Memory Clinic Visit

1. History (family)
2. Physical exam
3. Cognitive testing
   - AD8
   - MOCA

• Plan
  – Differential Diagnosis
  – Further testing
    • Brain scan
    • Lab tests
    • Other testing: neuropsychology,
  – Treatment plan: medications, lifestyle recommendations
“The best diagnostic test is a careful history and physical and mental status examination by a physician with a knowledge of and interest in dementia and the dementing diseases. Such an evaluation is time consuming, but nothing can replace it.”

How do we diagnose Alzheimer’s?

• No brain scan or blood test can make the diagnosis.

• Detailed History
  – Characteristics and pattern of changes
  – Importance of informant / caregiver

• Physical Examination
How do we diagnose Alzheimer’s?

• Rule out other potential causes
  – Blood tests
    • Thyroid hormone
    • Vitamin B12
  – MRI or CT of the brain
    • Stroke, tumor, other structural problems
  – Depression
  – Medications
Clues to Differential Diagnosis

- Alzheimer's Disease
- Visual hallucinations
- Parkinsonism

- Vascular dementia
- Stroke
- Behavior/personality

- Lewy body dementia
- Frontotemporal dementias

- Hallucinations
- Parkinsonism
Alzheimer’s Disease

• Most common cause of dementia (50 – 70%)
• Marked by early memory impairment, executive dysfunction

Alzheimer’s Facts

• 5.3 million Americans have AD in 2017
• One in ten (10 percent) over 65 have AD
• Every 66 seconds someone develops AD
• $259 billion in direct and indirect costs to Medicare, Medicaid, and businesses.
What is Dementia?

1. Decline in cognition
   - Memory
   - Executive Function: Planning / Organization
   - Language
   - Orientation

2. Interferes with everyday function
Clinical Hallmarks of Dementia

- Gradual onset
- Progressive decline
- Memory loss
- Other cognitive domains impaired
- Interferes with function
Causes of Dementia

- Alzheimer’s Disease: 50 - 70%
- Dementia With Lewy Bodies: 15%
- Vascular Dementia: 10%
- Frontotemporal Dementia: 5%
- Other
“Definite Alzheimer’s Disease”

Dementia Syndrome

+ 

Plaques and Tangles
“Probable Alzheimer’s Disease”
Clinical Criteria (1984)

1. Decline in cognition – insidious and progressive
   - Memory
   - Executive Function: Planning / Organization
   - Language
   - Orientation
   - Visual and visuospatial

2. Interferes with everyday function

3. Not related to other possible causes (delirium, depression, tumor, etc)
Memory Clinic Visit

1. **History (family)**

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3. Cognitive testing (15 minutes)
   - MMSE, Logical Memory I and II, Clock drawing, Verbal Fluency, Trailmaking A and B

**Plan**

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Dementia Detection

Informant
- Trust reliable informant report of memory problem
- Dementia suggested by:
  - Decline from past level of performance (key feature)
  - Consistency of deficits
  - Interference with usual activities (key feature)

Patient
- Self-reported complaints do not reliably predict dementia
- Impaired memory performance is key feature
Importance of Early Recognition

• Treatment
• Evaluate
  – Potential reversible or contributing conditions
• Family
  – Validates concerns, explains nature of problems
  – Access to services
• Plan for future
  – Reduce risks, proactive approach to transitions
# Keys to Early Detection

<table>
<thead>
<tr>
<th>Keys</th>
<th>Mistakes / Misconceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assumptions</strong></td>
<td>Cognitive function is stable with age</td>
</tr>
<tr>
<td><strong>ADL impairment</strong></td>
<td>Decline in performance / less well than before</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Informant-based</td>
</tr>
</tbody>
</table>
Common Symptoms

**Memory Loss**
- Forgetfulness (conversations; appointments; medicines; names)
- Repetition of questions, statements
- Misplacing items

**Executive Dysfunction**
- Managing household finances
- Driving
- Meal preparation
- Operating appliances
Questions to Ask: Early Recognition

- Forgetting details of recent events
- Need help in keeping the calendar?
- Navigating in unfamiliar places
- Judgment and problem solving as good as ever? Or, still good but not as good as before?
  - Billpaying / checkbook
- Cooking / following recipes
- Fixing stuff around the house
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Clues to Differential Diagnosis

Alzheimer’s Disease

- Vascular dementia
- Lewy body dementia
- Frontotemporal dementias

+ Parkinsonism

- Hallucinations

- Behavior/personality

- Visual

- Stroke
# Key Features of Dementing Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cognition</th>
<th>Motor and Cognition</th>
<th>Personality, Early Onset</th>
<th>Vascular</th>
</tr>
</thead>
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<tr>
<td>Alzheimer’s Disease</td>
<td>Cognition (memory, organization)</td>
<td>Motor and Cognition (Parkinsonism, visual hallucinations)</td>
<td></td>
<td>Vascular (Strokes, MRI vascular changes)</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
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AD-8

• Brief informant interview
  – 8 questions
  – Several minutes
• Good to excellent discrimination of nondemented and early AD.

