Are we over diagnosing Alzheimer's disease? AD is not all of dementia

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GOALS OF THE PRESENTATION

- Raise awareness of Vascular Dementia and Mild Cognitive Impairment
- Raise awareness of the many diagnostic tools and procedures available to diagnose types of dementia
- Clarify differences between Mild Cognitive impairment and dementia
- What may I ask for in terms of confirmation of my lived one’s diagnosis of dementia?
Projected Prevalence of AD

4 Million AD Cases Today—
Over 14 Million Projected Within a Generation

2000: 4
2010: 5.8
2020: 6.8
2030: 8.7
2040: 11.3
2050: 14.3

Evans DA et al. Milbank Quarterly. 1990;68:267-289
Treatment of Alzheimer’s Disease

- Prevalence: 4,523,100
- Diagnosed: 2,261,600
- Treated: 904,600
- Treated with AChEIs: 543,800

Any drug treatment, not limited to acetylcholinesterase inhibitors.
Psychosocial, lifestyle and somatic risk factors for MRI

- Age
- Education (cognitive reserve)
- Socioeconomic status
- Sleep disorder
- Substance abuse
- Ethnicity
- Living alone
- Gender
- Stress
- Depression
- Fatigue
- Low physical activity
- Smoking
Major risk factors for MRI and Dementia

- Increasing age
- History of heart attack (MI)
- Atherosclerosis
- High Cholesterol, exception HDL
- Hypertension
- Hypotension
- Diabetes mellitus
- Smoking
- Obesity
- Atrial fibrillation
'You're deliberately putting yourself at risk of ill health by being over 65...'}
The Progress of Alzheimer’s Disease

- Early diagnosis
- Mild-moderate
- Severe

Cognitive symptoms:
- Loss of ADL
- Behavioral problems
- Nursing home placement
- Death

MMSE score

Years
The continuum of Alzheimer's disease

Cognitive function

Preclinical

Ageing

MCI

Dementia

Years
Alzheimer’s Disease Progresses

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Memory loss</td>
<td>Behavioral, personality changes</td>
<td>Gait, incontinence, motor disturbances</td>
</tr>
<tr>
<td></td>
<td>Language problems</td>
<td>Unable to learn/recall new info</td>
<td>Bedridden</td>
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<tr>
<td></td>
<td>Mood swings</td>
<td>Long-term memory affected</td>
<td>Unable to perform ADL</td>
</tr>
<tr>
<td></td>
<td>Personality changes</td>
<td>Wandering, agitation, aggression, confusion</td>
<td>Placement in long-term care needed</td>
</tr>
<tr>
<td></td>
<td>Diminished judgment</td>
<td>Require assistance w/ADL</td>
<td></td>
</tr>
</tbody>
</table>
There are 3 consistent neuropathological hallmarks:

- Amyloid-rich senile plaques
- Neurofibrillary tangles
- Neuronal degeneration

These changes eventually lead to clinical symptoms, but they begin years before the onset of symptoms
B-amyloid Plaques

Immunocytochemical staining of senile plaques in the isocortex of a brain of a human with AD (anti-amyloid antibody)
Immunocytochemical staining of neurofibrillary tangles in the isocortex of the brain of a human with AD (anti-tau antibody)
Appearance of Plaques vs Dementia

- Amyloid Plaques at Autopsy
- Prevalence of AD Dementia

Percent positive (%)

Age (years)

46-50 51-55 56-60 61-65 66-70 71-75 76-80 81-85 86-90
VASCULAR DEMENTIA

- Development of cognitive deficits manifested by both
  - Impaired memory
  - Aphasia, apraxia, agnosia, disturbed executive function
- Significantly impaired social, occupational function
- Focal neurologic symptoms & signs or evidence of cerebrovascular disease
- Deficits occur in absence of delirium
Overlap Between Alzheimer’s Disease and Vascular Dementia

