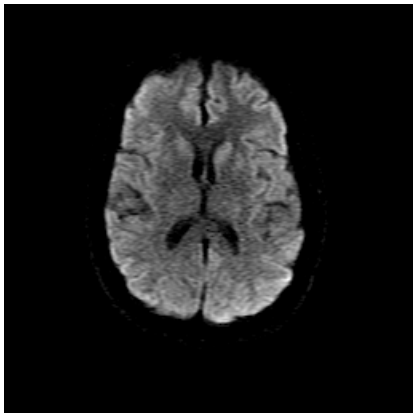
- Progression from normal cognition to dementia in less than 2 years BUT most progress over weeks to months
- Decline in MMSE by > 3 points/6 months
- Requires vigilance and careful evaluation
- Some causes are devastating
- Some causes are treatable

Rapidly Progressive Dementia

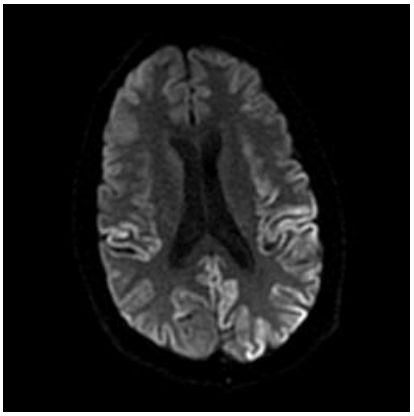
- Prion Disease: CJD
- Autoimmune/Paraneoplastic Encephalitis
- CNS/Systemic Infections
- Alzheimer's Disease and other neurodegenerative diseases
- Others

Vignette V

Brain MRI DWI



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

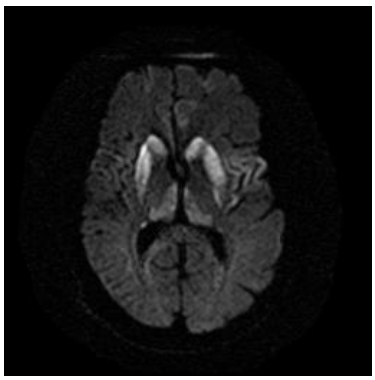
Vignette V

- 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

Creutzfeld-Jakob-Disease

- Rare: 1/1, 000 000
- Rapidly progressive dementia
- Rapidly progressive ataxia
- Behavioral changes
- Myoclonus
- Diagnosis based on clinical findings, MRI, EEG and CSF studies
- Neuropathological confirmation
- 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.

Autoimmune Encephalitis

Clues in the History

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

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