AD-8 Questionnaire

• Has there been a change in the last several years?
  – Problems with Judgment
  – Reduced interest in hobbies/activities
  – Repeats questions, stories, statements
  – Trouble learning how to use a tool, appliance, or gadget
  – Forgets correct month or year
  – Difficulty handling complicated financial affairs
  – Difficulty remembering appointments
  – Consistent problems with thinking and memory
MOCA

• Widely used
  – 0 – 30 pts
  – 10 minutes

• More sensitive but less specific
  – 26 and above is normal
Clock Drawing Test

• Useful in detecting mild dementia
• Insensitive in detecting the earliest clinical stages of AD.
Nondemented (CDR 0)  
Follow-up Time 0 3 years  

Very Mild Dementia (CDR 0.5)  
Follow-up Time 7 years 8 years 10 years 11 years  

Mild Dementia (CDR 1)  
Follow-up Time 11 years 12 years 14 years  

Moderate Dementia (CDR 2)  
Follow-up Time 15 years
Memory Clinic Visit

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• Plan
  – **Differential Diagnosis**
  – Further testing
    • Brain scan
    • Lab tests
    • Other testing: neuropsychology,
  – Treatment plan: medications, lifestyle recommendations
Differential Diagnosis

- Low thyroid or B12
- Medications
- Depression
- Sleep Apnea
- Medical issues
- Neurodegenerative dementias
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• Plan
  - Differential Diagnosis
  - **Further testing**
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  - Treatment plan: medications, lifestyle recommendations
Clinical Tests

Recommended

• Labs:
  – TSH, Vitamin B12
  – Electrolytes, CBC, LFTs

• Imaging: MRI or CT

Optional

• Neuropsychological testing
• Sleep apnea testing

VERY optional

• PET
• Amyloid PET
What do we learn from imaging?

• Rule things out

• Atrophy patterns
64 year old man with 4 years of behavioral and cognitive decline

Onset of behavioral changes at age 60
• Withdrew from friends, uninterested
• Drinking wine on a daily basis
• Increased interest in sex, inappropriate behavior (slapped her friends on the rear)
• Apathetic: “lounged around in his chair all day”
• Hygiene declined, not shaving or bathing.
• Language changes: loss of spontaneous speech, only short, simple answers.
Anterior Temporal and Frontal Atrophy
Frontal Hypometabolism on PET
When to Get Further Neuropsychological Testing

- Corroborates clinical impression
- Atypical dementia
  - Localize cognitive impairment
- Mild Cognitive Impairment
  - Value in longitudinal studies
Memory Clinic Visit

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• Plan
  - Differential Diagnosis
  - Further testing
    • Brain scan
    • Lab tests
    • Other testing: neuropsychology

  - Treatment plan: medications, lifestyle recommendations
Current AD Pharmacologic Therapy

• Two classes of approved medications
  – **Cholinesterase inhibitors** → increase acetylcholine levels
    • Aricept (donepezil)
    • Exelon (rivastigmine)
    • Razadyne (galantamine)
  – **NMDA antagonist**
    • Namenda (memantine)
Effect of Medications on AD Course

Initiate Medications

Namenda

Donepezil
Galantamine
Rivastigmine

Cholinesterase inhibitors
Management of Non-Cognitive Symptoms

• Cholinesterase inhibitors and memantine

• **Depression**
  – SSRI antidepressants

• **Agitation**
  – atypical neuroleptics
  – anticonvulsants
  – buspirone, trazodone

• **Hallucinations**
  – atypical neuroleptics

• **Sleep**
  – trazodone, melatonin, neuroleptics
Other Recommendations

Safety
• Driving
• Falls

Lifestyle
• Stay active mentally and physically
  – “What’s good for the heart is good for the brain”
• Mediterranean Diet Pattern
Where are we going?

