J Neuropathol Exp Neurol
Vol. 80, No. 7, July 2021, pp. 649–651
doi: 10.1093/jnen/nlab050

ORIGINAL ARTICLE

LATE Neuropathologic Changes with Little or No Alzheimer Disease is Common and is Associated with Cognitive Impairment but Not Frontotemporal Dementia

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Abstract

Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) often occur in aged brains that also contain appreciable Alzheimer disease neuropathologic changes (ADNC). Question has arisen as to whether LATE-NC can occur independently of ADNC. We evaluated data from the University of Kentucky Alzheimer's Disease Research Center autopsy cohort (383 included subjects) to address 2 questions: (i) Is LATE-NC seen in the absence of ADNC, outside of persons who had the frontotemporal dementia (FTD) clinical syndrome? and (ii) is LATE-NC associated with cognitive impairment across the full spectrum of ADNC severity? In the present study, the pathologic combination of LATE-NC (Stage >1) and low/no ADNC was common: 8.9% (34/383) of all subjects (including demented and non-demented individuals) showed this combination. There were no FTLD-TDP cases to be included from the community-based cohort. Across a broad range of ADNC severity, the presence of LATE-NC was associated with impaired cognition but was never associated with a FTD clinical syndrome.

Key Words: Community-based, Frontotemporal lobar degeneration (FTLD), Hippocampal sclerosis, Human, Lewy, Neuropathology.

INTRODUCTION

The terminology and classification recommended for the neuropathologic changes of limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) (1) have generated controversy and some important questions (2, 3). Two such questions are: (i) Is LATE-NC sometimes seen in the absence of Alzheimer disease neuropathologic changes (ADNC), outside of frontotemporal dementia (FTD) cases? and (ii) Is LATE-NC associated with cognitive impairment across the full spectrum of ADNC severity? Data are presented here to help address those questions.

MATERIALS AND METHODS

The University of Kentucky AD Research Center (UK-ADRC) operates a community-based autopsy cohort, recruiting cognitively normal subjects and following them longitudinally, often over decades, to autopsy (4). Methods of recruitment, autopsy diagnoses, and other aspects of the UK-ADRC autopsy cohort workflow have been described previously (5, 6). Occasionally, subjects are followed in the UK-ADRC cohort that derived from a local dementia clinic, and were demented at recruitment. Such individuals tend to have frontotemporal lobar degeneration (FTLD) and other rare conditions; these were excluded from the current study. To be clear, if a subject had been followed from normal status in the community-based cohort and developed full-blown FTD/FTLD, they would have been included in the present study. Otherwise, criteria for inclusion were: >75.0 years of age at death; hippocampal TDP-43 proteinopathy data were available; and final Mini-Mental State Examination (MMSE) scores were available.

RESULTS

Data on included subjects are presented in Table 1. Numbers of individuals autopsied, stratified by neuropathologic findings (Braak neurofibrillary tangle [NFT] stages and LATE-NC status [LATE-NC Stage >1]) are shown in Table 2. LATE-NC Stage > 1 was selected as the cut-point because that degree of pathologic involvement was shown previously to correlate with cognitive symptoms (7). Overall, 31.6% (121/383) of all cases had autopsy-confirmed LATE-NC Stage >1 (hereafter referred to as "LATE-NC+") and 8.9% of all cases (34/383) had the combination of LATE-NC+ with Braak NFT Stage <IV (bolded numbers in Table 2).

Whereas data on demographics, co-pathologies, and *APOE* information for all included subjects are provided in Table 1, Table 3 shows data comparing LATE-NC− and LATE-NC+ among individuals that had Braak NFT Stages 0–III. Table 4 shows the average final MMSE scores of all the subjects presented in Table 1. The lower MMSE scores in

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Funding included NIH grants P30 AG028383, R01 AG057187, R01 AG042475, R01 AG054060, and RF1 NS118584.
The authors have no duality or conflicts of interest to declare.

TABLE 1. Demographics, *APOE*, and Copathologies of Included Subjects (n = 383)

	LATE-NC-*	LATE-NC+*	p-value**
N	262	121	
Age of death, average (Avg)	87.8	89.4	0.014
Sex, %F	61.5	61.1	0.96
MMSE, Avg	24.0	17.7	6.4 E-13
APOE 4+ (%)	34.7	38.8	0.44
Brain weight (g), Avg	1174.5	1119.2	0.001
Cortical Lewy body pathology (%)	8.8	11.6	0.39
Arteriolosclerosis (0–3), Avg	1.08	1.23	0.13
Cerebral amyloid angiopathy (0–3), Avg	0.73	1.08	0.002
Gross infarcts, Avg	0.54	0.50	0.79
Braak NFT stage, Avg	3.35	4.32	n/a
CERAD neuritic plaque density (0–3), Avg	1.47	2.05	n/a
Hippocampal sclerosis (%)	5.3	68.6	1.7 E-52

*Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) indicates LATE-NC Stage >1.
**Comparing LATE-NC- versus LATE-NC+; Student t-test, 2-tailed.

TABLE 2. Numbers of Included Subjects Autopsied at the UK-ADRC, Stratified by Braak NFT Stages and LATE-NC* Status

Braak NFT Stages	LATE-NC-*	LATE-NC+*	Total
0–I	45	**11**	56
II	63	**15**	78
III	36	**8**	44
IV	26	9	35
V	54	43	97
VI	38	35	73
Grand total	262	121	383

*Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) indicates LATE-NC Stage >1.