AD
- Probable
- Possible
- Mixed
- Possible
- Probable

Genetic factors
Amyloid plaques
Neurofibrillary tangles
Vascular risk factors

Mixed
AD/CVD

VaD
- Stroke/TIA
- Hypertension
- Diabetes
- Hypercholesterolemia
- Heart disease

Kalaria RN, Ballard C. *Alzheimer Dis Assoc Disord*, 1999
Vascular Brain Disease

Cardiovascular Risk Factors
- Hypertension
- Diabetes
- Genetics
- Hypercholesterolemia
- Heart Disease

Damage to Cerebral Vasculature

Multiple Distinct Pathologies
- Large Vessel Infarcts
- Small Vessel Infarcts
- Hemorrhage
- Hypoperfusion
Differential Diagnosis

- Alzheimer’s disease
- Vascular (multi-infarct) dementia
- Dementia associated with Lewy bodies
- Delirium
- Depression
- Other
  - Alcohol, Parkinson’s disease (PD), Pick’s disease, frontal lobe dementia, neurosyphilis
WHY DOES IT MATTER?
Genetic and metabolic risk factors for MRI

- Hyperhomocysteine
- High cholesterol, except HDL
- High triglycerides
- Vitamin deficiency: B12, B6, D, E
- Apolipoprotein E4 (the neuronal repair allele)
- Folate deficiency
- Hypertension
- Low blood pressure
- Diabetes mellitus
- Metabolic syndrome
- Testosterone deficiency
- Subclinical thyroid dysfunction
- Reduced estrogen level
ASSESSMENT: HISTORY

- Ask both the patient and a reliable informant about the patient’s:
  - Current condition
  - Medical history
  - Current medications & medication history
  - Patterns of alcohol use or abuse
  - Living arrangements
Normal Lapses

- Trouble balancing checkbook
- Losing keys, glasses
- Getting blues in sad situations
- Gradual changes with aging

Dementia

- Not recognizing numbers
- Putting iron in freezer
- Rapid mood swings for no reason
- Sudden, dramatic personality change
Laboratory tests should include:

- Complete blood cell count
- Blood chemistries
- Liver function tests
- Serologic tests for:
  - Syphilis, TSH, Vitamin B12 level
MSLS Battery

**Visual Spatial Organization Composite**
- Visual Reproductions-Immediate Recall
- Visual Reproductions-Delayed Recall
- Matrix Reasoning
- Block Design
- Object Assembly
- Hooper Visual Organization

**Scanning and Tracking Composite**
- Trail Making A
- Trail Making B
- Digit Symbol Substitution
- Symbol Search

**Verbal Memory Composite**
- Logical Memory-Immediate Recall
- Logical Memory-Delayed Recall
- Hopkins Verbal Learning Test

**Working Memory Composite**
- Digit Span Forward
- Digit Span Backward
- Letter-Number Sequence
- Controlled Oral Word Associations

**MMSE Total Score**

**Global Composite**
HOW TO DISTINGUISH DELIRIUM FROM DEMENTIA

 Features seen in both:
  ◦ Disorientation
  ◦ Memory impairment
  ◦ Paranoia
  ◦ Hallucinations
  ◦ Emotional liability
  ◦ Sleep-wake cycle reversal

 Key features of delirium:
  ◦ Acute onset
  ◦ Impaired attention
  ◦ Altered level of consciousness

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DELIRIUM IN THE ELDERLY

- Incidence among elderly patients is HIGH
  - 1/3rd of patients presenting to ER
  - 1/3rd of inpatients aged 70+ on general med units
  - Incidence ranges from 5.1% to 52.2% after noncardiac surgery (Dasgupta M et al. J Am Geriatr Soc 2006;54:1578-89)
  - Highest rates after hip fracture and aortic surgeries
DIAGNOSIS: Confusion Assessment Method (CAM)

- (1) Acute change in mental status with a fluctuating course
- (2) Inattention
- (3) Disorganized thinking
- (4) Altered level of consciousness

AND

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AVOID RESRAINTS AT ALL COSTS:
Measure of LAST (!!!!) Resort

