Characterizing clinical variants of Alzheimer's disease

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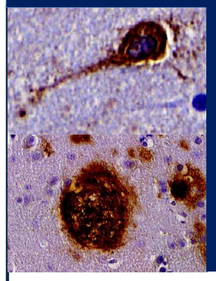
Summary: Quantitative measures to capture pathological burden may discriminate clinical frontotemporal dementia variants of neuropathological Alzheimer's disease (AD)

Introduction



Clinical FTD Types

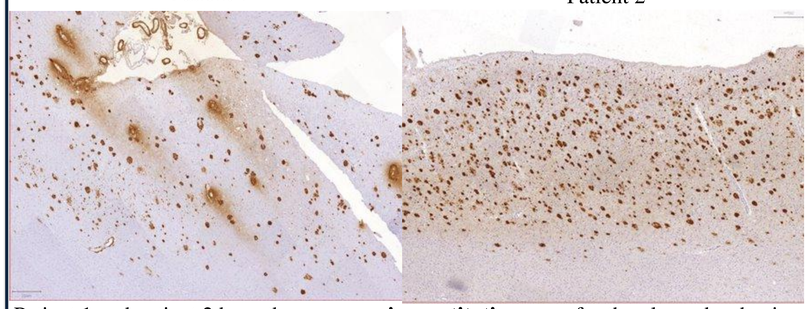
lvPPA CBS bvFTD

Neuropathological Alzheimer's

Neuropathological Alzheimer's disease (AD) is clinically heterogeneous and can present with non-amnestic symptoms. This can lead to a non-AD clinical diagnosis, including **corticobasal syndrome** (CBS), **logopenic variant primary progressive aphasia** (lvPPA), and **behavioral variant frontotemporal dementia** (bvFTD). What accounts for these "atypical" clinical presentations is currently unknown. Therefore, better characterizing these AD clinical variants may offer insight into understanding the underlying mechanisms.

Quantitative vs. Semi-Quantitative

Patient 1 Patient 2



Patient 1 and patient 2 have the same **semi-quantitative** score for the plaque burden in the temporal gyrus. But, within one semi-quantitative score may exist wide ranging variability. Both patients had neuropathological AD, but each presented with a different clinical phenotype (Patient 1: bvFTD, Patient 2: CBS). **Fully quantitative** measures may be able to discriminate AD variants based on their pathological burden.

Clinical Relevance

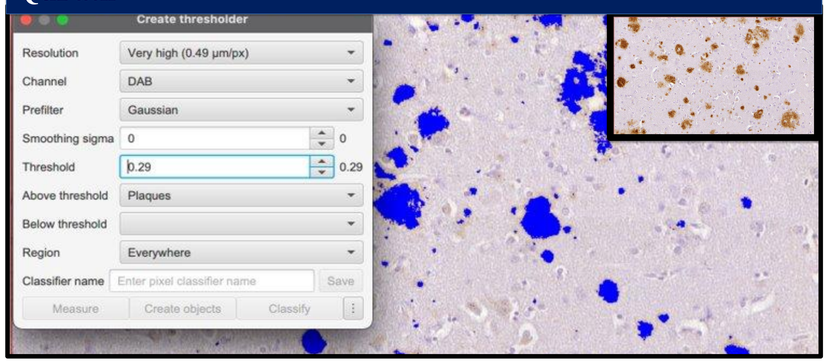
	Typical presentation	Atypical presentation	p Value
Initial clinical misdiagnosis, %	4	53	0.0003

Balasa et al. 2011 *Neurology*

Hypothesis

The orbitofrontal cortex in FTD-AD cases *(clinical frontotemporal dementia cases with neuropathological Alzheimer's)* have a greater pathological beta-amyloid and tau burden than that of AD-AD cases *(clinical Alzheimer's cases with neuropathological Alzheimer's).*

QuPath



Methods

Regions Sampled:
Orbitofrontal cortex
Middle frontal gyrus
Superior temporal gyrus
Angular gyrus

Antibodies:
NAB228 (beta-amyloid)
PHF1 (tau)

Quantitative Measures:
% Area occupied by pathology
Beta-amyloid/tau ratio
Beta-amyloid plaque counts
Cerebral amyloid angiopathy counts
Neurofibrillary tangle counts
Laminar distribution of plaques and tangles

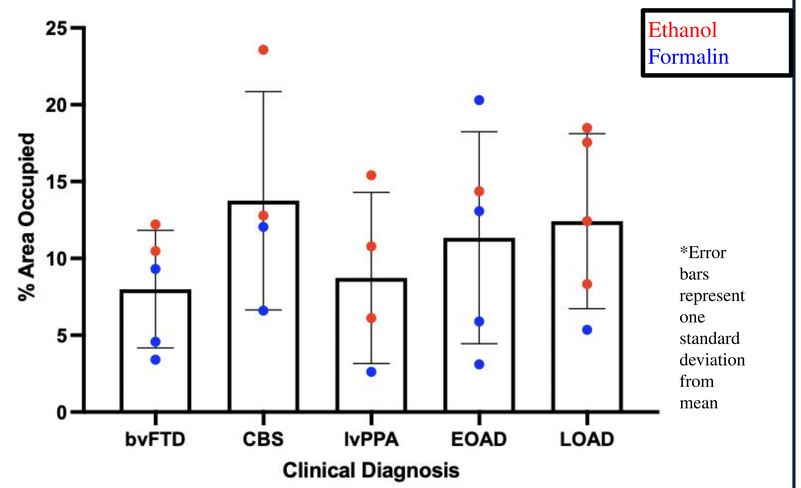
Cohort

Clinical Diagnosis	n	Female (%)	Right hemisphere (%)	Mean age at onset	Mean age at death	Proportion APOE e4 carriers (%)
CBS	5	80	40	58.7	69.3	0
bvFTD	4	50	25	54.8	63.8	25
lvPPA	5	80	20	57.5	68.2	0
Early-onset AD (EOAD)	5	40	40	58.8	67.2	100
Late-onset AD (LOAD)	5	80	100	72	79.2	100

*Sampled 4 additional formalin/ethanol cases from the same patient and brain region to test to fixative variability

Results

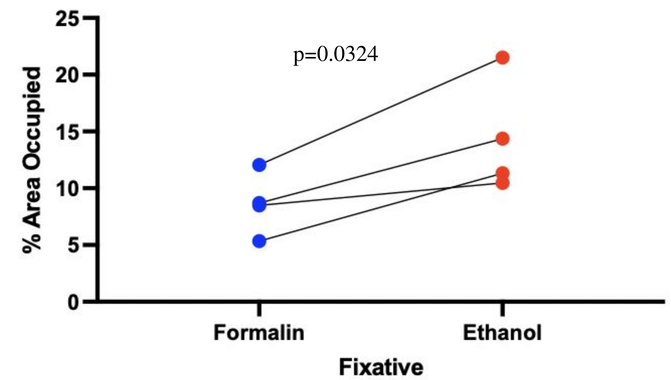
Figure 1 | Orbitofrontal beta-amyloid plaque % area occupied



*Error bars represent one standard deviation from mean

- To evaluate the reliability of this data, we asked if there was a significant difference between fixation in ethanol and formalin for corresponding cases.

Figure 2 | Fixative variability



Next Steps

1) Determine effect of fixative variability and other potential confounding variables on measurements
2) Gather beta-amyloid and tau measurements for other brain regions (temporal, frontal, angular)
3) Expand cohort size

Acknowledgements

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