Updates on Biomarkers in Dementia

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What are Biomarkers?
Definition of Biomarker

- A portmanteau of “biological marker”
- A broad subcategory of medical signs (i.e. objective indications of medical state observed from outside the patient)
- Can be measured accurately and reproducibly

Definition of Biomarker

- National Institutes of Health Biomarkers Definitions Working Group
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- International Programme on Chemical Safety, WHO
  - Any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease

Classification of Biomarkers

- **Type 0**
  - Markers of natural history of a disease
  - Correlate longitudinally with known clinical indices such as symptoms over the full range of disease states
  - e.g. C-reactive protein

- **Type 1**
  - Capture the effects of an intervention in accordance with the mechanism of action of the drug, e.g. HbA1c

- **Type 2**
  - Surrogate endpoints as a change in that marker predict clinical benefit, e.g. LDL cholesterol
Examples of Biomarkers

- Laboratory Tests (Omics, ELISAs)
- Electrophysiological (EEG, ECG, ...)
- Physiological (BP, heart rate, ...)
- Imaging (fMRI, PET, CT, etc.)
- Cytological (Pap smear, ...)
- Histological (IHC)
- Behavioral (cognition)
Biomarkers of Alzheimer’s Disease
Why do we need biomarkers for dementia

- Help doctors and scientists diagnose dementia
- Find health risks in a person
- Monitor responses to treatment
- Keep track of how a person's disease or health condition changes over time

https://www.nia.nih.gov/health/biomarkers-dementia-detection-and-research
Biomarkers for dementia are *not* new

- **1892**
  - Paul Blocq and Gheorghe Marinescu first described the presence of plaque deposits in grey matter

- **1906**
  - Alois Alzheimer discovered the connection between plaques and dementia

- **1911**
  - Max Bielschowsky proposed the amyloid-nature of plaque deposits

- **1911**
  - Teofil Simchowicz introduced the term senile plaques

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Alzheimer's diagnostic guidelines updated for first time in decades

- 2011
  - Led by National Institutes on Aging and Alzheimer’s Association
  - Reflected how experts think about and study Alzheimer’s disease
  - Original 1984 clinical criteria
    - Alzheimer’s is defined as having a single stage
    - Dementia diagnosis is based solely on clinical symptoms
    - People free of dementia symptoms are disease-free
    - Diagnosis was confirmed only at autopsy

Alzheimer's diagnostic guidelines updated for first time in decades

- 2011

- Key changes of NIA-AA criteria
  - Cover the full spectrum of the disease - an early, preclinical stage with no symptoms; a middle stage of mild cognitive impairment; and a final stage marked by symptoms of dementia
  - Expand the criteria for Alzheimer’s dementia beyond memory loss as the first or only major symptom
  - Better understanding of the distinctions and associations between Alzheimer’s and non-Alzheimer’s dementias, as well as between Alzheimer’s and disorders that may influence its development
  - Employ **biomarkers** (imaging, blood and spinal fluid) that may help determine whether changes in the brain and those in body fluids are due to Alzheimer’s disease

2011 NIA-AA criteria

- For probable AD with evidence of AD pathophysiological process:
  - Biomarkers of brain amyloid-beta protein deposition
    - ↓ CSF Aβ42
    - Positive PET amyloid imaging
  - Biomarkers of neuronal degeneration or injury
    - ↑ CSF total / phosphorylated tau
    - ↓ FDG uptake on PET in temporoparietal cortex
    - Disproportionate atrophy in medial, basal & lateral temporal
      & medial parietal lobe on MRI

Dynamic biomarkers – 2013 model

2018 NIA-AA Research Framework

- AD as a continuum
  - Cognitive decline in AD occurs continuously over a long period
  - Progression of biomarker is a continuous process that begins before symptoms
- AD is defined by its underlying pathologic processes documented by postmortem examination or in vivo by biomarkers
- Diagnosis is not based on the clinical consequences of the disease (i.e., symptoms/signs)
2018 NIA-AA Research Framework

