Updates in Dementia

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Disclosures:
Dr. Gierke has no significant financial interest in any of the products or manufacturers mentioned.
I have no disclosures
DEMENTIA: Organic loss of intellectual function  [ . . . From Dorland’s]

Dementia is a condition caused by many different diseases
Common causes of dementia

- Alzheimer’s Disease (AD): the most common cause after age 65 (50+ %)

- The following are in a rough tie for second place (each 10-20%):  
  - Frontotemporal Dementia  
  - Vascular Dementia  
  - Lewy Body Dementia
The traditional challenge has been the challenge of diagnosis

- The gold standard has been pathology (brain biopsy)
- As an alternative to brain biopsy, dementia has traditionally been defined by consensus clinical criteria.
- These criteria are man-made constructs and continue to change
Previous Common Dementia Criteria

- **Examples for Alzheimer’s Disease (AD)**
  - DSM-III (1980)
  - NINCDS-ADRDA (1984) - commonly used in research
  - DSM-IV (1994) - commonly used clinically

- **Examples for Vascular Dementia**
  - ADDTC (Alz Dis Dx & Tx Ctrs, 1992)
  - ICD-10 (Int’l Statistical Classif of Diseases, 10th ed, 1992)
  - NINDS-AIREN (1993)
  - DSM-IV (1994)
What is new

There are two new diagnostic criteria
- NIA-AA (2011) replaced the NINCDS-ADRDA
- DSM-V (2013) replaced the DSM-IV

There are new diagnostic tests, sometimes labeled biomarkers, such as Amyloid-PET Scans

Research into the pathophysiology of AD, and genetics of AD and other dementias, is ongoing and always worth discussing

The basic workup is worth discussing - note the MMSE is now copyrighted

Treatment - sadly, not enough is new
The NIA-AA Criteria (2011)

National Institute on Aging and Alzheimer’s Association

These replaced the NINCDS-ADRDA criteria of 1984

These defined a role for biomarkers, initially in research

These provides criteria for:
  - Dementia in general
  - Dementia due to AD

These further define a spectrum for AD
  - A pre-clinical, asymptomatic state
  - Mild Cognitive Impairment (MCI)
  - Probable or Possible AD Dementia
These replace the DSM-IV criteria of 1994

These divide cognitive disorders into

- **Mild Neurocognitive Disorders**
  - “Modest cognitive decline” in one or more domains which do not interfere with independence

- **Major Neurocognitive Disorders**
  - “Significant cognitive decline” in one or more domains which do interfere with independence

Once a Mild or Major Disorder is defined, there are secondary criteria for a Mild-Major disorder due to:

- AD Dementia, Frontotemporal, Lewy Body, Vascular, and others
One new development: a stage between normal and dementia

Both new criteria include recognition of a stage between normal and dementia is now formalized:

Mild Cognitive Impairment (MCI) in NIA-AA

Mild Neurocognitive Disorders (MND) in DSM-V

The hallmark of MCI-MND is cognitive decline without impairment of independent function in everyday activities
Another evolving development: what are biomarkers?

Common biomarkers of AD include

- Presence of Amyloid-Beta (AB): CSF AB-42 or Amyloid PET Scan
- Presence of neuronal injury: CSF-tau, FDG-PET, Hippocampal atrophy on volumetric MRI

The new NIA-AA criteria allow diagnosis of AD without biomarkers, with biomarkers intended for research.

