COMORBID PATHOLOGY IN CLINICAL TRIAL PARTICIPANTS: AUTOPSY FINDINGS AND CLINICAL FEATURES

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BACKGROUND

The presence of multiple comorbid pathologic features in late-onset dementia has been well documented across cohort studies that incorporate autopsy evaluation. It is likely that such mixed pathology potentially confounds the results of interventional trials that are designed to target a solitary pathophysiologic mechanism in Alzheimer's disease and related dementias (ADRD).

METHODS

No trial and trial data compared by:

Demographics (age, sex, education, race/ethnicity)
Genetics (ApoE4 allele)
Clinical info (MMSE, CDR global, CDR sum of boxes)

Trial groups were compared with NACC Neuropath criteria: (dichotomous fashion)

TDP-43 (yes=1 / no= 0)

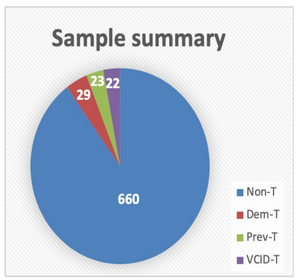
CERAD score *(Amyloid)* 0=A vs 1=B/C

Braak stage *(tau)* 0=1/2 vs 1= 3/4/5/6

LBP *(a-synuclein)* (yes=1 / no= 0)

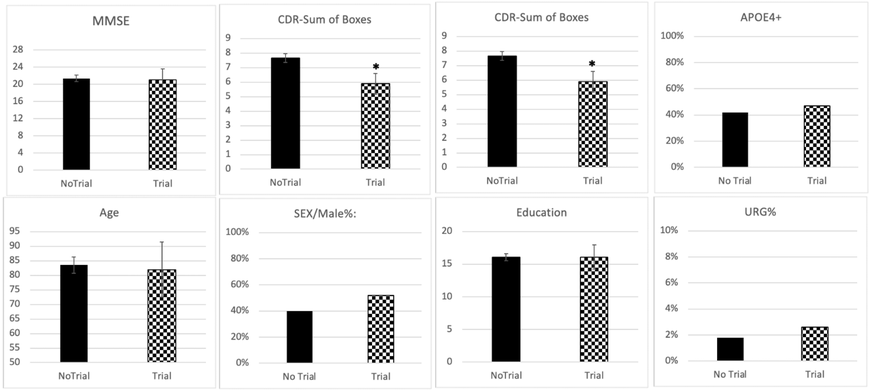
CVD score: CVD >1 if more than 1 of the following

- Total infarct *(0 vs 1)*
- Atherosclerosis *(0=0/1 vs 1=2/3/4)*
- CAA *(0=no/mild vs 1=mod/severe)*
- Arteriolosclerosis *(0=none/mild vs 1=mod/severe)*

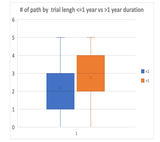


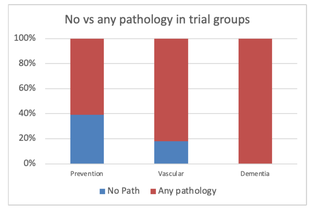
Standard descriptive and comparative statistics were applied to the resulting dataset

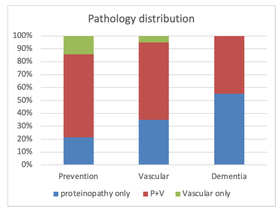
RESULTS

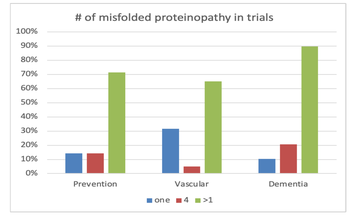


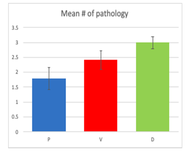
1: Autopsy cases for those who previously engaged in clinical trials did not differ significantly from those that were trial-naïve with respect to demographic (A: Age, B: Edu, C: Sex, D: Underrepresented group -URG-), clinical characteristics (E: MMSE at last visit, F: CDR-SUM, G: CDR-Global), or genetic (H: ApoE), *(*$p>0.05$*, Bars represents SE)*

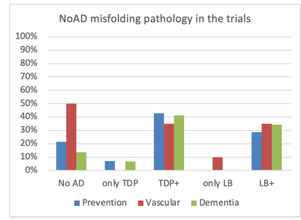












Summary of results

- Demographically trial participants who had autopsy are no different than nontribal participants in our cohort.
- The number of pathology did NOT change with duration of the clinical trials.
- Having no pathology seen 39% in preventive, 18% in the vascular group. The dementia trials have 100% some sort of pathology.
- In those pathologies, the majority of the pathology are coexisted as proteinopathy and vasculopathy.
- 2 or more misfolding proteinopathy ranged in 65 to 90 % range in 3 trials, with average pathology ranged 2-3 in trials
- While no pure AD pathology seen in preventive and vascular trial, only 28% of the dementia trials had pure AD pathology. In dementia trial, 90% of the participants had AD coexist with other pathology.
- Non AD proteinopathy (DLB and LATE) biomarkers are seen in the range of 30 to 43 % while clinically these participants described as clinical AD.

REFERENCES

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- *Erin Abner, Nelson PT 2017 Ann Neurol. 2017 Apr;81(4):549-559. Outcomes after diagnosis of mild cognitive impairment in a large autopsy series*
- *Duara R, Barker W. Neurotherapeutics (2022) 19:8–25, Heterogeneity in Alzheimer's Disease Diagnosis and Progression Rates: Implications for Therapeutic Trials*

CONCLUSIONS

70-90% of AD & ADRD trial participants had comorbid mixed pathologic features.

Our results provide evidence to consider the wide heterogeneity of pathologies in clinical trial participants. The following applications should be considered:

- Need to improve inclusion/exclusion criteria to minimize/maximize heterogeneity based on trial types
- Stratify the likelihood of mixed comorbid pathology by:
  - rational use of antemortem biomarkers
  - Implement clinical characteristics
- Set infrastructure for multimodal clinical trials for mix pathology
- Consider complex statistical designs to validate/improve the success rate of trials