- Shifts the definition of AD in living people from a syndromal (multidomain amnestic dementia) to a biological construct
  - Multidomain amnestic dementia is not sensitive
    - 30-40% of cognitively unimpaired elderly persons have AD neuropathologic changes at autopsy, and a similar proportion has abnormal amyloid biomarkers
  - Multidomain amnestic dementia is not specific
    - 10% - 30% of individuals clinically dx as AD dementia by experts do not display AD neuropathologic changes at autopsy / has normal amyloid PET or CSF Aβ42
Biomarkers are grouped into AT(N)

A: Aggregated Aβ or associated pathologic state
- CSF Aβ42, or Aβ42/Aβ40 ratio
- Amyloid PET

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
- CSF phosphorylated tau
- Tau PET

N: Neurodegeneration or neuronal injury
- Anatomic MRI
- FDG PET
- CSF total tau
2018 NIA-AA Research Framework

- Only biomarkers that are specific for hallmark AD proteinopathies (i.e., Ab and pathologic tau) are considered as potential biomarker definitions of the disease

- Neurodegeneration/injury, even in classic AD brain regions, also occurs in non-AD conditions

- Particularly so in older individuals where comorbidities are common

<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
<th>Alzheimer’s continuum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-T-(N)</td>
<td>Normal AD biomarkers</td>
<td></td>
</tr>
<tr>
<td>A+T-(N)</td>
<td>Alzheimer’s pathologic change</td>
<td></td>
</tr>
<tr>
<td>A+T+(N)</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>A+T+(N)+</td>
<td>Alzheimer’s disease</td>
<td></td>
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<tr>
<td>A+T-(N)+</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change</td>
<td></td>
</tr>
<tr>
<td>A-T++(N)</td>
<td>Non-AD pathologic change</td>
<td></td>
</tr>
<tr>
<td>A-T-(N)+</td>
<td>Non-AD pathologic change</td>
<td></td>
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<tr>
<td>A-T+(N)+</td>
<td>Non-AD pathologic change</td>
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A: Ab biomarkers determine whether or not an individual is in the Alzheimer’s continuum. T: Pathologic tau biomarkers determine if someone who is in the Alzheimer’s continuum has Alzheimer’s disease.
2018 NIA-AA Research Framework

- Biomarker-based research framework
  - Premature and inappropriate to use this framework in general medical practice
  - This framework should not be used to restrict alternative approaches to hypothesis testing that do not use biomarkers

Biomarkers of Non-Alzheimer’s Disease
Biomarkers of Vascular Dementia

- Omics/microRNA
  - Identifying subcellular components of VaD
- Genetic biomarkers
  - Identifying genes involved in cerebrovascular disease
- Neuroimaging biomarkers
  - Structural as well as functional imaging
- Biochemical biomarkers
  - Serum, plasma, CSF biomarkers
- Pathological biomarkers
  - Identifying cellular/histological changes
- Clinical biomarkers
  - Neurobehavioral assessment

Biomarkers of Vascular Dementia

- CSF biomarkers
  - c.f. AD, CSF biomarker studies in VaD report conflicting results and lack specificity due to the heterogenous nature of VaD
  - CSF biomarkers are not specific to VaD but can increase the diagnostic certainty of VaD
  - Biomarker levels in CSF are raised in VaD