- A biomarker protocol for daily clinical use is not yet established
- Per the NIA-AA original paper: “However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time.”
The relevance of biomarkers, or discussing an AD spectrum, infer a model of gradual pathology

- From Sperling RA, et al Alzheimers Dement 2011
Biomarker example: hippocampal atrophy in AD Dementia

NORMAL HIPPOCAMPI ←

ATROPHIED HIPPOCAMPI →

UCSF.EDU
Biomarker example: FDG PET Scan (labeled glucose) in AD Dementia -- temporal and parietal hypo-metabolism
Biomarker example: FDG PET Scan in AD Dementia versus Frontotemporal Dementia
Biomarker example: Amyloid-PET (florbetapir) to detect the presence of amyloid

Statistics

- 13% of people 65 and older have Alzheimer’s
- 45% of people 85 and older have Alzheimer’s
- In 2013 5.2 Million people in the US had Alzheimer’s
  - In 2030 this will be 7.7 Million
  - In 2050 this will be 13.8 Million
By 2050, Alzheimer’s Disease may be the 6th leading cause of death in the U.S.
This will have a non-trivial cost

- In 2013 15.4 Million caregivers provided 17.5 Billion hours of unpaid care
- In 2013 Alzheimer’s cost the U.S. $203 Billion. In 2050 this is projected to be $1.2 Trillion
Before going in to the the new criteria, it is worth reviewing the pathophysiology of Alzheimer’s Disease.
The pathologic hallmark of AD: Plaques of Amyloid-Beta outside cells, Tangles of phosphorylated tau inside cells
The Amyloid Hypothesis

- Amyloid-Beta (AB) peptides are natural products of 36-43 amino acids
- AB peptides are formed by cleavage of the Amyloid Precursor Protein (APP), a trans-membrane protein
- AB-40 is more common, but AB-42 is aggregate-prone and more damaging. Oligomers (2-6 peptides) of AB are the most neuro-toxic form.
- Disease may result from an imbalance of production and clearance of AB and consequent action of AB inside cell, at synapse, and outside cell.
Amyloid Precursor Protein

- APP is a single trans-membrane protein with a 590-680 aa long extracellular domain and a 55aa cytoplasmic tail.
- The normal function of APP is currently unknown.
- If cleaved in certain sequences, it is cleaved to AB-40 and B-42 and other size peptides which may be intracellular or extracellular and may form oligomers.
Processing of Amyloid Precursor Protein
Querfurth HW, et al, NEJM 2010
Actions of Amyloid Beta

- AB-42 oligomers are both intracellular and extracellular

- Extracellular AB Oligomers may act to impair synaptic function, especially in hippocampus, through toxicity to vesicle and membrane proteins.

- The severity of cognitive defect in AD correlates with levels of oligomers and synapse lost, not total AB burden or plaques.

- Intracellular AB oligomers may create mitochondrial dysfunction, possibly through increase in intracellular calcium via membrane channels and endoplasmic reticulum.

- Thus -- Amyloid Beta extracellular plaques may be a disease marker for AB activity, but not the active actor.
Synaptic Dysfunction in Alzheimer's Disease.

Oxidative Stress and Mitochondrial Failure.

The role of tau

- Tau is an abundant soluble protein in axons, tau promotes stability of microtubules and vesicle transport.

- Hyper-phosphorylated tau is insoluble and is the major component of neurofibrillary tangles, which are intracellular filamentous inclusions within neurons.

- Intermediate aggregates of abnormal tau are cytotoxic, but the actual tangles may be inert (an attempt to sequester cytotoxic tau, perhaps) as decrease in axonal transport is independent of tangle burden.

- Modification of phosphorylation of tau may be a treatment target.

- Tauopathies include: AD, Frontotemporal Dementia, Progressive Supranuclear Palsy.
Tau Structure and Function.

Phosphorylation of tau creates insoluble tau and microtubules (yellow) become unstable.
Amyloid-Beta and Tau strategies

Treatments aimed at Amyloid-Beta include
- Alteration APP cleavage to make less AB-42
- Prevention of aggregation of AB-42 oligomers
- Increased clearance of AB

Treatments aimed at Tau include
- Prevention of phosphorylation of tau
- Prevention of aggregation of tau
- Prevention of folding-misfolding of tau

PET Scan tracers for diagnosis-measurement
- Amyloid PET (eg florbetapir) - now available
- Tau PET - potentially to be developed
Returning to the diagnostic criteria

