USE OF BIOMARKERS TO DISTINGUISH SUBTYPES OF DEMENTIA

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Stanford University School of Medicine

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“Use of Biomarkers to Distinguish Subtypes of Dementia”

About the Presenter

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Q & A

- There will be a Q & A session at the end of the presentation. If you have any questions, please use the “Chat” feature located on the right side of your screen. Please send your chat to everyone if possible.
- After the Q and A, we would like to ask each of the participants to answer the short evaluation questionnaire.

Please complete our short survey. We appreciate your feedback.

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Use of Biomarkers to Distinguish Subtypes of Dementia

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STATE OF THE SCIENCE:
Dementia Evaluation and Management among Diverse Older Adults and their Families

CASE HISTORY

A 57 year-old man presents to clinic complaining of short term memory loss...

Use of Biomarkers in Dementia

DEFINITION: an easily-observable measurement (e.g., the concentration of a molecule, or size of a brain region) that serves as a proxy for a harder-to-determine biological state (the presence of Alzheimer’s disease pathology)

USES:
• Diagnosis (early, accurate)
• Disease Tracking
Use of Biomarkers in Dementia

WHY BOTHER?

• Our patients desire a confident diagnosis.
• Newly emerging drugs are more likely to help in the early stages of the disease, before symptoms take hold.
• Using biomarkers as an endpoint in clinical trials, we may be able to gauge a new drug’s efficacy more quickly, with fewer patients, and less money.

Use of Biomarkers in Dementia

AVAILABLE NOW

• CSF amyloid-beta and tau
• Amyloid PET imaging
• Metabolic imaging
• Structural MRI

POSSIBLE FUTURE BIOMARKERS

• High resolution structural MRI
• Functional MRI
• Others
Hypothetical Timeline

Age / Severity

- Normal
- MCI
- AD

Plaque deposition
Tangle accumulation and neurodegeneration
Hippocampal atrophy

Biomarkers for Alzheimer’s Disease

TWO CATEGORIES:

- Biomarkers of amyloidosis
  - CSF amyloid-beta
  - Amyloid PET imaging
- Biomarkers of neuronal injury
  - CSF tau
  - FDG PET
  - Structural MRI

NEW DIAGNOSTIC CLINICAL CRITERIA
(McKhann et al., 2011; Albert et al., 2011)

Three levels of certainty for “Probable AD” and for “Mild Cognitive Impairment due to AD”

- Uninformative (ie, unavailable, conflicting, or indeterminate)
- Intermediate (ie, one category positive, the other unavailable or indeterminate)
- High (positive results in both categories)
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Cerebrospinal Fluid Biomarkers

WHAT ARE WE MEASURING?
- Aβ(1-42) peptide
- Total tau protein
- Phospho-tau (Y181)

Tips:
- Use polypropylene tubes (not the ones typically supplied in kits), as Aβ interacts with other plastics
- Commercial labs offer this as a send-out service

Cerebrospinal Fluid Biomarkers

- In one test, you can obtain two biomarkers
  - CSF amyloid-beta – a marker of amyloidosis
  - CSF tau and phospho-tau – markers of neuronal injury

- CSF Aβ declines in AD
  - Equivalent to a positive amyloid PET scan
  - Shares same high sensitivity but questionable specificity as amyloid imaging

- CSF tau rises in AD
  - Probably reflects neuronal death
  - Nonspecific – also goes up in other neurodegenerative conditions, notably CJD
Cerebrospinal Fluid Biomarkers

Aβ(42) is very sensitive at distinguishing AD from control cases in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohorts. Note: Absolute levels vary depending upon the exact technique used to make the determination and are not well-harmonized from lab to lab. When you obtain these levels commercially, use that lab’s cut-offs.

Shaw et al., 2009

Cerebrospinal Fluid Biomarkers

Elevated tau adds some specificity, strengthening the suspicion of AD.

LIMITATIONS OF TAU
Any injury causing neuronal lysis could conceivably elevate tau. Prion disease is a notable example; other neurodegenerative diseases are less-studied.

Shaw et al., 2009

Cerebrospinal Fluid Biomarkers

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Amyloid Imaging:
Coming to a PET scanner near you...

Amyloid Imaging

AD
CONT

AD
CONT
Amyloid Imaging with $^{18}$F Compounds

Clark et al., JAMA, 2011

Amyloid Imaging: What does it tell us?

Although absolute PIB uptake differs according to diagnosis...

...the annual rate of change in PIB burden does not differ.

