The prevalence and severity of TDP-43 pathology in Alzheimer's disease.

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Summary: In presence of Alzheimer's disease (AD) dementia, limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is an additional correlate of cognitive decline

Introduction

About half of all individuals with AD dementia have TDP-43 proteinopathy as an additional co-pathology[4]. TDP-43 proteinopathy is primarily intraneuronal accumulations of phosphorylated TDP-43. The accumulation pattern of TDP-43 has recently been described as LATE-NC (limbic age-associated TDP-43 encephalopathy neuropathological change)[10]. To better understand the role of LATE-NC in AD dementia, we asked the following:

1) When in the clinical course of AD does LATE-NC appear?

2) When in the development of AD pathology does LATE-NC appear?

3) Is LATE-NC purely age-associated?

4) Besides prevalence, is LATE-NC severity also important?

We designed a clinicopathological study using 522 individuals in the CNDR (Center for Neurodegenerative Disease Research) cohort to assess the clinical significance of LATE-NC in AD dementia.

Methods

- Examined 522 cases available in the CNDR brain bank on AD clinical and pathological spectrum for LATE-NC and ADNC
- LATE-NC was staged: amygdala (stage 1), hippocampus (stage 2), middle frontal gyrus (stage 3)[10]
- ADNC (Alzheimer's disease neuropathological change) cases diagnosed low, intermediate, high, or PART (primary age-related tauopathy)[1,9]
- When CDR (Clinical Dementia Rating) was unavailable, score deduced from MMSE (Mini-Mental State Examination) score
- Logistic regression models used to quantify effect of dementia status, AD pathology, age, and APOE allele
- Statistical significance set at p-values <0.05

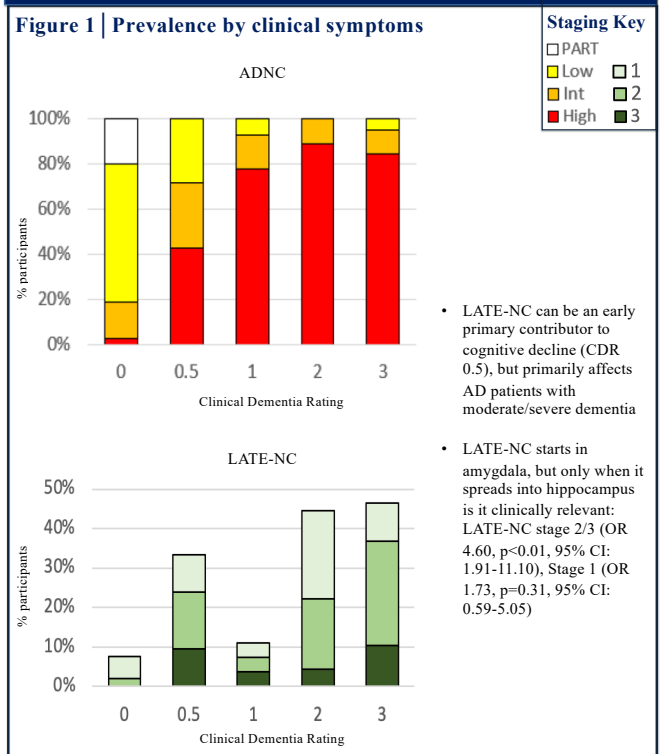
Cohort

Table 1 | CNDR cohort

- The Center for Neurodegenerative Disease Research (CNDR) cohort consisted of participants 50 years and older with and without clinical dementia. Of 665 participants referred to the CNDR autopsy program, 522 had enough tissue available to stage AD burden, CAA, LATE-NC and Lewy body pathology.

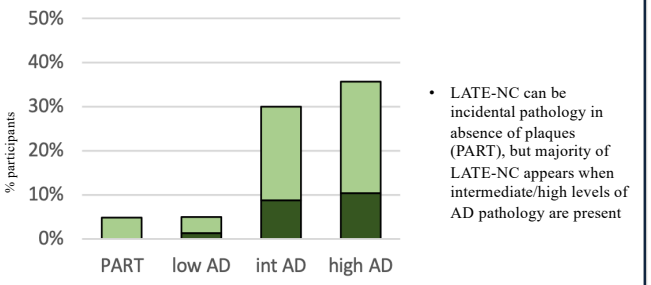
Results

Figure 1 | Prevalence by clinical symptoms



- LATE-NC can be an early primary contributor to cognitive decline (CDR 0.5), but primarily affects AD patients with moderate/severe dementia
- LATE-NC starts in amygdala, but only when it spreads into hippocampus is it clinically relevant: LATE-NC stage 2/3 (OR 4.60, p<0.01, 95% CI: 1.91-11.10), Stage 1 (OR 1.73, p=0.31, 95% CI: 0.59-5.05)

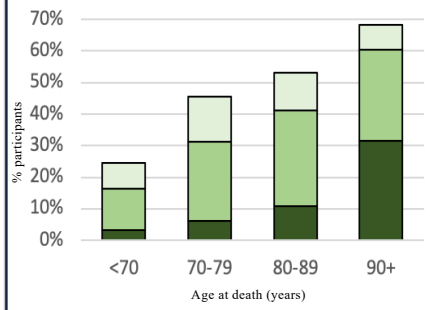
Figure 2 | Prevalence by level of AD pathology



- LATE-NC can be incidental pathology in absence of plaques (PART), but majority of LATE-NC appears when intermediate/high levels of AD pathology are present

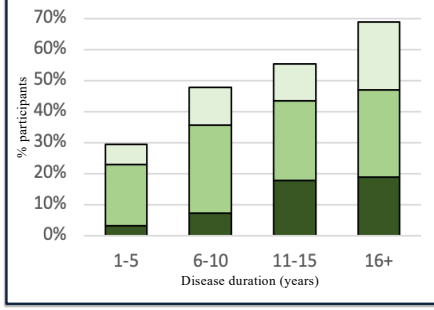
Results (continued)

Figure 3 | Prevalence by age at death



- Age is primary driver in cases with dementia (OR 1.30, p<0.01, 95% CI: 1.15-1.46) and without dementia (not shown, OR 1.48, p<0.01, 95% CI: 1.16-1.88)

Table 4 | Prevalence by disease duration



- Length of disease also plays role in LATE-NC prevalence (OR 1.06, p=0.01, 95% CI: 1.01-1.11)
- LATE-NC is independent of APOE status with dementia (not shown, ε4: OR 1.15, p=.52, 95% CI: .75-1.75, ε2: OR .68, p=.41, 95% CI: 0.28-1.69)

Interpretation

1) Our data argues for earlier disease interventions. AD trials may miss clinical targets in older age groups, especially since LATE-NC prevalence may influence early cognitive decline.

2) Anti-tau and anti-AB compounds may be effective treatments for LATE-NC as the majority of LATE-NC in AD is downstream of plaques and tangles

3) TDP-43 biomarkers and therapies should also be developed.

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References