... First the NIA-AA
NIA-AA first sets Criteria for (any) Dementia

• Interferes with ability to function at work or activities
• Represents a decline from previous levels of function
• Not due to delirium or psychiatric disorder
• Impairment diagnosed through (a) history and (b) objective cognitive assessment (bedside or N-Psych Testing)

• Cognitive impairment in at least two domains:
  • Ability to acquire-remember new information
  • Impaired reasoning-handling complex tasks (poor judgement)
  • Impaired language
  • Personality change
  • Visuospatial (impaired ability to recognize faces, objects)
NIA-AA then goes on to define two slightly different criteria for probable AD:

- Probable or Possible Alzheimer’s without biomarker testing - intended for clinical use
- Probable or Possible Alzheimer’s with biomarker testing - intended for research use
NIA-AA Criteria for Probable AD

- Meets criteria for dementia (prior slide)
- Insidious onset
- Clear-cut history of worsening of cognition
- Initial and most prominent deficits are in one of:
  - Amnestic (most common), impaired learning and recall
  - Non-amnestic: language, visuospatial, executive function (judgment, reasoning, problem solving)
- In addition, as per the dementia criteria, there must be deficits in at least one other cognitive domain
NIA-AA Criteria for MCI

- Concern for a change in cognition (from patient, observer or clinician)
- Lower performance in one or more cognitive domains than expected by age-education, or a decline from prior performance over time (domains: memory, attention, language, visuospatial skills, executive function)
- Preservation of independence in functional abilities
- Neither demented nor in delirium
Important differences between dementia and MCI

- In MCI there is preservation of independence in functional activities
- MCI requires impairment in only one cognitive domain - usually memory (ability to learn and retain new information)
NIA-AA Criteria for a Pre-Clinical Stage of AD

- This was a controversial aspect of the NIA-AA Criteria, and was focused at allowing research on the spectrum of disease over time.

- Stage 1: Asymptomatic with marker of Brain Amyloid: Amyloid-PET or reduced AB-42 in CSF.

- Stage 2: Asymptomatic - Stage 1 criteria plus marker for neuronal injury: CSF-tau elevated, abnormal FDG-PET, hippocampal atrophy on MRI.

- Stage 3: Stage 2 criteria plus subtle cognitive decline.
For the NIA-AA Criteria

The AD Dementia, MCI, and Pre-Clinical Criteria were released in three separate papers in 2011.

These papers are available, for free, from www.alz.org
Returning to the diagnostic criteria cont’d

... Next the DSM-V
DSM-V

- DSM-V does not use the term dementia,

- But rather DSM-V defines first
  - Major Neurocognitive Disorders,
  - Mild Neurocognitive Disorders,

- Following the determination of a Major-Mild Disorder, the condition may be further specified as due to Alzheimer’s, Frontotemporal, Lewy Body, etc

- COMMENT: The NIA-AA does not have separate criteria for Frontotemporal, Lewy Body, etc
DSM-V Criteria - Mild Neurocognitive Disorder

- Concern of patient, witness, or clinician for a mild decline in cognitive function

- A modest impairment in cognitive performance is confirmed by neuropsychological testing or other quantified clinical assessment

- Deficits do not interfere with capacity for independence

- Deficits do not occur in context of delirium and are not explained by another mental disorder
DSM-V Criteria - Major Neurocognitive Disorder

- Concern of patient, witness, or clinician for a significant decline in cognitive function

- A substantial impairment in cognitive performance is confirmed by neuropsychological testing or other quantified clinical assessment

- Deficits DO interfere with capacity for independence

- Deficits do not occur in context of delirium and are not explained by another mental disorder
Major neurocognitive disorder criteria met

The following three conditions are met

- Clear evidence of decline of memory and learning AND at least one other cognitive domain
- Progressive, gradual decline
- Not a mixed etiology (e.g., cerebrovascular disease or other disease affecting cognition)

Or, alternatively, a causative AD gene is found
DSM Criteria for Frontotemporal NCD

Major neurocognitive disorder criteria met

Relative sparing of learning-memory, and criteria for Behavioral variant or a Language variant met