Amyloid Imaging: What does it tell us?

Wolk et al., Annals of Neurology 2009

MILD COGNITIVE IMPAIRMENT

- The significance of plaques is still not completely worked out.
- While it may always be preferable to have a negative PIB scan, it may not always be a bad thing to have a positive one.

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Amyloid Imaging: What does it tell us?

Amyloid plaques appear densely in the neocortex, but rarely occur in the entorhinal cortex or CA1.

Arriagada et al., Neurology 1992

Limitations to Amyloid Biomarkers

Amyloid positivity ≠ AD
- Plaques may occur in normal elders in the absence of tangles, atrophy, or cognitive loss
- Does not exclude a comorbid pathogenic process that may be driving cognitive decline

Amyloid biomarkers do not track disease progression over time

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Metabolic Imaging

Modalities:
- Fluorodeoxyglucose (FDG) PET
- Arterial spin labeling (ASL) MRI

What it tells us:
- The anatomy of which brain areas are hypofunctional
- However, a well-trained neuropsychologist or cognitive neurologist can make the same observations from a detailed clinical exam

What it doesn’t tell us:
- Underlying neuropathology
- Especially in atypical cases, there is a poor correlation between the anatomical pattern of neurodegeneration and the underlying molecular diagnosis

Utility:
- Limited use in differential diagnosis
- Limited use in predictions about future cognitive decline
- Possible use in tracking disease progression or response to therapeutic intervention

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**MR-based hippocampal volumetry in the diagnosis of Alzheimer’s disease**

Clifford R. Jack, Jr., MD; Ronald C. Petersen, MD; Brian C. O’Kearney, PhD; and Eric G. T. Trojanowicz, MD

*Neurology* 2009;63(2):180-188

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**Hippocampal Volume**

Schuff et al., Brain 2009

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**Structural Neuroimaging**

Hippocampal atrophy is the key metric of interest

- Neither sensitive nor specific for AD
- May be helpful longitudinally (e.g., to demonstrate atrophy over 1-2 years), but the information may not be enough to justify subjecting a patient to multiple sequential scans.
- Newer techniques (like 7T) may improve sensitivity and specificity

Every older patient with a memory complaint should have a standard clinical MRI scan

- The purpose is to evaluate for cerebrovascular disease and other differential considerations; this remains a standard of care.
- At this time, however, it is of uncertain value at providing positive evidence in favor of AD.
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7.0 Tesla MRI
• Compare to 3.0 Tesla, the current standard at many state-of-the-art medical facilities
• ~140,000x stronger than Earth’s field
• Extra signal-to-noise
• Higher resolution
• Shorter scan times
• Some problems
  • Exaggeration of artifacts
  • Exaggeration of side effects
Hippocampal subfield metrics correlate with memory performance.

Kerchner et al., Neurology, 2010
Kerchner et al., Neuroimage, 2012
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Default-Mode Network in AD

Healthy Older Controls

Alzheimer's Disease

Single-Subject Default Mode Network Measure

85% sensitivity
27% specificity
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CASE HISTORY
A 57 year-old man presents to clinic complaining of short term memory loss...

- Neuropsychological testing is indeterminate
- Structural neuroimaging shows “mild global cerebral volume loss that may be excessive for age”
- CSF Aβ is low, and CSF tau is elevated
- You counsel the patient that based on his lumbar puncture, there is evidence in support of Alzheimer’s disease being the cause of his symptoms
CASE HISTORY
An 87-year-old woman has been depressed since her husband died a year ago. She no longer leaves home, and her family have taken over bill payments and scheduling appointments. Her children want to know if she is demented.

- Neuropsychological testing is limited by poor concentration
- Structural neuroimaging shows “mild global cerebral volume loss that may be excessive for age”
- CSF Aβ and tau are normal
- You counsel the family that there is no sign of Alzheimer’s disease, and that depression may be a primary cause of her symptoms.

CASE HISTORY
A 61-year-old man has severe word-finding problems. His personality is mostly normal, although he has become obsessive and has developed some odd habits. You want to distinguish between frontotemporal dementia (language variant) and Alzheimer’s disease

- Amyloid PET imaging is positive
- FDG-PET reveals left more than right temporal/parietal hypometabolism
- You conclude that Alzheimer’s disease is the more likely cause of his symptoms

Thank You!
Q & A

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NOTE: Continuing Education Participants must complete a final survey in order to receive CEU/CME credit.

Final Question

Thank You for Participating!