• Detect AD changes early or even before the onset of symptoms

• Halt or reverse the disease process
Revised AD Criteria
McKhann et al, 2011

- Key criteria remain unchanged
- Identify intra-individual decline in cognition and function as salient clinical features
- Consider AD biomarkers to enhance confidence in clinical diagnosis
80 yo with 2 years of progressive cognitive decline

- Forgetfulness
- Geographically challenged
- Broad but mild cognitive deficits in global cognition, memory, and executive function
  - MMSE 23; LMI 5, LMII 2, Trails 220, Free recall 7,5,2
- Enrolled in clinical trial for AD
New Age of Molecular Imaging: Plaque and Tangle Imaging

Clark, C. M. et al. JAMA 2011;305:275-283

Plaques and Tangles
Diffuse Amyloid Accumulation
Severe Tau Pathology in Limbic and Neocortical Association Areas
Potential Value of Biomarkers

• Accurate and early diagnosis
• Risk assessment
• Drug Development
  – Measure of disease progression
    • Surrogate endpoints
    • Shorter trials, smaller sample size
  – “Enriched” samples
• Identification of “preclinical AD”
Financial Advisor with Cognitive Concerns

• 70 yo man with complaints of “dropping details” for the last 5 years
• FH of dementia in his mother
• Working as a successful branch manager for investment firm.
• Wife notes no memory decline, “he’s never remembered trivial stuff”, “he does too much”
  – Frequent visits to library, avid reader, attends lectures, investment club, involved in local politics
Cognitive Testing

• MMSE 30 out of 30
• Logical memory I 20 (norm 14)
• Logical memory II 22 (norm 13)
• Trailmaking B 42 (norm 79)
• SRT recall 13/13/12 (norm 9/10/11)
Amyloid PET
Relevance of Asymptomatic Amyloid

- 30% of healthy adults have brain amyloid
  - Not a diagnosis of AD
  - Not all develop AD
- Risk factor for developing AD
  - Magnitude and timing of risk not yet well-defined
    - Likely plays out over 10+ years
New Era of Prevention Trials

- Identifying Alzheimer’s changes prior to onset of symptoms may be possible
  - Window of opportunity
- Foundation for AD prevention trials
  - Exercise
    - Alzheimer’s Prevention Through Exercise (APEX)
  - Anti-amyloid strategies
    - Anti-amyloid Treatment in Asymptomatic AD
      - Solanezumab
Are We Ready for Presymptomatic Scanning?

• Not currently justified clinically
  – Clinical significance not well defined
  – May have psychological and behavioral impact
  – Effective interventions not available

• Research setting
  – Increasingly common for identifying individuals for prevention trials
  – Careful disclosure process: education and monitoring

Grill, Johnson, Burns. Neurodegen Dis Manage 2013
Biomarker Conclusions

• Biomarkers are increasingly incorporated into diagnostic algorithms to increase confidence in diagnosis.

• Field of biomarkers is rapidly evolving in response to
  – Science / clinical studies
  – Reimbursement
  – Treatment options
  – Standardization
Why Participate in Research?

• Help develop new treatment for future generations
• Regular monitoring
• Learn about Alzheimer’s
• Improve access to services, support groups, resources
KU Alzheimer’s Disease Center

Mission
To improve the lives of patients and families with Alzheimer’s disease by eliminating the disease through research into its treatment and prevention
KU AD Center

- Clinical Services: Alzheimer and Memory Clinic
  - 3 physicians, 2 nurse practitioners
- Research Program
  - 88 members with $13 million annually in federal grants
  - Innovative Programs and Projects
    - Clinical Trials Unit
      - Prestigious national trials and drug development efforts
    - Alzheimer Treatment Program
    - Alzheimer’s Prevention Program
Treatment Trials: KU ADC Clinical Trial Unit

• Anti-Amyloid
  – Solanezumab (Eli Lilly)
  – Verubecestat (Merck)
  – Aducanumab (Biogen)
  – Azeliragon (vTV)

• Neuroprotection
  – TCAD study (Toyama)
  – Bryostatin (Neurotrope)

• Metabolic Studies (KU led)
  – Metabolic approaches (Diet, Exercise, OAA, S-equol)
Prevention is our biggest hope

• Identify brain changes before symptoms
• Stop the disease process
  – Drugs – anti-amyloid therapies
    • Anti-amyloid for Asymptomatic Amyloidosis (A4) Trial
  – Lifestyle interventions
    • Alzheimer’s Prevention thru Exercise (APEX) Trial
Accessing Research Opportunities

• KU Alzheimer’s Disease Center
  – www.KUAlzheimer.org

• Matching services
  • TrialMatch (www.alz.org/trialmatch)
  • ResearchMatch
  • Pioneers (www.pioneersresearch.org)

• Alzheimer’s Disease Centers

• ClinicalTrial.gov