Behavioral variant

- Decline in social cognition and-or executive abilities
- 3+ of: apathy, loss of empathy, perseveration, disinhibition, hyperorality or dietary changes

Language (Primary Progressive Aphasia): language decline

- Non-fluent type: word pronunciation disorders
- Semantic subtype: loss of single-word meaning, anomia
DSM Criteria for Lewy Body NCD

Major neurocognitive disorder criteria met

2+ of the following

- Fluctuating variations in attention-alertness
- Well formed visual hallucinations
- Parkinsonism develops AFTER cognitive decline begins
- REM Behavioral Sleep Disorder (acts out dreams)
- Severe neuroleptic sensitivity: catatonia, muscle rigidity

Note: A DatScan (SPECT with dopamine transport ligand) will be positive in Lewy Body Dementia and may be a useful new test, but also Parkinson’s Disease, PSP, and MSA
DSM Criteria for Vascular NCD

Major neurocognitive disorder criteria met

There is evidence of cerebrovascular disease from neuro-imaging or history and exam.

One of the following two:

- Onset temporally related to a stroke or strokes
- Prominent loss of executive function and loss of speed of processing (bradyphrenia)

Comment: this most commonly correlates with leukoaraiosis on MRI-CT: extensive white matter disease
DSM Criteria for NCD due to Multiple Etiologies

- Major neurocognitive disorder criteria met
- Evidence by history, exam, tests that the NCD is due to more than one of the other established etiologies
- One of the causes is NOT substances
- COMMENT: The most common scenario is AD with evidence or development of Vascular NCD. This may be one of the most common clinical NCDs.
Putting it together

- What do MCI and Biomarkers tell us
- Other risk factors for dementia
- Genes the cause dementia or increase risk
- Suggestions for evaluation or work-up
- Treatment options
- Resources
MCI, what does the construct tell us?

Mild Cognitive Impairment (NIA-AA) or Mild Neurocognitive Disorder due to AD (DSM)

- 10-15% per year will progress to dementia
- But up to 20% who are given a MCI diagnosis will later improve to normal [Lopez, OL et al 2012]
What do Biomarkers tell us?

- The most important points about Biomarkers (CSF tau-amyloid, Amyloid PET, hippocampal volumes, etc):
  - The presence of a biomarker does not establish an AD diagnosis
  - A diagnosis of dementia can be made without biomarkers

- Uses of biomarkers:
  - Amyloid PET Scan: if negative, it argues strongly against AD
  - FDG-PET: once a diagnosis of dementia is established, this can help distinguish between AD and Frontotemporal

- Biomarkers also speak to the risk of MCI converting to dementia - but this may not be of use in an individual patient
A Comment on Amyloid-PET Scans for AD

Amyloid PET (eg with florbetapir) detects amyloid.
- It does not make a diagnosis.
- It can be positive in AD, but also Lewy Body Disease and in normal elderly

A positive study does NOT rule in AD - about 20% of normal elderly will be positive.

A negative Amyloid PET does argue strongly against AD
FDG PET: Normal versus AD versus Frontotemporal

Risk of conversion from MCI to Dementia: Biomarkers increase risk of conversion (blue is negative biomarker, red positive)

1. CSF -tau/AB-42
2. Hippocampal volume loss

[from Heister, D, Neurology 2011]
CSF Total-Tau and AB42

- Alzheimer’s disease
  - Aβ42, t-tau and p-tau each differentiate AD from healthy elderly with 80-90% sensitivity and

- Performance is better in combination

- Aβ42 + t-tau together increase sensitivity to 86% (78-84% stand-alone) and specificity to 97% (84-90% stand-alone)

- CSF p-tau aids differentiation from other dementias including FTD and LBD
Modifiable risk factors

Mid-life cardiovascular risk factors are associated with dementia risk:

- Hypertension
- Hypercholesterolemia
- Diabetes
- Sleep apnea increases risk of stroke and heart attack and may independently produce a chief complaint of memory loss

NOTE: in 2012 the FDA added a warning for statins, noting:

“...impairment, such as memory loss, forgetfulness and confusion has been reported by some statin users.”