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<th>Biomarkers</th>
<th>Diagnostic utility</th>
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<tr>
<td>CSF:serum albumin ratio, CSF total protein</td>
<td>To identify blood–brain barrier damage to the small intravascular vessels</td>
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<tr>
<td>Sulfatide</td>
<td>To identify demyelination of white matter</td>
</tr>
<tr>
<td>Neurofilament</td>
<td>To identify axonal degeneration (marker of white matter damage)</td>
</tr>
<tr>
<td>Matrix metalloproteases</td>
<td>To identify changes in the extracellular matrix associated with cardiovascular disease (i.e. vascular disease with inflammation)</td>
</tr>
<tr>
<td>Serum to CSF Folate ratio</td>
<td>Low ratio in VaD</td>
</tr>
<tr>
<td>Increased total tau, p-tau, decreased amyloid β42</td>
<td>May differentiate VaD from Alzheimer’s disease and other NDD (Neurodegenerative Diseases)</td>
</tr>
</tbody>
</table>
Biomarkers of Vascular Dementia

- CSF protein biomarkers
  - Associated with all forms of dementia
  - Diagnostic utility is enhanced when used in combination with folate ratio, Aβ42, total tau, or p-tau levels

Biomarkers of Vascular Dementia

- Biomarkers of vascular dementia, apart from imaging changes, are less well developed than for Alzheimer’s disease
- Candidates have been proposed
  - Albumen
  - Metalloproteinases
  - Inflammatory markers
- Need further validation

Biomarkers of Dementia with Lewy Bodies

- Fourth consensus report of the DLB Consortium
  - Distinguish clearly between clinical features and diagnostic biomarkers
  - Increased diagnostic weighting to REM sleep behavior disorder and $^{123}$iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy
  - Describe diagnostic role of other neuroimaging, electrophysiologic, and laboratory investigations

McKeith I (2017) Neurology 89:88-100
Biomarkers of Dementia with Lewy Bodies

- Direct biomarker evidence of LB-related pathology is not yet available for clinical diagnosis
- Indicative biomarkers (If ≥1, plus at least 1 core clinical features -> probable DLB)
  - Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
  - Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy
  - Polysomnographic confirmation of REM sleep without atonia

McKeith I (2017) Neurology 89:88-100
Biomarkers of Dementia with Lewy Bodies

- Supportive biomarkers (consistent with DLB that help the diagnostic evaluation, but without clear diagnostic specificity)
  - Relative preservation of medial temporal lobe structures on CT/MRI scan
  - Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging
  - Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

McKeith I (2017) Neurology 89:88-100
Biomarkers of Frontotemporal Dementia

Currently validated biomarkers

- Grey matter atrophy
- Alterations in brain metabolism as detected by $^{18}$F-fluorodeoxyglucose-PET
- CSF levels of amyloid-$\beta_{1-42}$, phospho-tau$_{181}$ and total-tau

Biomarkers of Frontotemporal Dementia

- Currently validated biomarkers
  - New imaging biomarkers by arterial spin labelling & diffusion tensor imaging are sensitive to the subtle changes that precede grey matter atrophy in FTD, potentially enabling use in diagnosis and disease monitoring
  - Promising fluid biomarkers include neurofilament light chain (for staging, monitoring and prognosis in all FTD subtypes) and dipeptide-repeat proteins and progranulin (for target engagement in gene-specific forms of FTD)
  - Reliable biomarkers that differentiate between tau pathology and TDP-43 pathology are still needed

Time to embrace biomarkers?

- Accessibility
- Affordability
- Acceptability
- Validity of cut-off
  - e.g. Due to variability in absolute levels between laboratories, there is no consensus on medical cut-off value for the CSF AD signature
  - e.g. Lack of cross-validation across academic laboratories, methodologies, cohorts, and industry laboratories

First Alzheimer's Guidelines for Clinical Practice

- Recommendations reported at AAIC 2018 by AADx-CPG workgroup
  - "A" recommendations - must be done and in almost all circumstances will improve outcomes
    - When diagnostic uncertainty remains, obtain additional (Tier 2-4) laboratory tests guided by the patient’s individual medical, neuropsychiatric, and risk profile
    - Neuropsychological evaluation is recommended when office-based cognitive assessment is not sufficiently informative
    - If autosomal dominant family history is likely, should consider whether genetic testing is warranted + genetic counselor involved throughout the process

