Identification and Diagnosis of Early Symptomatic Alzheimer’s Disease

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Categories in Cognitive Disorders Spectrum

Symptomatic Cognitive Impairment

- Cognitively Normal
- Mild Cognitive Impairment
- Dementia

• Distinctions are based on history and exam
What Should Evaluation Include?

- Competent history and neurological exam
- Bedside cognitive assessment versus neuropsychological testing
  - What is added value of neuropsychological testing?
- Standard laboratory testing as in dementia
- Standard imaging (MR, no contrast) as in dementia
What is a Sufficient Cognitive Assessment in MCI?

- Bedside exams lack precision
  - Overlap with both normal and dementia
  - Very insensitive with respect to prognosis
- Neuropsychological testing is helpful but not always available, expensive
  - Characterization of persons with MCI according to cognitive domain(s) involved and degree of abnormality adds to prediction of decline
Prognosis of MCI

- A risk state for progression to dementia
- Not all MCI progresses
- Sometimes improvement can occur
- Probability of progression is a function of:
  - Age
  - Cognitive status at time of diagnosis
  - Presence of abnormal biomarkers
Overlap of Dementia Etiologies

Case Study

- 63 year old Caucasian male accompanied by wife
- Working in family business - parts distribution company
- Holds associate degree in bookkeeping
- Referred by primary care physician for evaluation of memory loss
- Presents with history of insidious onset of cognitive difficulties that have progressed over the last two years
  - Deficits steady from day to day and within a day
- Wife says that work colleagues have started to notice and have raised concerns; deficits not obvious to people who know him casually
- He considers memory similar to peers of same age – but does have some stress, disconnect from feelings of worry/fear
# Initial Patient Assessment

## Memory
- Subtle impairment in short term memory
- No long term memory impairment
- Hints helpful but other times cannot recall new information, parts of conversations or events even if described to him
- Difficulty with remembering names but only those he has met recently
- Uncharacteristically confuses orders at work
- More repetitive, misplaces items but no difficulty in tracking time
- Requires reminders from family and friends for events
- Forgets mid-task but not mid-sentence

## Language
- Minor word finding difficulties
- No difficulty participating in conversations or expressing himself
- Reading, writing (and simple math) intact

## Executive Function
- Difficulty with complex instructions
- Harder to organize day and execute plans
- Requires more input than normal
- Difficulty shifting between tasks
- Minor impairment in planning, sequencing, logic and reasoning through a complicated problem

## Daily life
- Manages finances with help
- Complex instrumental activities starting to show erosion
- Manages own medication with auto-refills and weekly medi-set
- Likely to forget appointments and gets reminders from family and friends
- Greater dependence on a calendar
- Makes copious notes and lists
- Harder to retain plots of books and movies
- Starting to struggle with technology
- Basic activities of daily life intact

## Visuospatial function
- Still drives; no navigational problems but wants to drive only in familiar areas
Neuropsychiatric Symptoms

- More labile mood
- More emotional and feels more down
- Feels fear and frustration which he attributes to what is happening to him
- Sometimes feels helpless, but not worthless or hopeless
- Anxious and irritable
- Good sleep and appetite
- No anhedonia, apathy or decreased motivation
- No hallucinations or delusions
- No social withdrawal
Past Medical History

- Significant hypertension
- Ex-smoker
- Dyslipidemia
- Glucose intolerance
- Mild obesity

No history of:

- Neurotoxic exposure
- Head injuries
- Strokes
- Seizures
- Gait difficulty or balance problems
- Falls
- RLS or REM sleep disorder
- Excessive alcohol use
Family History

- Positive family history of dementia in father and paternal grandmother
- Onset in the late sixties
Neurological Examination

- NE was non-focal
- Faint bilateral palmomental reflex
- Mental status examination (MSE) was unremarkable except for a couple of episodes of tearfulness
Montreal Cognitive Assessment

- Overall score 21/30
  - One point each lost on Trails B, naming, repeating a sentence, serial 7s and the date
  - 4 points lost on recall
  - 2 recovered on multiple choice cue
Imaging Examination

- 3T MRI Head
  - Mild small vessel disease
  - Mild generalised atrophy
  - 25% reduction in hippocampal volume and ratio

