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ORIGINAL ARTICLE

Limbic Predominant Age-Related TDP-43 Encephalopathy (LATE): Clinical and Neuropathological Associations

Lilah M. Besser, PhD, Merilee A. Teylan, MPH, and Peter T. Nelson, MD, PhD

Abstract

Recently, a consensus working group provided new terminology for a common disease entity, limbic predominant age-related TDP-43 encephalopathy (LATE), and its neuropathological substrate (LATE-NC). LATE-NC not only often co-occurs with Alzheimer disease neuropathological change (ADNC), but also may present in isolation. The present study aimed to investigate potential risk factors and neuropathological characteristics associated with LATE-NC. A sample of 616 autopsied participants (>75 years at death), with TDP-43 immunohistochemical studies performed, was obtained from the National Alzheimer's Coordinating Center. Logistic regression analyses examined associations between demographic, clinical and neuropathological characteristics and LATE-NC (TDP-43 in amygdala, hippocampus, or entorhinal/inferior temporal cortex) (alpha = 0.05). Adjusted models indicated that ADNC, hippocampal sclerosis (HS), arteriolosclerosis, and limbic or amygdala-predominant Lewy body disease (LBD), but not other LBD subtypes, were associated with higher odds of LATE-NC, whereas congestive heart failure (CHF) and motor problems as first predominant symptom were associated with lower odds of LATE-NC. Our findings corroborate previous studies indicating associations between LATE-NC and ADNC, HS, and arteriolosclerosis. Novel findings suggest the association with LATE-NC is restricted to amygdala/limbic-predominant subtype of LBD, and a possible protective (or competing risk) association with CHF. This study may inform future hypothesis-driven research on LATE-NC, a common brain disease of aging.

From the Institute for Human Health and Disease Intervention (I-HEALTH), School of Urban and Regional Planning, Florida Atlantic University, Boca Raton, Florida (LMB); National Alzheimer's Coordinating Center, Department of Epidemiology, University of Washington, Seattle, Washington (MAT); and Sanders-Brown Center on Aging, Division of Neuropathology, Department of Pathology, University of Kentucky, Lexington, Kentucky (PTN).

Send correspondence to: Lilah M. Besser, PhD, Institute for Human Health and Disease Intervention (I-HEALTH), School of Urban and Regional Planning, Florida Atlantic University, 777 Glades Rd, SO-284H, Boca Raton, FL 33431; E-mail: lbesser@fau.edu

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Key Words: Alzheimer, Hippocampus, LATE, Limbic predominant age related TDP-43 encephalopathy, Risk factors, TDP-43.

INTRODUCTION

A consensus working group recently published diagnostic criteria for a previously undefined neuropathological entity, limbic predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) (1). LATE-NC is a common pathologic finding in aged brains and is characterized by transactive response DNA binding protein of 43 kDa (TDP-43) proteinopathy primarily located in the limbic region. Individuals with LATE-NC experience an amnestic syndrome similar to Alzheimer disease (AD), and yet neuropathological and MRI-based studies have demonstrated that LATE-NC is distinct (1). Additionally, while LATE-NC appears to share genetic risk alleles with AD (*APOE*) and frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP; *GRN*, *TMEM106B*), it has also been associated different risk alleles (*ABCC9* and *KCNMB2* [1]).

The clinical and neuropathological correlates of LATE-NC remain to be definitively determined. There is a growing appreciation that there may be interactions (synergies) between the pathologic features of LATE-NC and other brain pathologies. Histopathologic similarities exist between LATE-NC and FTLD-TDP, particularly FTLD-TDP Type A (2), and many individuals with autopsy-confirmed LATE-NC also have comorbid Alzheimer disease neuropathologic change (ADNC) (3–5). However, the clinical features and epidemiology of LATE-NC are very distinct from FTLD-TDP (1). LATE-NC is usually found in older individuals (>80 years), whereas ADNC and frontotemporal dementia clinical syndrome decline in prevalence with advanced old age. Further, ADNC is a very common pathology (~80% in advanced old age), yet a very large number of individuals with advanced ADNC have no evidence of LATE-NC. Notably, Lewy body disease (LBD) may also be a comorbid pathology in persons with LATE-NC (2, 6). Far more specific to LATE-NC, hippocampal sclerosis (HS), found in up to 90% of LATE-NC cases, was one of the initial characteristics found to differentiate LATE-NC from ADNC (1, 7, 8). While neither ADNC nor HS are a prerequisite to the presentation of LATE-NC, a recent pathway analysis suggested that the pathological

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processes/mechanisms in LATE-NC are related to those for ADNC and HS (9).

There also is evidence that brains with LATE-NC have a relatively high likelihood of also harboring arteriolosclerosis—Thickening and dysmorphic features in brain arterioles. This association has been found in a number of different datasets, using different operationalizations of brain arteriolosclerosis (10–12). The association seems relatively specific since other subtypes of brain cerebrovascular pathologies (e.g. large infarcts, lacunar infarcts, and microinfarcts) were not associated with LATE-NC type pathology (10). Further work is needed to understand the specifics and the directions of these mechanistic relationships.

Despite the fact that it has been observed in 20%–60% of aged brains in large autopsy cohorts, there has been relatively sparse research on the clinical features and risk factors related to LATE-NC (1). Therefore, much remains unknown about the associated clinical manifestations, risk factors, and biomarkers for LATE-NC that could ultimately aid in clinical diagnosis and care, and for clinical trials. Given the paucity of the research to date, this study aimed to investigate the clinical and neuropathological correlates of LATE-NC in a sample of autopsied participants from 28 National Institute on Aging-funded Alzheimer's Disease Centers (ADCs).

MATERIALS AND METHODS

Sample

Data were obtained from the National Alzheimer's Coordinating Center (NACC) on individuals meeting our eligibility criteria from one of 28 National Institute of Aging-funded ADCs. NACC coordinates data collection across a network of ~30 active ADCs and distributes the multi-center data for research use. ADC participants complete approximately annual Uniform Data Set (UDS) visits in which they receive detailed assessments including physical and neurological exams, the CDR Dementia Staging Instrument (13), a neuropsychological test battery, and clinical diagnosis, as well as forms/questionnaires that assess medical history, family history, medication use, functional abilities, and neuropsychiatric symptoms. UDS data collected from September 2005 to February 2019 were used in this study. Additional details about the UDS are available elsewhere (14–16). Written informed consent is obtained from participants at the ADCs.