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DEPRESSION vs DEMENTIA

- The symptoms of depression and dementia often overlap
- Patients with primary depression:
  - Demonstrate lower motivation during cognitive testing
  - Express cognitive complaints that exceed measured deficits
  - Maintain language and motor skills
LEWY BODY DEMENTIA

- Dementia
- Visual hallucinations
- Parkinsonian signs
- Alterations of alertness or attention
Concern of a change in cognition

Evaluate the biomarker probability of AD etiology (T2, S4); add to primary diagnosis

Dementia present? (T2, S1)

Yes

MCI present? (T5, S1)

No

MCI present? (T5, S1)

No

Normal aging, depression, or other etiology

Yes

Diagnosis: MCI due to other etiology such vascular

Probable AD? (T2, S2)

Yes

MCI - AD? (T5, S2)

No

Probable AD Dementia

Yes

Increased level of certainty? (T2, S3)

No

Dementia due to etiology such as vascular

No

Possible AD? (T3)

Yes

Diagnosis: Possible AD Dementia

No

Diagnosis: Probable AD Dementia

Note: T = Table, S = Step
STEP 1: Consider obvious criteria for all cause dementia

- Presence of poor cognitive performance representing a decline from previous ability
- The cognitive impairment involves two domains (controversial)
- Rule out immediately other explanations:
  - Acute stroke, delirium, brain tumor, etc.
- Decision: yes/no on all cause dementia
  - But if the person is functional, keep MCI in mind
  - Must consider rate and variability of decline at some point
STEP 2: IF meets step 1 for all cause dementia THEN consider *probable dementia*

- Onset is gradual, month or years
- Clear cut case of worsening, not variable
- Amnesic (memory) presentation is prominent, BUT may also be an issue with:
  - Language-object naming as example
  - Visual-spatial/visual spatial constructive
  - Executive dysfunction

*Non amnesic symptoms can occur as AD progresses, but need to rule out vascular dementia or mixed*
STEP 3: IF probable AD THEN look for increased certainty

- Cognitive decline has been documented with cognitive testing
- Pattern of cognitive decline seen with cognitive testing
- Little or no evidence of another cause
  - Stroke, injury, etc.

Note: you get what you pay for here as insurance will often not pay for a comprehensive exam
STEP 4: IF probable AD, THEN look for increased medical certainty

- Evaluate the *biomarker evidence*
- MRI: losing brain volume; atrophy medial, basal and lateral temporal cerebral cortex and medial parietal cortex
- Other markers (see next table)
- *Why bother with cognitive testing when you have real medical data?*
Note: we use the term possible or probable until we have had a brain autopsy and pathological examination

- Visible citing of brain volume decrease
- Amyloid deposition
- Neurofibrillary tangles
- Evidence of:
  - Vascular type dementia
  - Mixed dementia
  - Other dementia

Note: the brain refuses to give nice neat examples

Note: the correlations between pathology and cognition are imperfect
THE GENETICS OF DEMENTIA

- Mutations of chromosomes 1, 14, 21
  - Rare early-onset (before age 60) familial forms of dementia
  - Down syndrome

- Apolipoprotein E4 on chromosome 19
  - Late-onset AD
  - APOE*4 allele raises risk and lowers onset age in dose-related fashion
  - APOE*2 allele may have protective effect
PHARMACOLOGIC

- Cholinesterase inhibitors: donepezil, rivastigmine, galantamine
- Other cognitive enhancers: estrogen, NSAIDs, ginkgo biloba, vitamin E
- Antidepressants
- Antipsychotic
Drugs used to treat Alzheimer’s disease act by inhibiting acetylcholinesterase activity.

These drugs block the esterase-mediated metabolism of acetylcholine to choline and acetate. This results in:

- Increased acetylcholine in the synaptic cleft
- Increased availability of acetylcholine for postsynaptic and presynaptic nicotinic (and muscarinic) acetylcholine receptors
FUTURE TRENDS

- Brain ultrasound
- Vaccine
- Genetic therapy