Diagnosis and Management of Alzheimer’s Disease and Other Dementias

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Diagnosis and Management of Alzheimer’s Disease and Other Dementias
Objectives

• Review diagnostic criteria for MCI and dementia
• Review diagnostic criteria for AD
• Discuss clinical features suggesting non-AD dementia
• Review select cases of non-AD dementia
Vignette I

- 78 y/o woman seen in Neurology Clinic in 2011
- “My mind is getting bad”
- Gradually increasing forgetfulness since 2008
- Living independently until fall of 2010
Vignette I

• Forgot to prepare Thanksgiving dinner
• Household in disarray
• Hoarding food
• No longer managing medications or finances
• Now requiring increasing oversight and assistance with most IADL’s and some ADL’s
• Angry and evasive when help offered
Vignette I

- DM II, HTN, dyslipidemia
- Divorced, 12 years of education, retired x 18 years, no nicotine or alcohol
- One sister with advanced AD
- Normal general physical and neurological exam
- Normal TSH, Vitamin B12
COGNISTAT
(THE NEUROBEHAVIORAL COGNITIVE STATUS EXAMINATION)

Cognitive Status Profile

<table>
<thead>
<tr>
<th>LOC</th>
<th>ORI</th>
<th>ATT</th>
<th>LANGUAGR</th>
<th>CONST</th>
<th>MEM</th>
<th>CALC</th>
<th>REASONING</th>
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<td>COMP</td>
<td>REP</td>
<td>NAM</td>
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<td>ALERT</td>
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<td>-12</td>
<td>-08</td>
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<tr>
<td>MILD</td>
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<td>MODERATE</td>
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<td>SEVERE</td>
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</tbody>
</table>

Write in lower scores:

11 4 3 11 5 4 9 3 3 5
Non-Contrast Head CT
Brain MRI

Sagittal Flair Images

Coronal Flair Images
Mild-Major NCD

**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)

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
Criteria for All-Cause Dementia
National Institute on Aging-Alzheimer's Association, 2011

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
   
a) Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

b) Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

c) Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d) Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e) Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Probable AD Dementia
National Institute on Aging-Alzheimer's Association, 2011

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

AD Biomarkers

- Markers of **amyloid accumulation**
- Markers of **neuronal injury or neuro-degeneration**
- Improve diagnostic accuracy in symptomatic patients
- May allow prediction of cognitive decline in MCI
- Helpful in the pre-symptomatic stages (research)
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 (PiB imaging)
Markers of Neuronal Injury or Neuro-Degeneration

CSF
Elevated P-tau and total tau in combination with low CSF Aβ 1-42
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
Genetic Testing in AD

• Should be offered in the context of strong family history/early onset AD
• Should be performed only after consultation with a genetic counselor
• Not recommended in the pediatric population
Genetic Testing in AD

ApoE gene

- **Susceptibility gene**
- **E₂, 3 and 4 alleles**
- **E₄ homozygous**: risk of developing AD increases 8-12 times
- **E₄ heterozygous**: risk of developing AD increases 2-3 times
- Earlier onset, greater severity
- **E₂ potentially protective**
- **40% of patients with AD do not carry ApoE gene mutations**
Genetic Testing in AD

APP, PSEN 1, PSEN 2:

- Determinative genes
- Autosomal dominant forms of AD
- APP and PSEN 1 fully penetrant
- PSEN 2 95% penetrant
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)

**Grade 2A** recommendation is a weak recommendation, and the best action may differ depending on circumstances or patient or societal values.

**Grade 2B** recommendation is a weak recommendation; alternative approaches may be better for some patients under some circumstances.
Recommended Testing in Dementia

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

**Optional**
- Sedimentation rate
- Chest x-ray
- Electrocardiogram
- Urinalysis
- Drug levels
- HIV testing
- Lyme serology
- 24-urine for heavy metal
- Electroencephalogram
- Cerebrospinal fluid
- PET/SPECT

*Suggested by the American Academy of Neurology*
Reversible Causes of Dementia

- Depression (“pseudo-dementia”)
- Metabolic or endocrine disorders: hypothyroidism, uremia, hepatic insufficiency, hypercalcemia etc.
- Vitamin deficiencies (B12, B1, B6, D)
- Severe anemia
- Medication effects (pain meds, sedatives)
- Others
Causes of Dementia

- Alzheimer's Disease (AD): 65%
- AD & Vascular: 10%
- Lewy body: 7%
- AD and Lewy body: 5%
- Vascular: 5%
- FTLD: 8%

Courtesy of Dr. Sterling Johnson
Other Causes of Dementia

- Normal Pressure Hydrocephalus
- Traumatic Brain Injury (TBI)/Chronic Traumatic Encephalopathy (CTE)
- Substance abuse
- HIV infection
- Neurosyphilis
- Prion Disease
- Parkinson’s Disease
- Huntington’s Disease
- Multiple Sclerosis
### Causes of Dementia <Age 65

