Neuroimaging/neuropathology correlates: a study in the “older old”

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Overview

1. The population of particular interest at the Oregon ADC
2. The dementia phenotype associated with white matter hyperintensities (WMHs)
3. A “twin” study: pathologic structural correlates of WMHs
4. A serendipitous “discovery”
5. Implications for how we think about dementia in older patients
The Oregon ADC

• Focus on healthy aging

• The Oregon Brain Aging Study:
  – Initiated 1989
  – Community-dwelling, >65, free of known risk factors for cognitive decline (vascular disease, hypertension, diabetes)
  – Annual neurological/neuropsych/mental functioning/balance tests, MRIs

• 74% convert to MCI at average 89.9 years

• 43% of MCI convert to dementia
Overall US life expectancy is now 79 years

US life expectancy for 40M+ >65 is now 84 years

- The “older old” are relatively unique as a study population, but are the dominant population that is susceptible to dementia in western societies
NP and NFT scores in younger and older demented, all OADC subjects (without synucleinopathy, FTLD, non-AD tauopathy), past 10 years (%)

CERAD neuritic plaque scores

- None
- Sparse
- Mod
- Frequent

Braak neurofibrillary tangle stages

- Braak 1
- Braak 2
- Braak 3
- Braak 4
- Braak 5
- Braak 6
Biochemical hallmarks of AD decrease with age

Insoluble Aβ42

Insoluble phosphotau

ELISA signal x42

ELISA signal pTau199

P<0.001

P<0.001
A plateau occurs at around age 80-85

**Insoluble Aβ42**

**Insoluble phosphotau**
Phenotypes of cognitive impairment at age >85

- “Pure AD”: relatively rare
- Hippocampal sclerosis: more common
- “Mixed dementia”: very common
  - Sparse neuritic plaques
  - Braak stage 4 NFTs
  - Variable microvasculature-based tissue injury
  - “Dementia of the oldest (older?) old” (“DOOOO”)
White matter hyperintensities

• A possible marker of non-cortical based contribution to dementia in older subjects
• Observed on T2-weighted MRI scans
• Age and vascular risk factors are main clinical associations
• Associated with cognitive impairment
• Accelerated WMH volume change point 10 years before MCI [Silbert et al., 2012]
• Neuropathologic correlates described previously: “incomplete ischemic destruction” with myelin pallor proceeding to tissue infarction
**Change point: 10.6 years**

(95% CI 5.16, unknown) prior to conversion; WMH trajectory accelerates 6.5% of the previous value annually, $p < 0.0001$

After change point, WMH increased by an additional 3.3% of the previous value annually, $p = 0.04$

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Enter the twins (stage left and right)
• Mild cognitive impairment, MRI showed moderate to high WMH burden; the twins died within days of each other
• Neuropathology: sparse neuritic plaques, Braak 4 NFTs, high microvascular lesion burden
• Prototypical “mixed” or “DOOO” pathologic findings investigated by postmortem MRI followed by histopathologic correlation

12 paired WM areas each brain
Myelin pallor correlates with WMH abnormality

Nonimpaired control  Twin non-WMH  Twin WMH
Many myelin proteins affected in areas of myelin pallor

Non-WMH

WMH
Axons affected in areas of most marked myelin pallor

Non-WMH

WMH
Progressive WM injury in WMHs

- Ongoing work: what imaging findings correlate with clinical and histologic features of these types of tissue injury?
Changes in cortex overlying WMHs

Non-WMH

[Images showing Synaptophysin and AQP4 in Non-WMH regions]

WMH

[Images showing Synaptophysin and AQP4 in WMH regions]
Other astrocyte changes in cortex overlying WMHs

GFAP

AQP1

Non-WMH

WMH
Aquaporin 1

- Normally expressed in choroid plexus; water-selective (non-ionic) channel for CSF production
- Not detected in astrocytes in normal brain
- Increased in reactive astrocytes in a host of injuries including trauma, AD (plaque-associated), MS, CJD, epilepsy
- A sensitive marker of altered vascular permeability associated with brain responses to disease?
Frontal cortex in impaired (CDR=1 or greater) vs. non-impaired (CDR=0) patients >85 years (none with high-burden AD)
Open questions

• Is AQP1 merely a supersensitive GFAP surrogate (“pathology integrator”), or does it inform us of the presence and nature of a clinically relevant disease process in older patients?
• Is AQP1 expression a purely reactive phenomenon to injury, or do changes in astrocyte function (“astrocytopathy”) contribute to brain dysfunction in this population?
• Is astrocytopathy a viable therapeutic target?
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