- Amyloid PET scan
  - Diffuse binding in the grey matter
Rationale for Amyloid PET Imaging

PAST

**Diagnosis:** Symptomatic  
**Treatment:** Symptomatic (treat late disease)

FUTURE

**Diagnosis:** Molecular biomarkers  
**Treatment:** Modifiable molecular mechanisms

Aβ Amyloid

- A defining pathological feature
- Genetically linked to disease
- Implicated in the etiology
- Target for therapy
- Potential biomarker for diagnosis and treatment monitoring
- In-vivo imaging provides a direct measure of amyloid pathology
Pathophysiology of AD in MCI

- Elevated brain amyloid, accumulation decelerating
- In typical MCI due to AD, marked neurodegeneration in medial temporal lobe present and begins to extend to lateral temporal
  - Hippocampal atrophy often prominent
  - FDG PET changes in parietal & temporal regions more prominent in younger persons
  - Tau PET in temporal lobe, beginning to appear in lateral parietal
  - (low CSF abeta, elevated t-tau, p-tau)
- AD related MCI appears to have worst prognosis
  - Will anti-amyloid or anti-tau therapies work in MCI-AD?
Risk for Alzheimer’s Disease-Type Dementia Survival Probability Based on Amyloid (A) and Neurodegeneration (N) Status in Persons with MCI

Pathophysiology of Non-Progressive MCI

- Longstanding low cognition
- Indolent cerebrovascular disease
- Synucleinopathy
- Hippocampal sclerosis (TDP43)
- Non-AD tauopathies (low or no amyloid)
  - Argyrophilic grain disease (4R tauopathy)
  - Primary Age-related Tauopathy (3R/4R tauopathy)
- Amyloidosis without neurodegeneration (sometimes called pathological aging by neuro-pathologists)
Medical Assessment

- Lumbar puncture performed for CSF for phospho-tau/total-tau/Ab42 testing revealed increased phospho-tau, total-tau and reduced Ab42, and a tau/Abeta ratio of 0.23
- Genotyping showed him to be homozygous for APO-E4
- No autosomal dominant genes

**Latest blood test results**

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<th>Test</th>
<th>Result</th>
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<tr>
<td>B12 level</td>
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<tr>
<td>Folate</td>
<td>&gt;20 ng/ml</td>
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<tr>
<td>TSH</td>
<td>2.28 mU/L</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Normal</td>
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<tr>
<td>Glucose</td>
<td>115 mg/dL</td>
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<tr>
<td>HgbA1c</td>
<td>6.5%</td>
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<td>Erythrocyte sedimentation</td>
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<tr>
<td>C-reactive protein (CRP)</td>
<td>2.2 mg/L</td>
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<tr>
<td>Lyme titer</td>
<td>Negative</td>
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</table>
Diagnostic Impression (I)

- Slow progressing insidious onset of cognitive difficulties
- Meets criteria for very mild range dementia
- Global and cortical deficits
- Experiences functional impairment in more complex activities of daily living
- Short term memory and executive function most affected
Diagnostic Impression (II)

- Mixed neuropsychiatric symptoms, sub-syndromal
- Non-focal Neurological exam
- Positive family history with similar age of onset
- Imaging and CSF biomarkers are amyloid positive

Most likely etiology: Alzheimer’s disease

- Medical conditions and current medications unlikely to be causal factors
- Meaningful vascular risk factors, possibly contributory
- Blood test results normal
- Post appointment imaging performed
Patient Management

- Reviewed nature of the disorder and likely course
- Discussion and advice on:

- **Lifestyle modifications**
- **Controlling vascular risk**
- **Optimizing other medical problems**
- **Treatment options**
- **Research opportunities**

- **Diet**
- **Physical activity**
- **Social interaction**
- **Cognitive stimulation**
Patient Management

- No treatment intervention required for neuropsychiatric symptoms at this time
- Neuropsychiatric symptoms (depression) unlikely cause of cognitive impairment
- Reminded of the availability of a social worker and the resources at the Alzheimer's Association
- Encouraged regular follow-up and monitoring
- Discussion of FDA approved and experimental treatment options