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

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 RN with 3 year h/o behavioral changes and cognitive decline, seen in 2014
- 2011 medical leave due to depression and insomnia
- 2012 let go from her job due to declining work performance
- Reckless financial transactions: loss of >$15,000
- Compulsive internet shopping and financial transactions
- New hobby of jewelry making: obsessive about making and selling her work
Vignette II

- Inappropriately happy, but irritable if redirected
- Lack of insight
- Lack of interest in newborn grandchild
- “No filter”
- Change in food preference: initially limited choices, but later stealing and hoarding food
- No pertinent PMH, SH, FH
- Normal general physical and neurological exam
- Normal B12, TSH
Vignette II
Neuropsychological Testing 12/2013

• Mild impairment in language
• Normal memory and executive function
• Impulsive test taking
Vignette II
Neuropsychological Testing 3/2015

- MMSE 29/30
- Clock 10/10
- Severely impaired abstract reasoning and phonemic fluency
- Intact attention, visuospatial function/construction
- Refused testing of memory, judgment
MRI Brain 2014

- Sagittal Flair Images
- Coronal Flair Images
FDG-PET 2014
# Behavioral Variant-FTD

## Diagnostic Criteria

<table>
<thead>
<tr>
<th>CLINICAL SYMPTOMS</th>
<th>NEUROPSYCHIATRIC FINDINGS</th>
<th>NEUROIMAGING</th>
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<tbody>
<tr>
<td>A. Early behavioral disinhibition: socially inappropriate behavior, loss of manners or decorum, or impulsive, rash or careless action</td>
<td>F. Executive and/or generation deficits with relative sparing of episodic memory and visuospatial functions</td>
<td>Frontal and/or anterior temporal atrophy on MRI or CT, or</td>
</tr>
<tr>
<td>B. Early apathy or inertia</td>
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<td>Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT</td>
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<tr>
<td>C. Early loss of sympathy or empathy</td>
<td>If 3/6 (\rightarrow) POSSIBLE bv FTD</td>
<td>If &gt;3/6 and above PROBABLE bv FTD</td>
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<td>D. Early perseverative, stereotyped, or compulsive/ritualistic behavior</td>
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<td>E. Hyperorality and dietary changes</td>
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Frontotemporal Dementia and Related Disorders

- Behavioral Variant FTD
- Primary Progressive Aphasia
  - Nonfluent/Agrammatic Variant
  - Semantic Variant
    - (Logopenic Variant)
- Corticobasal Syndrome
- Progressive Supranuclear Palsy
- FTD/MND
FTD Treatment

- Trazodone up to 100 mg tid
- SSRI’s
- Cholinesterase inhibitors ineffective
- Symptomatic and supportive treatment for patient and family
- **Monitor for the development of MND or movement disorders**
- Genetic Counseling
Vignette III

• 67 year old retired high school science teacher presenting with 1 year h/o increasing forgetfulness in September 2013
• Word retrieval problems, repetitive statements and questions
• Prominent difficulties with numbers and calculations
• Difficulties with time
Vignette III

- Driving “without difficulties”
- Needs help with meds
- Otherwise independent, although some fluctuations in his function
- No behavioral changes
- Brief and non-threatening hallucinations
- Very active sleep, wife sleeps in different room
- Intermittent resting tremor
Vignette III

- No significant medical history
- Married, 18 year education, retired science teacher; remote smoking, no alcohol
- Possible Parkinson’s Disease in brother and father
Vignette III

- Normal general exam
- Neurological exam: mild resting tremor, rigidity in both arms, mild bradykinesia in both hands, normal gait
- Normal TSH, Vitamin B12
Vignette III

- Return visit September 2014
- Requiring help with meal preparation, dates and times, dressing
- Driving very rarely now
- Several syncopal spells
- Sleep improved, still some shouting and thrashing
- More prominent resting tremor
- Persistent mild rigidity, bradykinesia
Neuropsychology MAC Battery Summary Sheet (NCSE)

Handedness: L  Education level: 18

COGNITIVE STATUS PROFILE

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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:   
Brain MRI 2013

Sagittal Flair Images

Coronal Flair Images
Dementia with Lewy Bodies

Central Feature

Dementia

• progressive cognitive decline
• prominent deficits on tests of attention, executive function and visuospatial ability
Core Features

• **Fluctuating cognition**: pronounced variations in attention and alertness

• **Recurrent visual hallucinations**: well formed and detailed; present early on

• **Spontaneous motor features of parkinsonism**: “axial tendency”
Suggestive Features

- REM sleep behavior disorder
- **Severe neuroleptic sensitivity**: >50% in typical antipsychotics → severe motor, autonomic and cognitive dysfunction
- Low dopamine transporter uptake in basal nuclei (SPECT or PET): marker of neuronal loss in BG
Supportive Features