Neuropathology Data

The subset of UDS participants that consented to autopsy have data collected on the standardized NACC Neuropathology Form (11), which sets forth a minimum number of recommended brain regions to be assessed as recommended by Montine et al (17). The ADCs conduct autopsies based on established criteria for assessment of AD, LBD, FTLD, cerebrovascular disease (CVD), and rarer pathologies such as prion disease and multiple system atrophy. Staining procedures and additional information regarding the neuropathological exam can be found in NACC's Neuropathology Form Guidebook (18).

Braak staging for neurofibrillary degeneration (19) (Stages 0–VI) and CERAD semiquantitative scores for neuritic plaque density (17, 20) (none, sparse, moderate, frequent) are available for the vast majority of participants who have NACC Neuropathology Form data. Thal phase for amyloid plaques (17, 21) (Phases 0–5) is available for participants assessed with version 10 of NACC's Neuropathology Form, which was implemented in 2014. For individuals with Thal phase data, ADNC score (none, low, intermediate, or high ADNC) (17) is also available. Using the data on Thal phase and Braak stage, we defined definite primary age-related tauopathy (PART) as having Braak stage $\geq$1 and Thal Phase 0 (22).

The presence/absence of FTLD with tau pathology (e.g. corticobasal degeneration, progressive supranuclear palsy), FTLD with TDP-43 pathology, and other FTLD subtypes (e.g. atypical FTLD-U) were assessed, and LBD was classified based on a modification to the McKeith criteria to assess brainstem predominant, limbic, neocortical, or amygdala predominant disease (23). ADC neuropathologists semiquantitatively assess arteriolosclerosis on a global scale (none, mild, moderate, severe) and note the presence of at least one lacunar/gross infarct or microinfarct (infarcts and microinfarcts assessed separately). Arteriolosclerosis was dichotomized as moderate/severe or none/mild in this study. HS is captured as absent, unilateral, bilateral, or present but laterality not assessed, and for our analyses was categorized as present/absent. Starting with version 10 of NACC's Neuropathology Form, the presence/absence of TDP-43-immunoreactive inclusions has been assessed in the spinal cord, amygdala, hippocampus, entorhinal/inferior temporal cortex, and neocortex. Any TDP-43-immunoreactive inclusions are indicated, including neuronal intranuclear inclusions, neuronal cytoplasmic inclusions, glial cytoplasmic inclusions, and dystrophic neurites. For our analyses, LATE-NC was defined as present if TDP-43 inclusions were found in the limbic region (amygdala, hippocampus, or entorhinal/inferior temporal cortex) and absent if no TDP-43 inclusions were found in any of these 3 regions.

Inclusion Criteria

The analytic sample was restricted to UDS participants who: (i) died and have neuropathology data; (ii) were >75 years old at the time of death; (iii) had no clinical or neuropathological indication of FTD/FTLD, multiple system atrophy, Down syndrome, or prion disease; and (iv) were not missing data on the presence of TDP-43 inclusions in the amygdala, hippocampus, and entorhinal/inferior temporal cortex.

Participant Characteristics

Demographics include age at death (years), sex, race (nonwhite or white), and years of education. We describe diagnosed cognitive status (normal cognition, impaired not mild cognitive impairment [MCI], MCI, dementia), global CDR score (range: 0–3; 3 = severe dementia) (13), and primary clinical diagnosis (normal cognition, AD, LBD/Parkinson disease; vascular disease, other) at the participant's last visit

before death. Apolipoprotein E (*APOE*) genotype data were available for 91% of the analytic sample and for our analyses was dichotomized into *APOE* ε4 carriers and noncarriers.

Comorbidities include self/coparticipant report or clinician-confirmed diabetes, hypertension, hypercholesterolemia, cardiovascular disease (congestive heart failure [CHF], angina, atrial fibrillation, cardiac bypass, pacemaker/defibrillator), CVD (stroke/transient ischemic attack), traumatic brain injury (remote), thyroid disease, depression (self/coparticipant report of active depression or clinical diagnosis of depression), and sleep apnea. First predominant symptom (cognitive, behavioral, or motor) is also described. Clinician-assessed cognitive, behavioral, and motor symptoms at the last visit are also reported. Medications (reported use at any UDS visit) examined in this study include antihypertensives, lipid lowering medications, antidepressants, antipsychotics, diabetes medications, anticoagulants, anxiolytics/sedatives/hypnotics, AD medications (cholinesterase inhibitors/memantine), and anti-Parkinson agents. The specific drugs that fall under each of these categories are delineated in NACC's UDS Researcher's Data Dictionary (24).

Statistical Analyses

Sample demographics and clinical and neuropathological characteristics are described using means and standard deviations (SD) or frequencies and percentages. The percentage of participants with and without LATE-NC experiencing cognitive (e.g. language), behavioral (e.g. apathy), and motor symptoms (e.g. tremor) at the most recent visit before death are reported, stratified by global CDR score. Differences in these symptoms between those with and without LATE-NC were tested using chi-square/exact tests. In addition to providing the primary clinical diagnosis for those with and without LATE-NC, it is also provided for 4 neuropathological groups to assess differences in diagnosis among those with LATE-NC and the presence/absence of ADNC and LBD: (i) LATE-NC with no ADNC and no LBD; (ii) LATE-NC with ADNC but not LBD; (iii) LATE-NC with LBD but not ADNC; and (iv) LATE-NC with ADNC and LBD.

Unadjusted logistic regression models using generalized estimating equations (to account for clustering of data by ADC) were run to examine bivariate associations between demographics and clinical and neuropathological characteristics and presence of LATE-NC. Separate adjusted models (using logistic regression with generalized estimating equations) were run to examine the clinical characteristics associated with LATE-NC and the neuropathological characteristics associated with LATE-NC. Any clinical characteristics or pathology associated with LATE-NC at $p < 0.20$ was included in the multivariable models. The multivariable model focused on clinical predictors was rerun to additionally include the variable for first predominant symptom (data are not available for most participants with normal cognition). Neuropathological associations with LATE-NC were examined in separate multivariable models, controlling for age at death, sex, and education (i.e. separate models were run for associations between LATE-NC and ADNC, HS, LBD, PART, and arteriolosclerosis). Statistical significance for the adjusted models was based on an alpha = 0.05.

RESULTS

The final sample consisted of 616 participants, 253 with LATE-NC and 363 without LATE-NC (Supplementary Data Fig. S1). The mean age at death was 86 years (SD: 6 years), 8% were of nonwhite race, and 48% were *APOE* ε4 carriers (Table 1). The majority of the sample had dementia at their last visit (77%), and most had a primary clinical diagnosis of AD (75%).

