Amyloid-Beta and Beyond: Clues from Biosignatures

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Alois Alzheimer

- Described the first AD case in 1906
The case of Auguste D.

- Rapid memory loss
- Disoriented to time and place
- Delusions
- Postmortem heavy build-up of unusual deposits that will later become known as amyloid plaques and neurofibrillary tangles
Dementia subtypes

- **Primary dementia**
  - Alzheimer’s disease (AD) 63 %
  - Frontotemporal lobar degeneration 9 %
  - Creutzfeldt – Jacob disease 1 %
  - Hippocampal sclerosis 1 %

- **Dementia “plus”**
  - Vascular dementia 10 %
  - Dementia with parkinsonism
    - Parkinson disease 2 %
    - Dementia with Lewy bodies 15 %
    - Progressive supranuclear palsy rare
    - Corticobasal degeneration 1 %

The Aging-Dementia Cascade

- Normal Cognition
- Age-Associated Memory Impairment (AAMI)
- Mild Cognitive Impairment (MCI)
- Dementia
DSM-V Dementia Definitions

- **Minor Neurocognitive Impairment**
  - Cognitive decline 1-2 SD from normal on formal cognitive testing
  - Do not interfere with independence
  - Not due to delirium or other medical or psychiatric disorder

- **Major Neurocognitive Impairment**
  - Cognitive decline ≥2 SD from normal on formal cognitive testing
  - Interfere with independence
  - Not due to delirium or other medical or psychiatric disorder
NIA-AA Dementia Syndrome

- Objective cognitive or behavioral impairment in **at least 2 of the following**:  
  - Memory  
  - Reasoning and handling complex tasks  
  - Visuospatial abilities  
  - Language functions  
  - Personality, behavior or comportment

- Decline from previous level of functioning

- Functional impairment

Sperling et al, Alzheimer’s and Dementia 2011
NIA-AA Probable Alzheimer’s Dementia Criteria

- Meets criteria for dementia
- Insidious onset
- Gradual progression
- Initial symptoms
  - Amnestic
  - Nonamnestic (language, executive)
- No other contributors (VaD, DLB, FTD, other)
- Positive biomarkers increase Dx certainty
NIA-AA Mild Cognitive Impairment

- Concern for cognitive decline by patient, informant or physician
- Objective evidence of cognitive decline in 1 or more domains
- Intact functional abilities
- Not Demented
- Positive AD biomarkers can support MCI due to AD

Albert et al, Alzheimer’s and Dementia 2011
NIA-AA - Preclinical AD

- Stage 1 – asymptomatic amyloidosis
- Stage 2 – asymptomatic amyloidosis and neurodegeneration
- Stage 3 – amyloidosis, neurodegeneration and subtle cognitive impairment

Sperling et al, Alzheimer’s and Dementia 2011
The AD Biomarker Cascade

- Aβ
- Tau-mediated neuronal injury and dysfunction
- Brain structure
- Memory
- Clinical function

Abnormal

Normal

CLINICAL DISEASE STAGE

Cognitively normal

MCI

Dementia

FACE
VELVET
CHURCH
DAISY
RED

E End
A
B
C
D
1 Begin
2
3
4
Amyloid Imaging Pathologic Validation

BTA-1 = PIB  Ikonomovic et al, 2008
Amyloid PET Ligands

- Flutemetamol\(^1\)
- Florbetapir\(^2\)
- Florbetaben\(^3\)
- Navidea NAV4694\(^4\)
The Amyloid PET Spectrum
Prevalence of brain amyloidosis in ADNI
The AD Biomarker Cascade

- Abnormal:
  - Aβ
  - Tau-mediated neuronal injury and dysfunction
  - Brain structure
  - Memory
  - Clinical function

BIOMARKER MAGNITUDE

- Normal

CLINICAL DISEASE STAGE

- Cognitively normal
- MCI
- Dementia

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End
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Functional Neuroimaging: FDG-PET

- Classic pattern of hypometabolism in temporoparietal regions and medial parietal lobes bilaterally in AD

- Approved by MediCare in the differential diagnosis between AD and frontotemporal dementia
Positron Emission Tomography in Alzheimer’s Disease
Positron Emission Tomography in Alzheimer’s Disease

Ghosh PM et al. AAIC, 2014.
The AD Biomarker Cascade
Normal vs. Severe Alzheimer’s Brain

MRI in MCI

No MTA; less likely to progress to dementia

MTA; likely to progress to dementia

AD progression as seen on 3D Cortical Imaging

Apostolova et al, Arch Neurol 2007

Thompson et al, Cereb Cortex 2004
Biosignatures can assist accurate diagnosis and prognosis

Jack et al. Brain 2010
AD or not AD?
AD or not AD?
AD or not AD?
The AD Biomarker Cascade
Tau Imaging

Fodero-Tavoletti et al, 2011
Amyloid and Tau PET Patterns

Images generated through CapAIBL® (milxcloud.csiro.au)
CSIRO Biomedical Imaging Group

Villemagne, AAIC 2014
Tau PET and MRI patterns

\(^{18}\text{F-THK5117}\)

Voxelwise analysis

Tau (neurofibrillary tangles)

Cortical grey matter atrophy
Amyloid and Tau PET cognitive correlations

Value of Biomarkers in the Clinic

- Improved diagnostic accuracy
  - Nearly 50% of patients with clinically diagnosed MCI, and 20% of those with dementia are misdiagnosed with AD

- Accurate diagnosis can prevent:
  - Excess diagnostic testing
  - Inappropriate treatments
  - Inappropriate long term planning and use of resources
  - INCREASED COST

- Accurate diagnosis promotes:
  - Education
  - Safety
  - Future planning
Amyloid PET Interpretation

- A negative amyloid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition.

- A negative scan reduces the likelihood that a patient's cognitive impairment is due to AD.

- A positive amyloid scan indicates moderate to frequent Amyloid neuritic plaques.

- Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.
Amyloid imaging is appropriate in the following situations:

- A cognitive complaint with objectively confirmed impairment
- Performed only after full standard w/u is completed:
  - Structured clinical evaluation with objective neurocognitive testing
  - Structural brain imaging
  - Relevant laboratory tests
- AD as a possible diagnosis, but uncertain
- Knowledge of Aβ pathology would increase diagnostic certainty and alter management
- Should only be ordered by dementia experts
  - Specialty training, ≥25% dementia care practice
  - Geriatric Psychiatry and Neurology

Inappropriate Use Amyloid PET Imaging

- For evaluation of individuals without cognitive complaints
- For evaluation of individuals with cognitive complaints but without objective cognitive decline
  - NOTE: preclinical AD may become indication for Amyloid Imaging if preventive treatments are proved to be effective
- In the absence of complete standard work up
- As a stand alone diagnostic for AD dementia
- To assess disease progression