TABLE 3. Demographics, *APOE*, and Copathologies: Braak NFT Stage 0-III Cases Only

	LATE-NC-*	LATE-NC+*	p-value**
N	144	34	
Age of death, average (Avg)	87.6	90.9	0.004
Sex, %F	61.1	58.8	0.91
MMSE, Avg	27.1	21.8	3.7 E-09
APOE 4+, %	23.6	30.6	0.71
Brain weight (gms), Avg	1202.1	1169.4	0.19
Cortical Lewy body pathology, %	7.6	5.9	0.73
Arteriolosclerosis (0–3), Avg	1.03	1.15	0.45
Cerebral amyloid angiopathy (0–3), Avg	0.56	0.50	0.72
Gross infarcts, Avg	0.57	0.76	0.46
Braak NFT Stage, Avg	1.92	1.82	n/a
CERAD Neuritic plaque density (0–3), Avg	0.60	0.44	n/a
Hippocampal sclerosis, %	4.1	67.6	4.3 E-25

*Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) indicates LATE-NC Stage >1.
**Comparing LATE-NC- versus LATE-NC+; Student t-test, 2-tailed.

low-Braak NFT Stage cases with LATE-NC (Table 4) were not due to low-Braak LATE-NC cases having a different frequency of large infarcts, arteriolosclerosis, cerebral amyloid angiopathy, or Lewy body disease (Table 3).

DISCUSSION

The pathologic combination of LATE-NC+ and low/no ADNC is commonly encountered in community-based cohorts such as ours. In the current study, across a broad range of ADNC severity, LATE-NC+ pathology was associated with impaired cognition, but did not imply a FTD clinical syndrome.

Prior reports from other community-based autopsy cohorts have yielded similar results, with the caveat that readouts change according to site-specific recruitment methods, diagnostic thresholds and cut-points applied, etc. In the Rush University community-based autopsy cohort (8), 978 persons had ADNC and/or LATE-NC. Among these 978 individuals, 91 had LATE-NC without ADNC (8). Other community-based autopsy cohorts have documented similar results among the elderly, with substantial numbers of non-FTD (clinically), non-ADNC (pathologically) associated TDP-43 proteinopathy (9–12). It has also been reported previously that the presence of LATE-NC was associated with worse cognition for a given level of other pathologic changes (e.g. ADNC) (1, 13–15). The data presented here are thus confirmatory and in-line with prior studies. However, substantial differences in perspective still persists in the field.

Some discrepancies in points of view may stem from the procedures by which different academic autopsy cohorts recruit their subjects (16). Studies employing clinic-based cohorts have achieved many spectacular advances in the field of dementia research. However, as compared with the total population of a region at a given time, clinic-based cohorts are often enriched in early onset, relatively severe dementia phenotypes, especially FTLD and other unusual conditions. By contrast, community-based cohorts are more representative of common pathologic phenotypes in brain aging (16). These cohorts typically comprise older subjects, many dying beyond

TABLE 4. Average Final MMSE Scores, Stratified by Braak NFT Stages and LATE-NC* Status

Braak NFT Stages	LATE-NC-*	LATE-NC+*
0–I	27.1	23.0
II	27.5	19.5
III	26.4	24.4
IV	24.5	17.2
V	21.0	17.0
VI	15.9	14.9
Total (average)	24.0	17.7

*Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) indicates LATE-NC Stage >1.

Number of cases followed from normal status with primary progressive aphasia (PPA) or behavioural variant FTD (bvFTD) in the cohort = 0.

age 85 with subtle (or no) detected cognitive loss. Subjects in community-based cohorts with dementia show mixed pathologies more often than not, including prevalent vascular pathologies and LATE-NC (1, 16).

Among the brains with low-Braak NFT stages (Table 3), the presence and severity of neuritic amyloid plaques was also very low, as expected, with or without comorbid LATE-NC+. Also, as expected, hippocampal sclerosis was higher in the LATE-NC+ group. As discussed previously (1, 17, 18), hippocampal sclerosis seems likely to be mechanistically downstream of the TDP-43 proteinopathy in LATE-NC.

LATE-NC does not tend to evolve to FTD/FTLD. Quite the contrary: the vast majority of research participants in community-based cohorts who died with LATE-NC lacked an FTD-type syndrome clinically (1, 19). In over 3 decades of operation, no UK-ADRC case followed from normal cognitive status has developed the full-blown clinical and pathological features of FTLD-TDP (see reference [19]). Lifetime risk of LATE-NC is >100 times greater than for FTLD-TDP and each of these diseases affects a different age range (1, 20, 21). The neocortical pathology of FTLD-TDP is also far more severe than that seen in LATE-NC (19). Nonetheless, there are overlapping biological pathways, and genetic pleiotropy, indicating pathogenetic connections between LATE-NC, ADNC, and FTLD-TDP, as there are overlapping pathways and genetic pleiotropy for ADNC and Lewy body diseases, and for many other subtypes of dementia-inducing diseases (22).

ACKNOWLEDGMENTS

Heartfelt thanks to research volunteers and to clinicians and staff at the UK-ADRC. Thanks to Dr. Karin B. Nelson for editing the manuscript and to Dr. Erin L. Abner for curating the data.

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