Compared with those without LATE-NC, those with LATE-NC more often had dementia (LATE-NC: 3% with normal cognition, 91% with dementia; without LATE-NC: 17% with normal cognition, 67% with dementia). Ninety percent of participants with LATE-NC and 64% of participants without LATE-NC had a primary clinical diagnosis of AD. A higher percentage of those without LATE-NC received a primary clinical diagnosis of normal cognition or LBD/Parkinson disease.

Comparing medical comorbidities in those with and without LATE-NC did not reveal many differences, although CHF and CVD were slightly less frequent in those with LATE-NC (CHF: 7%; CVD: 10%) than those without LATE-NC (CHF: 12%; CVD: 16%; Table 2). In both those with and without LATE-NC, cognitive changes were most often the first predominant symptom (LATE-NC: 97%; no LATE-NC: 90%). Although infrequently the first symptom in those with or without LATE-NC, motor symptoms were more often the first symptom in those without LATE-NC (6%) than those with LATE-NC (1%). Antihypertensives were used less frequently among those with LATE-NC (58%) than those without LATE-NC (67%), whereas AD medications were taken more often in those with LATE-NC (64%) than those without LATE-NC (45%).

Table 3 presents the cognitive, behavioral, and motor symptoms experienced by individuals with and without LATE-NC at their most recent visit before death. Too few (n = 7) of those with LATE-NC had a global CDR = 0; therefore, comparisons were not made to those without LATE-NC and global CDR = 0. Among those with a global CDR = 0.5, the only significant difference between those with and without LATE-NC was a higher percentage of those with LATE-NC (44%) that had depressed mood compared with those without LATE-NC (23%). More differences were observed between those with and without LATE-NC among those with a global CDR score indicating dementia (i.e. CDR = 1, 2, or 3). Individuals with LATE-NC more often experienced problems with orientation, and less often experienced visual or auditory hallucinations, gait disorder, falls, and tremor.

Focused on the neuropathological exam findings, a higher proportion of those with LATE-NC had intermediate to high ADNC (85%) compared with those without LATE-NC (73%; Table 4). Correspondingly, individuals with LATE-NC more frequently had moderate/frequent neuritic plaques and Braak stage V–VI. Definite PART was present in 2% of those with LATE-NC and 8% of those without LATE-NC. HS was more common, but not present in the majority of those with LATE-NC (42%) and was uncommon in those without LATE-

TABLE 1. Demographics and Clinical Characteristics Among Those With and Without LATE-NC

Characteristic*	Total Sample	LATE-NC/Limbic TDP-43+	
		Yes	No
n	616	253	363
Age at death, mean (SD)	86.4 (6.3)	86.9 (6.6)	86.0 (6.2)
Female, n (%)	303 (49.2%)	136 (53.8%)	167 (46.0%)
Non-white race, n (%)	50 (8.2%)	20 (8.0%)	30 (8.3%)
Education (years), mean (SD)	16.6 (10.0)	17.2 (12.1%)	16.1 (8.3%)
APOE ε4 carrier, n (%)	267 (47.8%)	121 (53.5%)	146 (43.8%)
Cognitive status at last visit, n (%)			
Normal cognition	67 (10.9%)	7 (2.8%)	60 (16.5%)
MCI	16 (2.6%)	2 (0.8%)	14 (3.9%)
Impaired not MCI	59 (9.6%)	13 (5.1%)	46 (12.7%)
Dementia	474 (77.0%)	231 (91.3%)	243 (66.9%)
Global CDR, last visit, n (%)			
0	66 (10.7%)	7 (2.8%)	59 (16.3%)
0.5	103 (16.7%)	25 (9.9%)	78 (21.5%)
1	107 (17.4%)	45 (17.8%)	62 (17.1%)
2	161 (26.1%)	92 (36.4%)	69 (19.0%)
3	179 (29.1%)	84 (33.2%)	95 (26.2%)
CDR Sum of Boxes, last visit, mean (SD)	9.5 (6.4)	11.4 (5.4)	8.2 (6.7)
Primary clinical diagnosis at last visit, n (%)			
Normal cognition	67 (11.0%)	7 (2.8%)	60 (16.5%)
Alzheimer disease	457 (74.7%)	225 (90.0%)	232 (64.1%)
Lewy body disease/ Parkinson disease	43 (7.0%)	8 (3.2%)	35 (9.7%)
Vascular disease	22 (3.6%)	7 (2.8%)	15 (4.1%)
Other	23 (3.8%)	3 (1.2%)	20 (5.5%)
Years of UDS follow-up, mean (SD)	5.3 (3.0)	5.1 (3.1)	5.3 (3.0)

*Missing data: race, n = 3; *APOE*, n = 57; primary clinical diagnosis, n = 4.

Abbreviations: LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; NACC, National Alzheimer's Coordinating Center; *APOE*, apolipoprotein E; OR, odds ratio; CI, confidence interval; UDS, Uniform Data Set; CDR, Clinical Dementia Rating; MCI, Mild cognitive impairment.

TABLE 2. Medical History for Those With and Without LATE-NC

Characteristic*	Total Sample n (%)	LATE-NC/TDP-43+ in Limbic Region	
		Yes n (%)	No n (%)
Diabetes	95 (15.4%)	36 (14.2%)	59 (16.3%)
Hypertension	426 (69.2%)	177 (70.0%)	249 (68.6%)
Hypercholesterolemia	371 (60.2%)	152 (60.1%)	219 (60.3%)
Congestive heart failure	63 (10.2%)	18 (7.1%)	45 (12.4%)
Angina	20 (3.3%)	7 (2.8%)	13 (3.6%)
Atrial fibrillation	130 (21.1%)	45 (17.8%)	85 (23.4%)
Cardiac bypass	38 (6.2%)	11 (4.4%)	27 (7.4%)
Pacemaker/defibrillator	46 (7.5%)	16 (6.3%)	30 (8.3%)
Cerebrovascular disease (stroke/TIA)	85 (13.8%)	26 (10.3%)	59 (16.3%)
Traumatic brain injury (remote)	47 (7.6%)	14 (5.5%)	33 (9.1%)
Thyroid disease	169 (27.4%)	67 (26.5%)	102 (28.1%)
Depression	199 (32.3%)	75 (29.6%)	124 (34.2%)
Sleep apnea	31 (5.0%)	11 (4.4%)	20 (5.5%)
First predominant symptom			
Cognitive	501 (93.0%)	233 (96.7%)	268 (89.9%)
Behavioral	17 (3.2%)	6 (2.5%)	11 (3.7%)
Motor	21 (3.9%)	2 (0.8%)	19 (6.4%)
Medication use, any visit			
Antihypertensive	369 (63.3%)	136 (57.6%)	233 (67.2%)
Lipid lowering medication	230 (39.5%)	95 (40.3%)	135 (38.9%)
Antidepressant	244 (41.9%)	100 (42.4%)	144 (41.5%)
Antipsychotic	79 (13.6%)	42 (17.8%)	37 (10.7%)
Diabetes medication	54 (9.3%)	18 (7.6%)	36 (10.4%)
Anticoagulant	324 (55.6%)	125 (53.0%)	199 (57.4%)
Anxiolytic/sedative/hypnotic	88 (15.1%)	35 (14.8%)	53 (15.3%)
AD medication	307 (52.7%)	152 (64.4%)	155 (44.7%)
Antiparkinson agent	42 (7.2%)	11 (4.7%)	31 (8.9%)

*Missing data: first predominant symptom, n = 77; medications, n = 33.