- Repeated falls and syncope
- Transient, unexplained loss of consciousness
- Severe autonomic dysfunction
- Other hallucinations/delusions
- Depression
Supportive Features

- Relative preservation of medial temporal lobe structure on CT/MRI
- Generalized low uptake on SPECT/PET with reduced occipital activity
- Abnormal myocardial scintigraphy
- Prominent slow wave activity on EEG with transient sharp waves
## Neuropsychological Findings

<table>
<thead>
<tr>
<th></th>
<th>DLB/PDD</th>
<th>AD</th>
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<tbody>
<tr>
<td>Memory Impairment</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Visuospatial Impairment</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Hallucinations</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Delusions</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Depression</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Apathy</td>
<td>+++</td>
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</table>
Neuropsychological Findings

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
- Response to levodopa variable
- Response to cholinesterase inhibitors more robust than in AD due to greater cholinergic deficit
- SSRI’s for depression/anxiety
- Clonazepam or melatonin for REM sleep behavior disorder
Vignette IV

• 72 y/o gentleman presenting with cognitive decline in 2014
• Sudden onset of forgetfulness in June 2013
• Subtle personality changes
• Difficulties with names, checkbook, appointments
• Sudden R sided weakness in December 2013, lasting 6 hours
Vignette IV

• PMH: “always healthy”, no medical care in 8 years
• Married, retired assembly worker, 12 years of education
• 50 pack year h/o smoking
• Family history of stroke in father, uncle and 2 brothers
Vignette IV

- BP 167/98
- MoCA 22/30
- Mild right sided weakness, difficulties with tandem gait
- Labs: fasting glucose 187, total cholesterol 285, creatinine 1.8, nl TSH and B 12
MRI head
Coronal T2FLAIR Images
Vascular Cognitive Impairment

- Coexistence of cognitive impairment and vascular disease
- Clinical scenario suggests that vascular disease causes the cognitive impairment
- Post-stroke vascular cognitive impairment
- Non-stroke vascular cognitive impairment
- Similar diagnostic criteria established by:
  - AHA/ASA
  - Vas-Cog Society
  - DSM 5
Vascular Cognitive Impairment

Clinical Findings

- 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
- Frontal Release Signs
# Vascular Cognitive Impairment

## Radiographic Findings

<table>
<thead>
<tr>
<th>Predominant Cortical Vascular Disease</th>
<th>Predominant Subcortical Vascular Disease</th>
<th>Hypoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Vessel Stroke</td>
<td>Multiple Lacunar Infarcts</td>
<td>Hippocampal Sclerosis</td>
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<tr>
<td>Hemorrhagic Stroke</td>
<td>Ischemic White Matter Disease</td>
<td>Laminar Cortical Necrosis</td>
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<tr>
<td>Multiple Microbleeds</td>
<td>Dilated Perivascular Spaces</td>
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<tr>
<td>Subarachnoid Hemorrhage</td>
<td>Microinfarcts</td>
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<td></td>
<td>Microhemorrhages</td>
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</tbody>
</table>
Vascular Cognitive Impairment

**CADASIL: cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy**

- Hereditary disorder with autosomal dominant inheritance
- Migraine with aura
- Early onset dementia
- Early and multiple subcortical strokes
- Prominent and confluent white matter disease
- Involvement of anterior temporal poles and external capsule

**Axial Flair Images**
Vascular Cognitive Impairment

Cerebral Amyloid Angiopathy

- Cognitive Disorder with or without stroke like episodes
- May occur in isolation or coexist with AD
- Multiple small cortical or subcortical hemorrhages
- Large lobar hemorrhages can occur
- Superficial siderosis

Axial T2* MPGR
Vignette IV

- Treatment should 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
Rapidly Progressive Dementia

- Progression from normal to dementia in less than 2 years BUT most progress over weeks to months
- Requires vigilance and careful evaluation (beyond the scope of today’s talk)
- Some causes are devastating
- Some causes are treatable
Rapidly Progressive Dementia

- Prion Disease: CJD
- Autoimmune/Paraneoplastic Encephalopathy
- Alzheimer’s Disease and other neurodegenerative diseases
- Many others
Creutzfeld-Jakob-Disease

- Rare: 1/1,000,000
- Rapidly progressive dementia
- Behavioral changes and myoclonus most common
- Phenotype depends on molecular subtype
- Diagnosis based on clinical findings, MRI, EEG and CSF studies
- Neuropathological confirmation required
- No treatment

Axial DWI “high B value”
Autoimmune Encephalitis

- Rapidly progressive dementia and/or behavioral changes
- Difficult to control seizures and other neurological signs
- Some autoimmune encephalopathies have “classic” presentations
- 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
- Maintain low level of suspicion even in the absence of a definite antibody
- Treatment may reverse or improve the symptoms
- Steroids, IVIG, plasma exchange, other immunosuppressive treatment
Autoimmune/Paraneoplastic Disorders

Brain MRI: Axial Flair Images