Alzheimer’s Disease - the spectrum of clinical presentations

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How do we characterize Alzheimer’s disease?

• Age of onset
• Family history/genetics
• Initial clinical features
• Subsequent clinical features
• Pathology
• Neuroimaging/other biomarkers
Alzheimer’s ain’t Alzheimer’s

• Spectrum of initial presentations and subsequent course
• Likely correlates with distribution and progression of pathology
  – and development/presence of any additional pathology
• Reflected in neuroimaging
• Autopsy only shows us the final picture
  – by then, most pathological patterns have merged
THE BINDING OF PIB MATCHES THE HISTOPATHOLOGY OF Aβ.

Braak Stages (1997) 
A  B  C
Clinical presentations (“phenotypes”) of AD

• Amnestic
  – Most common
• Language
  – Logopenic aphasia
• Visuospatial
  – Posterior cortical atrophy
• Behavioural
  – Frontal variant AD
Amnestic AD

• Memory loss a prominent early feature
  – esp episodic memory
  – not greatly assisted by cueing

• Early pathology in the limbic system, including hippocampus

• Over time, pathology spreads, as in the Braak stagings
  – and clinical features expand to include visuospatial, language and behavioural features
  – more advanced stages involve executive function and eventually motor function

• But much variation in progression and timing of subsequent clinical features
Hippocampal atrophy in amnestic AD
Logopenic Aphasia

• Prominent early language changes
  – Slow speech rate
  – Long word-finding pauses
  – Repetition and comprehension impaired for sentences but preserved for single words
  – Naming moderately affected

• Left superior and middle temporal gyri and inferior parietal lobules affected

1. Gorno-Tempini Neurology 2008;71:1227-34
Logopenic apahasia-MRI and SPECT

Voxel-based morphometry analysis: Pattern of gray matter atrophy (Cases 1-4)

Case 1  
Case 2

Case 3  
Case 4

99mTc-ECD SPECT analysis: Pattern of cerebral blood hyperfusion (Cases 5-6)

Case 5  
Case 6
Logopenic Aphasia: FDG-PET
Posterior Cortical Atrophy

• Early difficulties with visual and spatial functions
  – recognizing faces
  – working out what an object is
  – working out how to dress/undress
  – locating chair position when sitting

• Later, can develop difficulties with literacy and numeracy

• Memory and language preserved early on

• Often affects younger people (50s and 60s)

• Prominent atrophy of the posterior cortical regions
Posterior Cortical Atrophy
Posterior Cortical Atrophy
Frontal variant AD

- Older patient
- Behavioural/frontal features prominent early
- Amnestic disorder usually also present
- Clinical features suggest AD but differential diagnosis is FrontoTemporal Lobar Degeneration
- Neuroimaging often consistent with AD
Pathology in FvAD/FTLD

• Johnson: predominant frontal NFTs in AD with behavioural onset
  
• Woodward: 37 of 45 autopsied cases from ACCORD dementia cohort had AD pathology – 8 had coexisting FTLD-TDP43 pathology
  
• but only one had clinical diagnosis of AD + FTLD

• In a pathological series of 60 patients with clinically diagnosed FTLD, 7% had AD pathology alone and a further 10% had mixed AD and glial pathology


Distinguishing AD with frontal features from FTLD

- Can be difficult if relying on diagnostic criteria
- NINCDS-ADRDA criteria show low specificity in distinguishing AD from FTLD
  - most FTLD patients fulfil criteria for AD¹
- Lund- Manchester criteria for FT(L)D frequently misdiagnose AD
  - 34% of 185 community dementia cases with AD fulfilled these criteria for FTLD²
- FDG-PET scanning in a series of autopsy proven FTLD and AD cases demonstrated much overlap in patterns of hypometabolism³
  - AD cases were not evaluated for frontal clinical features

FTLD- also not a single clinical entity

• Rapid evolution in our understanding of FTLD
• Can be cut pathologically, clinically, genetically and other ways
  – correlation not always strong
• Clinically, 3 main clusters:
  1. Frontal/behavioural onset (sometimes called FvFTLD or BvFTLD)
  2. Language onset
  3. Motor onset/ features
Using assessment scales to distinguish AD, FvAD and FTLD

- Several scales suitable for assessing frontal function
  - Frontal Assessment Battery (FAB)
    - Assesses executive dysfunction
  - Exit-25
    - Executive, cognitive
  - Frontal Behavioural Inventory (FBI)
    - Behavioural
  - Neuropsychiatric Inventory (NPI)
    - Psychiatric features
Defining FvAD - ACCORD Cohort

ACCORD Cohort- FBI Scores

- Selected cut point: 25 (close to suggested score for Dx FTLD-27; higher=more frontal)