Abbreviations: LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; TIA, Transient ischemic attack; Alzheimer disease.

NC (6%). The regional distribution of LBD was similar in those without and without LATE-NC, except there was a higher proportion of those with limbic or amygdala-predominant LBD in those with LATE-NC (30%) than those without LATE-NC (17%). Moderate/severe arteriolosclerosis affected a higher proportion of those with LATE-NC (62%) than those without LATE-NC (49%). TDP-43 inclusions were found ~30% of the time in the amygdala, hippocampus, and entorhinal/inferior temporal cortex (Supplementary Data Table S1). Among individuals with LATE-NC, 17.5% also had TDP-43 inclusions in the neocortex.

Individuals with LATE-NC but with no other major pathology (i.e. no ADNC, LBD, or FTLD) received a primary clinical diagnosis of AD 67% of the time and a diagnosis of vascular disease 12.5% of the time (Table 5). Compared with individuals with LATE-NC and no ADNC, those with both pathologies received a primary diagnosis of AD substantially more frequently. LBD was the primary diagnosis in 17% of the cases with LATE-NC and LBD but no ADNC, but only 4% of the cases with LATE-NC, LBD, and ADNC. The presence or absence of ADNC or LBD as copathologies appeared to have more of an influence over the primary clinical diagnosis than the presence or absence of diagnosed HS (Supplementary Data Table S2). Additionally, while 5 out of 9 participants (56% among this small group) with LATE-NC and with no ADNC, LBD, or HS were diagnosed with normal cognition, only 3% of the overall LATE-NC sample received that diagnosis (Supplementary Data Table S2).

In the unadjusted regression analyses, female sex, a higher CDR Sum of Boxes score, CHF, having a pacemaker/defibrillator, motor problems as the first predominant symptom,

TABLE 3. Cognitive, Behavioral, and Motor Symptoms at Last Visit Among Those With and Without LATE-NC

Symptom, Most Recent Visit†	CDR = 0		CDR = 0.5		CDR = 1, 2, or 3	
	LATE-NC n = 7	No LATE-NC n = 59	LATE-NC n = 25	No LATE-NC n = 78	LATE-NC n = 221	No LATE-NC n = 226
Cognitive						
Memory	0 (0.0%)	2 (3.4%)	24 (96.0%)	65 (83.3%)	220 (99.6%)	225 (99.6%)
Orientation	0 (0.0%)	0 (0.0%)	1 (12.5%)	7 (22.6%)	89 (97.8%)**	85 (92.4%)
Executive function	0 (0.0%)	3 (5.1%)	18 (72.0%)	42 (53.9%)	216 (99.1%)	221 (98.7%)
Language	0 (0.0%)	0 (0.0%)	11 (44.0%)	23 (29.5%)	172 (79.6%)	186 (83.0%)
Visuospatial function	0 (0.0%)	0 (0.0%)	2 (8.0%)	8 (10.4%)	151 (70.6%)	159 (72.9%)
Attention/concentration	0 (0.0%)	1 (1.7%)	7 (28.0%)	10 (13.0%)	144 (66.7%)	155 (72.1%)
Fluctuating cognition	0 (0.0%)	0 (0.0%)	1 (4.2%)	2 (2.9%)	36 (17.6%)	52 (25.4%)
Behavioral						
Apathy/withdrawal	0 (0.0%)	0 (0.0%)	6 (25.0%)	12 (15.6%)	114 (51.8%)	129 (57.6%)
Depressed mood	0 (0.0%)	1 (1.7%)	11 (44.0%)*	18 (23.1%)	63 (29.2%)	72 (32.7%)
Visual hallucinations	0 (0.0%)	0 (0.0%)	1 (4.4%)	4 (5.2%)	21 (9.7%)**	44 (20.4%)
Auditory hallucinations	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)	3 (1.4%)**	20 (9.4%)
Delusional beliefs	0 (0.0%)	0 (0.0%)	1 (4.4%)	2 (2.6%)	42 (19.4%)	48 (22.3%)
Disinhibition	0 (0.0%)	0 (0.0%)	1 (4.2%)	10 (13.0%)	44 (20.3%)	54 (24.4%)
Irritability	0 (0.0%)	0 (0.0%)	4 (16.7%)	15 (19.5%)	75 (34.3%)	75 (34.1%)
Agitation	0 (0.0%)	0 (0.0%)	2 (8.3%)	6 (7.9%)	58 (26.5%)	54 (24.2%)
Personality change	0 (0.0%)	1 (1.7%)	1 (4.2%)	2 (2.6%)	29 (13.4%)	36 (16.2%)
RBD	0 (0.0%)	0 (0.0%)	2 (10.0%)	1 (2.0%)	10 (5.6%)	15 (7.7%)
Anxiety	0 (0.0%)	1 (3.5%)	2 (28.6%)	4 (12.9%)	25 (27.2%)	32 (36.4%)
Motor						
Gait disorder	0 (0.0%)	5 (8.5%)	4 (16.7%)	18 (23.7%)	96 (44.9%)**	121 (55.3%)
Falls	0 (0.0%)	2 (3.4%)	3 (12.5%)	13 (16.7%)	47 (22.2%)**	76 (35.7%)
Tremor	0 (0.0%)	3 (5.1%)	5 (20.0%)	11 (14.1%)	42 (20.1%)**	61 (28.9%)
Slowness	0 (0.0%)	3 (5.1%)	8 (32.0%)	18 (23.4%)	105 (49.1%)	121 (57.6%)