But there is no controlled data.
For Frontotemporal Dementia, there are 3 known autosomal dominant genes:

- **MAPT** - on chromosome 17, seen with Frontotemporal Dementia with Parkinsonism, FTDP-17
- **GRN** (or **PGRN**, progranulin), also on Chromosome 17
- **C9orf72**: new gene, most common cause of hereditary ALS with or without Frontotemporal Dementia

For AD, there are 3 known autosomal dominant genes:

- **APP**, Presenilin 1, Presenilin 2.
- The first two deal with Amyloid Precursor Protein or enzymes which cleave it.
Apolipoprotein E: has a role in the transportation of Amyloid Beta. There are three forms, Apo E2, E3, E4. Every person has two copies (one from each parent).

For AD: E2 is protective, E3 neutral, E4 harmful
- E2-2, E2-3, E3-3: 9% risk of AD at age 85
- E2-4, E3-4: 27% risk of AD at age 85
- E4-4: 55+% risk of AD at age 85

The presence of E4 also reduces the age of onset of AD

But testing an individual patient does not markedly aid the diagnostic workup
Clinical work-up suggestions

- History
  - Look for history of repeating questions in particular
  - Information from relatives, co-workers is appropriate

- Bedside cognitive testing
  - Orientation to year is important
  - The Animal Naming Test is sensitive, normal is 16+
  - The MMSE is now copyrighted -- $1.20 per use to Psychology Assessment Resources
  - The MoCA test is a free alternative to the MMSE -- available in many languages for free (www.mocatest.org), score 0-30, ≥26 is normal. This is better than the MMSE for executive function, but note the memory section is harder
Work-up with Tests: focusing on reversible causes

- Labs: CBC, Metabolic Panel, Thyroid studies, Methylmalonic Acid, B12, Folate. Possibly: ESR, CRP, RPR, HIV, Urine screen for heavy metals, drugs

- Neuro-Imaging: CT or MRI for hydrocephalus, vascular disease, subdural hematoma. If MS is a concern, use MRI

- Neuro-Psychological Testing: not mandatory, but useful in ambiguous situations, young onset, or complex histories. This is useful to separate depression from dementia.

- Consider sleep testing
Treatment - sadly, little is new: Cholinesterase Inhibitors

Overall improve ADAS-Cog score (0-70 scale) 2.4 points

Side effects: nausea, diarrhea, anorexia, 69% increased risk of bradycardia, 49% increased risk of need for a pacemaker

Approved for mild-mod AD (exception: Donepezil 23mg), not for MCI

Donepezil, approved 1996, 5-10mg daily
  - A 23mg daily pill was approved for severe AD, but is controversial with increased side effects and only a 2.2 point improvement on the Severe Impairment Battery (0-100 scale)

Rivastigmine, approved 2000
  - 3-6mg bid orally
  - 4.6mg, 9.5mg, 13.3mg daily patch

Galantamine, approved 2001, 8-12mg bid
Treatment Cont’d: Memantine

- Non-competitive NMDA receptor antagonist, which may inhibit glutamate and calcium-mediated neurotoxicity
- Approved 2003
- Usually given with a cholinesterase inhibitor. Minimal effect on decline or behavior, and a 2009 German study of almost 2000 patients showed no significant benefit
- Dosage: 5mg daily x 1 week, increase by 5mg weekly to 10mg bid
- Showed efficacy in 2 of 3 trials of patients with MMSE < 15. Approved for moderate-to-severe AD, not mild-to-moderate
Where to get more help

• Alzheimer’s Association - www.alz.org
  • Includes articles with diagnostic criteria
  • Resources for support groups

• Alzheimer’s Foundation - www.alzfdn.org

• Our Clinics: Swedish Neuroscience Institute Neurology:
  • Seattle (Cherry Hill) 206-320-3494
  • Issaquah 425-313-7077