First Alzheimer's Guidelines for Clinical Practice

- Recommendations reported at AAIC 2018 by AADx-CPG workgroup
  - “B" recommendations - should be done and in most cases will improve outcomes
    - Should obtain MRI to aid in establishing etiology
    - If MRI is not available or is contraindicated, CT should be obtained
    - FDG PET when there is continued diagnostic uncertainty regarding aetiology after structural imaging has been interpreted

First Alzheimer's Guidelines for Clinical Practice

- Recommendations reported at AAIC 2018 by AADx-CPG workgroup
  - “C" recommendations - may be done and may improve outcomes
    - If there is continued diagnostic uncertainty regarding aetiology after structural imaging and/or FDG-PET, obtain cerebrospinal fluid of amyloid beta-42 and tau/p-tau profiles to evaluate Alzheimer's disease pathology
    - If diagnostic uncertainty still exists, an amyloid PET scan may be obtained

Case Vignette

- Ms T, F/52, ground crew, living in Canada with ex-common-law spouse and his current girlfriend
- Good past health except hypothyroidism
- Insidious onset of forgetfulness x 1 year with gradual deterioration
- Difficulty in word finding
- Slow in reading + could not comprehend simple instructions
- Could not cope with work and has been on sick leave since early 2018
- IADL: needed assistance in drug and financial management
Case Vignette

- No feature of DLB, VaD, FTD, PSP, corticobasal degeneration, CJD, Huntington’s
- No Hx of alcohol / substance abuse
- No Hx of head injury
- No depressive symptoms
- MoCA = 9/30
- FHx: mother with dementia, onset 80 yo
- Dx: early onset Alzheimer’s disease
Case Vignette

- Investigation:
  - Anti-NMDA, Rheumatoid factor, HIV, B12, syphilis serology – ve
  - Antinuclear antibody 1/320 +ve
  - CSF culture –ve
  - CTB (9/2017): mild parenchymal loss without focal abnormality
  - MRI (1/2018): mild diffuse cerebral and cerebellar parenchymal vol loss
Case Vignette

- Amyloid PET (10/2018): Positive amyloid scan, with distribution involving bil frontal, posterior cingulate / precuneus, bil lateral temporal, bil parietal, and bil sensorimotor regions
Biomarkers in development

- Blood biomarkers
  - Proteins that originate in brain may be measurable with sensitive blood tests
  - New methods to measure beta-amyloid 42 have improved, suggesting that blood tests may be used in the future for screening and perhaps diagnosis

- Genetic Testing
  - Not routinely used in clinical settings
  - Used under certain circumstances, e.g. when a person has an early age of onset or a strong family history of Alzheimer's or a related brain disease
  - Should be accompanied by genetic counselling before the test and when results are available

https://www.nia.nih.gov/health/biomarkers-dementia-detection-and-research
Biomarkers in development

- Ocular biomarkers
- Reduced ability to smell
- Biomarkers for TDP43, α-synuclein, activation of the innate immune system (astrocytosis, microgliosis), synaptic degeneration and loss (CSF neurogranin), and axonal injury (neurofilament light chain) are either not available or require further investigation
- At this point, these biomarkers are not used to diagnose dementia

https://www.nia.nih.gov/health/biomarkers-dementia-detection-and-research
The Future of Biomarkers

- Develop and validate a full range of biomarkers, particularly those that are less expensive and/or less invasive
- Advance the use of novel PET imaging, CSF, and blood biomarkers to identify specific changes in the brain related to dementia
- Use new MRI imaging to measure brain structure, function, and connections
- Develop and refine sensitive clinical and neuropsychological assessments to help detect and track early-stage disease
- Use biomarkers in combination to build a model of Alzheimer's disease progression over decades, from its earliest, presymptomatic stage through dementia

https://www.nia.nih.gov/health/biomarkers-dementia-detection-and-research
Thank you