Abbreviations: LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; RBD, Rapid eye movement sleep behavior disorder.
*$p < 0.05$, versus no LATE-NC and CDR = 0.5.
**$p < 0.05$ versus no LATE-NC and CDR = 1–3 (chi-square/exact tests).
†Missing data, LATE-NC: orientation, n = 150; executive function, n = 3; language, n = 5; visuospatial function, n = 7; attention, n = 5; fluctuating cognition, n = 24; apathy, n = 2; depressed mood, n = 5; visual hallucinations, n = 6; auditory hallucinations, n = 6; delusions, n = 7; disinhibition, n = 5; irritability, n = 3; agitation, n = 3; personality change, n = 6; RBD, n = 53; anxiety, n = 150; gait, n = 8; falls, n = 10; tremor, n = 12; slowness, n = 7; Missing data, LATE-NC: orientation, n = 211; executive function, n = 2; language, n = 2; visuospatial function, n = 9; attention, n = 12; fluctuating cognition, n = 84; apathy, n = 3; depressed mood, n = 6; visual hallucinations, n = 11; auditory hallucinations, n = 14; delusions, n = 12; disinhibition, n = 6; irritability, n = 7; agitation, n = 5; personality change, n = 6; RBD, n = 115; anxiety, n = 215; gait, n = 9; falls, n = 13; tremor, n = 15; slowness, n = 17.

intermediate/high ADNC, HS, definite PART, limbic predominant LBD, and moderate/severe arteriolosclerosis were associated with LATE-NC at $p < 0.05$ (Supplementary Data Tables S3 and S4). In addition, taking antihypertensives or was associated with a lower odds of LATE-NC, whereas taking antipsychotics or AD medications was associated with a higher odds of LATE-NC ($p < 0.05$). Additional variables that were associated with LATE-NC at $p < 0.20$ (and thus included in multivariable analyses) include age at death, years of education, being an *APOE* ε4 carrier, diabetes, atrial fibrillation, and traumatic brain injury (remote). In subanalyses, we examined whether medications commonly used for CHF/edema (e.g. furosemide, hydrochlorothiazide) were associated with LATE-NC, and found no significant associations in multivariable models (data not shown).

In the adjusted model focused on clinical characteristics, greater years of education (OR: 1.005, 95% CI: 1.001–1.009), a higher CDR Sum of Boxes score (OR: 1.011, 95% CI: 1.005–1.018), and AD medication use (OR: 1.16, 95% CI: 1.06–1.28) were associated with a higher odds of LATE-NC, whereas having CHF was associated with a lower odds of LATE-NC (OR: 0.88, 95% CI: 0.79–0.98; Table 6). The model additionally examining first predominant symptom found that initially experiencing motor problems (vs cognitive problems) was associated with a lower odds of LATE-NC (OR: 0.76, 95% CI: 0.63–0.91; Table 6).

In the adjusted models focused on neuropathological characteristics, intermediate/high ADNC (OR: 1.16, 95% CI: 1.09–1.25), HS (OR: 1.49, 95% CI: 1.34–1.65), limbic/amygdala-predominant LBD (OR: 1.14, 95% CI: 1.05–1.24), and arteriolosclerosis (OR: 1.11, 95 CI: 1.04–1.19) were associated with a higher odds of LATE-NC (Table 7), and definite PART was associated with a lower odds of LATE-NC (OR: 0.84, 95% CI: 0.75–0.94).

TABLE 4. Neuropathology by Presence of LATE-NC at Autopsy

Neuropathology*	Total Sample	LATE-NC/Limbic TDP-43+	
		Yes	No
Intermediate/high ADNC, n (%)	479 (78.0%)	215 (85.3%)	264 (72.9%)
Neuritic plaques, n (%)			
None	81 (13.2%)	24 (9.5%)	57 (15.8%)
Sparse	74 (12.0%)	17 (6.7%)	57 (15.8%)
Moderate	129 (21.0%)	40 (15.8%)	89 (24.6%)
Frequent	331 (53.8%)	172 (68.0%)	159 (43.9%)
Braak NFT stage, n (%)			
0	8 (1.3%)	1 (0.4%)	7 (1.9%)
I/II	92 (15.0%)	27 (10.7%)	65 (17.9%)
III/IV	133 (21.6%)	34 (13.5%)	99 (27.3%)
V/VI	382 (62.1%)	190 (75.4%)	192 (52.9%)
Definite PART, n (%)	34 (5.5%)	6 (2.4%)	28 (7.7%)
Hippocampal sclerosis, n (%)	127 (20.7%)	105 (41.7%)	22 (6.1%)
Lewy body disease, n (%)			
None	358 (58.3%)	131 (52.0%)	227 (62.7%)
Brainstem-predominant	25 (4.1%)	8 (3.2%)	17 (4.7%)
Limbic or amygdala-predominant	137 (22.3%)	76 (30.2%)	61 (16.9%)
Neocortical	78 (12.7%)	30 (11.9%)	48 (13.3%)
Lewy bodies present, region unspecified/olfactory bulb	16 (2.6%)	7 (2.8%)	9 (2.5%)
Arteriolosclerosis (moderate/severe)	333 (54.2%)	155 (61.5%)	178 (49.2%)
Lacunar/gross infarct(s)	109 (17.7%)	39 (15.4%)	70 (19.3%)
Microinfarct(s)	159 (25.8%)	69 (27.3%)	90 (24.8%)

*Missing data: ADNC, n = 2; neuritic plaques, n = 1; Braak stage, n = 1; hippocampal sclerosis, n = 2; Lewy body disease, n = 2; arteriolosclerosis, n = 2; infarct, n = 1.

Abbreviations: LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; PART, primary age-related tauopathy; NFT, neurofibrillary tangle; ADNC, Alzheimer Disease Neuropathologic Change.

DISCUSSION

Our findings corroborate previous studies in demonstrating that LATE-NC is associated with the presence of ADNC, HS, LBD, and arteriolosclerosis, with the strongest association found for HS. Novel findings include a positive association with LBD that was restricted to the limbic region/amygdala, and negative associations with definite PART, CHF, and motor problems (vs cognitive) as the first predominant symptom.

HS was present in 42% of individuals with LATE-NC, paralleling prior findings (1). As has been delineated previously, HS as diagnosed at autopsy can be due to non-neurodegenerative medical conditions such as epilepsy, hypoglycemia, and hypoxia; and HS is observed unilaterally in up to half of cases of LATE-NC when both sides are evaluated (1, 25, 26). We also note that different groups have applied different criteria for the neuropathological diagnosis of HS and we hypothesize that this multi-center database includes diagnostic data from neuropathologists who applied widely different protocols for sampling and diagnosing HS (17, 27). Therefore, HS is a heterogeneously operationalized pathologic endpoint, with differing etiologies and topographic distribution within the hippocampus, and was not the specific focus of the current study.

