

Postmortem Microinfarcts and White Matter Hyperintensities in Dominantly Inherited Alzheimer Disease

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Introduction

- In sporadic or late-onset AD, the presence of cerebral microinfarcts and white matter hyperintensities (WMH) on imaging have been strongly associated with dementia and with age
- Dominantly inherited Alzheimer disease (DIAD) is a rare form of Alzheimer's disease (AD) caused by pathogenic mutations in the amyloid precursor protein (APP), presenilin-1 (PSEN1), or presenilin-2 (PSEN2) genes

Objective of Study

Investigate whether amyloid (A β) burden and clinical symptoms are associated with microinfarcts and WMH detected on ex vivo imaging.

Study Design

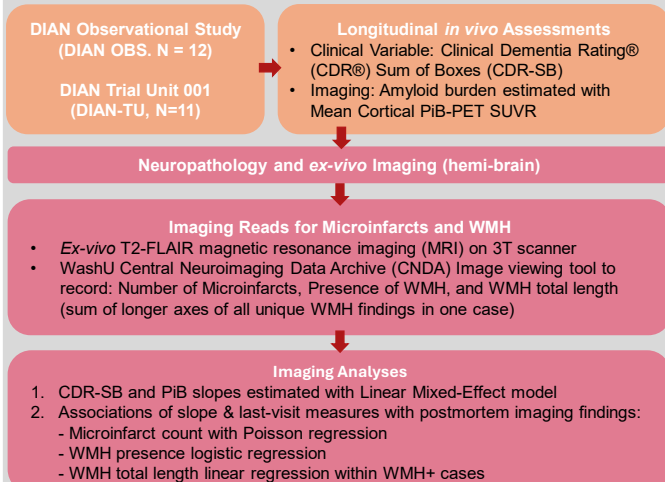


Figure 1. Study workflow and analyses. Models adjusted for APOE- $\epsilon 4$ carrier status, age at death, years between final visit and death, DIAN vs DIAN-TU, anti-A β treatment exposure (DIAN-TU participation)

Clinical Features and Postmortem Imaging Findings

Participant Characteristics

Table 1 - Clinical Characteristics

Variable	Overall (n=23)	DIAN OBS (n=12)	DIAN-TU Untreated (n=3)	DIAN-TU Treated (n=8)
Age baseline, mean $\pm$ SD (years)	54.95 $\pm$ 8.32	55.75 $\pm$ 7.92	59.00 (NA)	52.67 $\pm$ 10.01
Age at last visit, mean $\pm$ SD (years)	51.52 $\pm$ 8.21	51.17 $\pm$ 8.08	54.67 $\pm$ 11.15	50.88 $\pm$ 8.31
Time between last visit and death, mean $\pm$ SD (years)	3.58 $\pm$ 2.36	4.58 $\pm$ 2.19	0.00 (NA)	2.17 $\pm$ 1.47
Female, n (%)	10 (43.5)	6 (50.0)	2 (66.7)	2 (25.0)
APOE- $\epsilon 4$ carrier status, n (%)	12 (52.2)	6 (50.0)	1 (33.3)	5 (62.5)
EYO baseline, mean $\pm$ SD	2.28 $\pm$ 3.55	3.84 $\pm$ 3.17	0.92 $\pm$ 2.72	0.44 $\pm$ 3.58
CDR-SB, mean $\pm$ SD	8.74 $\pm$ 4.67	9.83 $\pm$ 4.58	5.33 $\pm$ 3.18	8.38 $\pm$ 5.04
Mean Cortical PiB SUVR, mean $\pm$ SD	3.43 $\pm$ 1.24	3.39 $\pm$ 1.02	3.32 $\pm$ 1.01	3.50 $\pm$ 1.55

Postmortem Imaging Reads

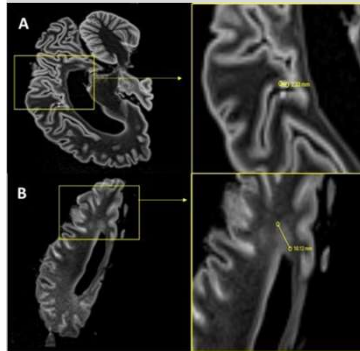


Table 2 - Postmortem Characteristics				
Variable	Overall (n=23)	DIAN OBS (n=12)	DIAN-TU Untreated (n=3)	DIAN-TU Treated (n=8)
Microinfarct Count, median (IQR)	7.00 (7.00)	6.50 (7.75)	4.00 (7.00)	8.50 (4.75)
WMH Present, n (%)	13 (56.5)	9 (75.0)	0 (0.0)	4 (50.0)
WMH Length, mean $\pm$ SD	12.46 $\pm$ 13.37	17.89 $\pm$ 14.51	0.00 $\pm$ 0.00	9.00 $\pm$ 10.03

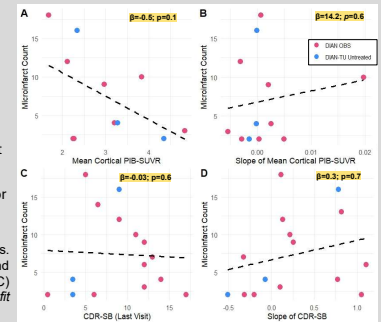
Figure 2. Microinfarct (A) and white matter hyperintensity (B) on 3T ex-vivo T2 FLAIR MRI

Disease Progression and Treatment Exposure

Evaluation of the relationship between disease progression and postmortem findings

- Microinfarct count tended to be associated with last visit mean cortical PiB-PET SUVR but was not associated with rate of change
- Last visit CDR-SB and rate of change were not associated with microinfarct
- No associations of PiB or CDR-SB were found with the WMH presence or severity

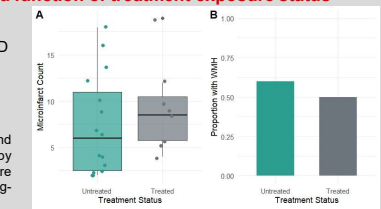
Figure 3. Scatterplots of microinfarct count vs. Mean Cortical PiB-SUVR at last visit (A) and slope (B), and versus CDR-SB at last visit (C) and slope (D). *Dash line represents linear fit of raw data. Actual statistics are highlighted.



Postmortem imaging findings as a function of treatment exposure status

- No difference in microinfarct count between treated and untreated DIAD participants
- Similar number of cases with WMH regardless of treatment status

Figure 4. Boxplot for microinfarct count (A) and bar graph for WMH proportions (B) by treatment status. Anti-A β treatment exposure was examined as a secondary analysis. Drug-specific treatment effects were not evaluated.



Conclusion

- In DIAD, postmortem microinfarcts and WMH show limited association with antemortem amyloid burden
- These findings suggest that microvascular pathology may play a limited role in shaping the clinical and biomarker phenotype of dominantly inherited AD