ADNC occurred more frequently in those with LATE-NC versus those without LATE-NC, as expected. However, we note that both ADNC and LATE-NC are very common brain pathologies in aging. LATE-NC is not an inevitable sequelae of severe ADNC—Only half of the sample with Braak NFT stage VI ADNC had comorbid LATE-NC. When present, there is strong evidence that LATE-NC is not a passive agent, because comorbid TDP-43 proteinopathy in ADNC has been associated with significantly worse cognitive status (28, 29). Further, LATE-NC can occur in the context of minimal or no ADNC. A topical question is how these 2 processes tend to co-exist, and whether LATE-NC is a downstream process linked to ADNC, or vice versa.

Amygdala- or limbic-predominant LBD was also relatively more common in those with LATE-NC than those without LATE-NC in the present study, but there were no differences in the presence of LBD in any other regions between those with and without LATE-NC. Enrollment in the UDS and autopsy consent among UDS participants is weighted toward AD (and LBD, a common ADNC copathology), consistent with the largely AD-focused research at the ADCs. As such, although the findings from this study confirm the relationship between LATE-NC and both ADNC and LBD, population-based cohorts will be needed to estimate the prevalence and correlates of ADNC and LBD among individuals with LATE-NC. More research will also be needed to probe the shared risk factors and biological mechanisms linking LATE-NC to ADNC and to LBD. Our findings, especially for LATE-NC-associated LBD copathology restricted to the limbic region, are at least suggestive that the misfolded proteins associated with these neurodegenerative diseases may interact in a way that results in their localized, common co-occurrence. This would seem consistent with recent observations of "beta"-type pathology in the human amygdala with tau and TDP-43 proteinopathies colocalized (30). Additional research is required to understand if these observed relationships are causal or due to shared risk factors and pathological mechanisms.

Arteriolosclerosis has been previously associated with the type of HS that co-occurs with TDP-43 proteinopathy, and was also found to be associated with LATE-NC in our analyses. In contrast to arteriolosclerosis, other subtypes of cerebrovascular pathology (infarcts, lacunes, and microinfarcts) were not associated with LATE-NC in any of the analyses. Importantly, neither hypertension nor diabetes (2 risk factors linked to arteriolosclerosis) were associated with LATE-NC. Two preliminary explanations for a potential association with arteriolosclerosis have been postulated (10). The first is that genetic risk factors help to explain the arteriolosclerosis-LATE association (31). The second is that the neurovascular unit could be disrupted by neurovascular unit (e.g. pericyte) damage, and this process may be due to the effects of TDP-43 proteinopathy instead of ADNC (32).

Definite PART was associated with a lower odds of LATE-NC in the adjusted analysis. A very small percentage of individuals with and without LATE-NC had PART,

TABLE 5. Clinical Diagnosis Among Those With LATE-NC and the Presence or Absence of Major Copathologies

	Participants With LATE-NC and the Presence/Absence of Copathologies:			
	ADNC andLBD Absent n = 25 n (col %)	**ADNC Present, LBD Absent n = 106 n (col %)**	**LBD Present, ADNC Absent n = 20 n (col %)**	**ADNC and LBD Present n = 101 n (col %)**
Primary clinical diagnosis, n (%)				
Normal cognition	5 (20.8%)	0 (0.0%)	2 (11.1%)	0 (0.0%)
Alzheimer disease	16 (66.7%)	102 (96.2%)	11 (61.1%)	95 (94.1%)
Lewy body disease/PD	0 (0.0%)	1 (0.9%)	3 (16.7%)	4 (4.0%)
Vascular disease	3 (12.5%)	1 (0.9%)	1 (5.6%)	2 (2.0%)
Other	0 (0.0%)	2 (1.9%)	1 (5.6%)	0 (0.0%)

Missing data on primary clinical diagnosis, n = 3.
Abbreviations: LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; ADNC, Alzheimer disease neuropathologic change; LBD, Lewy body disease; PD, Parkinson disease.

TABLE 6. Adjusted Associations Between Clinical Characteristics and LATE-NC

	Model 1—All Participants			Model 2—Participants With Data on First Predominant Symptom		
	OR	**95% Confidence Interval**	**p Value**	**OR**	**95% Confidence Interval**	**p Value**
Age at death (years)	1.007	0.998–1.016	0.15	1.005	0.996–1.015	0.28
Female	1.05	0.95–1.16	0.32	1.07	0.96–1.19	0.25
Education (years)	1.005	1.001–1.009	0.03	1.005	1.001–1.009	0.02
APOE ε4 carrier	1.01	0.91–1.12	0.81	1.00	0.88–1.12	0.94
CDR Sum of Boxes	1.011	1.005–1.018	0.001	1.008	1.001–1.015	0.04
Diabetes	1.11	0.97–1.28	0.14	1.14	0.98–1.34	0.10
Congestive heart failure	0.88	0.79–0.98	0.03	0.88	0.79–0.99	0.03
Atrial fibrillation	0.98	0.89–1.07	0.66	0.96	0.86–1.08	0.51
Pacemaker/defibrillator	0.99	0.89–1.09	0.82	1.00	0.90–1.11	0.99
Traumatic brain injury (remote)	0.90	0.75–1.08	0.26	0.87	0.72–1.07	0.19
Antihypertensive	0.97	0.88–1.06	0.49	0.98	0.90–1.07	0.69
Antipsychotic	1.07	0.92–1.24	0.40	1.09	0.95–1.26	0.21
Diabetes medication	0.83	0.66–1.05	0.11	0.81	0.63–1.03	0.09
Anticoagulant	1.01	0.91–1.12	0.83	1.00	0.89–1.13	0.99
AD medication	1.16	1.05–1.28	0.003	1.13	1.02–1.25	0.02
Antiparkinson agent	0.92	0.76–1.10	0.36	0.93	0.79–1.10	0.42
First predominant symptom						
Behavior vs cognitive	–	–	–	1.03	0.83–1.28	0.78
Motor vs cognitive	–	–	–	0.76	0.63–0.91	0.003

Abbreviations: OR, Odds ratio; *APOE*, Apolipoprotein E; LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; AD, Alzheimer disease.

although the percentage with PART was higher in those without LATE-NC (8% vs 2%). These data demonstrate that at least in the NACC sample, a large proportion of LATE-NC cases are not associated with PART (33–35). In addition, previous studies demonstrated differences in the impaired cognitive domains between PART and ADNC. We also note that cases with LATE-NC may have tau proteinopathy that is outside of the canonical Braak NFT staging system (4), which may be a confounder in this analysis. Considered altogether, while PART and LATE-NC may co-occur, they may be due to different mechanisms. However, they share a commonality in that both pathologies often involve regions affected by ADNC, yet are usually limited to the medial temporal lobe. A smaller proportion of those with LATE-NC or PART display pathology beyond the medial temporal lobe, and it has been posited that in these cases, some currently unknown factor(s) may be accelerating disease progression (10).

The 2 main clinical characteristics (negatively) associated with LATE-NC were CHF and motor symptoms as the first predominant symptom. CHF appeared slightly protective against LATE-NC, and controlling for medications for edema/heart failure did not change these findings (data not shown). However, the medication data in the UDS are limited by possible reporting bias and lack of detailed information on drug

TABLE 7. Adjusted Associations Between Neuropathological Characteristics and LATE-NC

Neuropathological Characteristic*	OR†	95% CI	p Value
ADNC	1.16	1.09–1.25	<.0001
Hippocampal sclerosis	1.49	1.34–1.65	<.0001
Definite PART	0.84	0.75–0.94	0.002
Lewy body disease (vs none)			
Brainstem-predominant	0.90	0.80–1.01	0.07
Limbic/amygdala-predominant	1.14	1.05–1.24	0.002
Neocortical	1.06	0.98–1.15	0.13
Present, region unspecified/ olfactory bulb	0.92	0.70–1.20	0.54
Arteriolosclerosis (moderate/severe)	1.11	1.04–1.19	0.003

*Separate model was run for each pathology with LATE-NC as the outcome variable (e.g. first model had the following predictors: ADNC, age at death, sex, education).
†Controlling for age at death, sex, education.
Abbreviations: LATE-NC, limbic predominant age-related TDP-43 encephalopathy neuropathological change; ADNC, Alzheimer's disease neuropathologic change; PART, primary age-related tauopathy; OR, odds ratio; CI, confidence interval.

adherence and dose. Further exploration of these findings is needed in community-based autopsy cohorts to test if the observed CHF-LATE-NC association persists and whether there could be an explanatory biological mechanism or associated protective factor such as medication use.

Almost all of the individuals with LATE-NC first presented with cognitive symptoms (97%), and the same held true for those without LATE-NC (90%). However, motor symptoms were relatively more common as the first symptom among those without LATE-NC (6%) and were extremely rare for those with LATE-NC (<1%). This association persisted in the adjusted analyses. In addition, compared with those without LATE-NC, individuals with LATE-NC more often experienced depressed mood at the MCI stage (CDR = 0.5). Among those with dementia (CDR = 1, 2, or 3), those with LATE-NC more often experienced problems with orientation and less often experienced hallucinations and motor symptoms. These findings suggest differences in clinical presentation that could help differentiate LATE-NC from other pathologies during life, but further work will be needed to fully characterize the cognitive, behavioral, and motor differences that are distinguishing characteristics of LATE-NC at different stages of the disease.

APOE genotype was not associated with LATE-NC in this sample. Although some studies have shown an association between the *APOE* ε4 allele and LATE-NC (36–38), other studies found no association between *APOE* ε4 and HS, a strongly but not perfectly correlated pathology associated with LATE-NC (26, 39–41). The *APOE* ε4 allele was found in approximately half of those with LATE-NC and almost half of those without LATE-NC, and therefore, this UDS autopsy sample was highly weighted toward individuals with ADNC and increased risk of AD dementia. We note that almost everyone with the *APOE* ε4 allele acquires β-amyloid pathology in advanced age (42, 43), and this is a very challenging potential confounder to address using statistical models. Additional studies using population-representative cohorts will be required to better evaluate *APOE*-LATE-NC associations.

Although the consensus criteria for LATE-NC recommend 3 stages of neuropathological change (stage 1: amygdala; stage 2: hippocampus; stage 3: middle frontal gyrus), TDP-43 in the middle frontal gyrus was not recorded/reported to NACC as the LATE-NC criteria have not yet been incorporated into NACC Neuropathology Form. Therefore, we chose to study LATE-NC in a dichotomous manner (present/absent) based on presence of TDP-43 inclusions in the amygdala, hippocampus, and entorhinal/inferior temporal cortex. Future work will be needed to replicate our findings with the inclusion of individuals with TDP-43 in the middle frontal gyrus, and to tease apart how associations may differ depending on stage of disease. Other limitations of this study are the very small sample of underrepresented groups (e.g. minorities), the potential for selection bias due to the selected sample (i.e. not population-based) of participants followed at the ADCs and factors influencing autopsy consent, and that we did not account for multiple comparisons. However, it has been argued that adjustment for multiple comparisons can be overly conservative and is not necessary for exploratory analyses such as those conducted in this study. Further, there is no specific TDP-43 detection methodology that is prescribed, either based on consensus guidelines or NACC/ADC guidelines, and consequently ADCs applied different immunohistochemical methods. Although this is a drawback to the NACC data, the ADCs are among the most advanced U.S. academic centers studying neurodegenerative diseases and, arguably, better represent the concept of TDP-43 pathology than a single center would, as has been discussed previously (10). A major additional strength of the approach is that it provides a large sample with extensive clinical and neuropathological data with which to explore potential associations, such as those between clinical risk factors, copathologies, and LATE-NC.

This is one of the first studies to examine potential risk factors for LATE-NC following the recently published consensus criteria. Our study not only verifies previous findings in demonstrating associations between LATE-NC and ADNC, HS, LBD, and arteriolosclerosis, but also provides avenues for future research on LATE-NC in suggesting clinical characteristics such as motor symptoms that may help distinguish LATE-NC from other neurodegenerative diseases. Additional studies, particularly those using community-based autopsy cohorts, are required to tease apart the full spectrum of clinical manifestations and biomarkers of LATE-NC that differentiate it from related but distinct copathologies, including AD and LBD.

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REFERENCES

1. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. Brain 2019;142:1503–27
2. Aoki N, Murray ME, Ogaki K, et al. Hippocampal sclerosis in Lewy body disease is a TDP-43 proteinopathy similar to FTLD-TDP Type A. Acta Neuropathol 2015;129:53–64

3. Josephs KA, Whitwell JL, Knopman DS, et al. Abnormal TDP-43 immunoreactivity in AD modifies clinicopathologic and radiologic phenotype. Neurology 2008;70:1850–7
4. Smith VD, Bachstetter AD, Ighodaro E, et al. Overlapping but distinct TDP-43 and tau pathologic patterns in aged hippocampi. Brain Pathol 2018;28:264–73
5. James BD, Wilson RS, Boyle PA, et al. TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia. Brain 2016;139:2983–93
6. Robinson JL, Corrada MM, Kovacs GG, et al. Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+ Study. Acta Neuropathol 2018;136:377–88
7. Amador-Ortiz C, Lin WL, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol 2007;61: 435–45
8. Nelson PT, Smith CD, Abner EL, et al. Hippocampal sclerosis of aging, a prevalent and high-morbidity brain disease. Acta Neuropathol 2013; 126:161–77
9. Power MC, Mormino E, Soldan A, et al. Combined neuropathological pathways account for age-related risk of dementia. Ann Neurol 2018;84: 10–22
10. Katsumata Y, Fardo DW, Kukull WA, et al. Dichotomous scoring of TDP-43 proteinopathy from specific brain regions in 27 academic research centers: Associations with Alzheimer's disease and cerebrovascular disease pathologies. Acta Neuropathol Commun 2018;6:142
11. Besser LM, Kukull WA, Teylan MA, et al. The Revised National Alzheimer's Coordinating Center's Neuropathology Form—Available Data and New Analyses. J Neuropathol Exp Neurol 2018;77:717–26
12. Neltner JH, Abner EL, Baker S, et al. Arteriolosclerosis that affects multiple brain regions is linked to hippocampal sclerosis of ageing. Brain 2014;137:255–67
13. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology 1993;43:2412–4
14. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): Clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord 2006;20:210–6
15. Weintraub S, Besser L, Dodge HH, et al. Version 3 of the Alzheimer disease centers' neuropsychological test battery in the uniform data set (UDS). Alzheimer Dis Assoc Disord 2018;32:10–7
16. Besser L, Kukull W, Knopman DS, et al. Version 3 of the national Alzheimer's coordinating center's uniform data set. Alzheimer Dis Assoc Disord 2018;32:351–8
17. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. Acta Neuropathol 2012; 123:1–11
18. National Alzheimer's Coordinating Center. Neuropathology Data Set: Coding Guidebook. Available from: http://www.alz.washington.edu/NONMEMBER/NP/npguide10.pdf. Accessed December 2, 2019
19. Braak H, Alafuzoff I, Arzberger T, et al. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 2006;112:389–404
20. Mirra SS, Hart MN, Terry RD. Making the diagnosis of Alzheimer's disease. A primer for practicing pathologists. Arch Pathol Lab Med 1993; 117:132–44
21. Thal DR, Rüb U, Orantes M, et al. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 2002; 58:1791–800
22. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): A common pathology associated with human aging. Acta Neuropathol 2014;128:755–66
23. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. Neurology 2005;65:1863–72
24. National Alzheimer's Coordinating Center. NACC Uniform Data Set Researchers Data Dictionary. Available from: http://www.alz.washington.edu/WEB/rdd_uds.pdf. Accessed December 2, 2019
25. Zarow C, Weiner MW, Ellis WG, et al. Prevalence, laterality, and comorbidity of hippocampal sclerosis in an autopsy sample. Brain Behav 2012; 2:435–42
26. Nelson PT, Schmitt FA, Lin Y, et al. Hippocampal sclerosis in advanced age: Clinical and pathological features. Brain 2011;134:1506–18
27. Hatanpaa KJ, Raisanen JM, Herndon E, et al. Hippocampal sclerosis in dementia, epilepsy, and ischemic injury: Differential vulnerability of hippocampal subfields. J Neuropathol Exp Neurol 2014;73:136–42
28. Makkinejad N, Schneider JA, Yu J, et al. Associations of amygdala volume and shape with transactive response DNA-binding protein 43 (TDP-43) pathology in a community cohort of older adults. Neurobiol Aging 2019;77:104–11
29. Nelson PT, Abner EL, Schmitt FA, et al. Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. Brain Pathol 2010;20:66–79
30. Josephs KA, Murray ME, Tosakulwong N, et al. Pathological, imaging and genetic characteristics support the existence of distinct TDP-43 types in non-FTLD brains. Acta Neuropathol 2019;137:227–38
31. Nelson PT, Jicha GA, Wang WX, et al. ABCC9/SUR2 in the brain: Implications for hippocampal sclerosis of aging and a potential therapeutic target. Ageing Res Rev 2015;24:111–25
32. Sagare AP, Bell RD, Zhao Z, et al. Pericyte loss influences Alzheimer-like neurodegeneration in mice. Nat Commun 2013;4:2932
33. Besser LM, Mock C, Teylan MA, et al. Differences in cognitive impairment in primary age-related tauopathy versus Alzheimer disease. J Neuropathol Exp Neurol 2019;78:219–28
34. Josephs KA, Murray ME, Tosakulwong N, et al. Tau aggregation influences cognition and hippocampal atrophy in the absence of beta-amyloid: A clinico-imaging-pathological study of primary age-related tauopathy (PART). Acta Neuropathol 2017;133:705–15
35. Jefferson-George KS, Wolk DA, Lee EB, et al. Cognitive decline associated with pathological burden in primary age-related tauopathy. Alzheimers Dement 2017;13:1048–53
36. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain 2018;141:2181–93
37. Wennberg AM, Tosakulwong N, Lesnick TG, et al. Association of apolipoprotein E epsilon4 with transactive response DNA-binding protein 43. JAMA Neurol 2018;75:1347–54
38. Yang HS, Yu L, White CC, et al. Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to APOE epsilon4 haplotype status: A community-based cohort study. Lancet Neurol 2018;17:773–81
39. Leverenz JB, Agustin CM, Tsuang D, et al. Clinical and neuropathological characteristics of hippocampal sclerosis: A community-based study. Arch Neurol 2002;59:1099–106
40. Brenowitz WD, Monsell SE, Schmitt FA, et al. Hippocampal sclerosis of aging is a key Alzheimer's disease mimic: Clinical-pathologic correlations and comparisons with both alzheimer's disease and non-tauopathic frontotemporal lobar degeneration. JAD 2014;39:691–702
41. Pao WC, Dickson DW, Crook JE, et al. Hippocampal sclerosis in the elderly: Genetic and pathologic findings, some mimicking Alzheimer disease clinically. Alzheimer Dis Assoc Disord 2011;25:364–8
42. Berr C, Hauw JJ, Delaere P, et al. Apolipoprotein E allele epsilon 4 is linked to increased deposition of the amyloid beta-peptide (A-beta) in cases with or without Alzheimer's disease. Neurosci Lett 1994;178: 221–4
43. Abner EL, Neltner JH, Jicha GA, et al. Diffuse amyloid-beta plaques, neurofibrillary tangles, and the impact of APOE in elderly Persons' brains lacking neuritic amyloid plaques. JAD 2018;64:1307–24