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Impact and Risk Factors of Limbic Predominant Age-Related TDP-43 Encephalopathy Neuropathologic Change in an Oldest-Old Cohort

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Abstract

Background and Objectives

Limbic predominant age-related TAR DNA binding protein 43 (TDP-43) encephalopathy neuropathologic change (LATE-NC) is a prevalent degenerative pathology in the oldest-old who are the fastest-growing segment of our population with the highest rates of dementia. We aimed to determine the relationship between LATE-NC and cognitive impairment and to identify its potential risk factors by studying its relationship with common past medical histories in an oldest-old cohort.

Methods

Participants from The 90+ Study with longitudinal evaluations and autopsy data were included. Dementia status and impairment in 5 main cognitive domains were determined at postmortem conferences leveraging all clinical and neuropsychological data blind to neuropathologic diagnosis. Medical history information was obtained from patients and their informants. LATE-NC and Alzheimer disease neuropathologic change (ADNC) were considered present in those with TDP-43 pathology in the hippocampus and/or neocortex and those with high likelihood of ADNC according to NIA-AA guidelines, respectively. We examined the association of degenerative pathologies with cognitive outcomes and multiple comparisons–adjusted relationship of medical history variables with LATE-NC and ADNC using logistic regressions adjusted for age at death, sex, and education.

Results

Three hundred twenty-eight participants were included in this study. LATE-NC was present in 32% of the participants. It had a significant association with the presence of dementia (OR 2.8, 95% CI 1.7–4.6) and impairment in memory (OR 3.0, 95% CI 1.8–5.1), language (OR 2.6, 95% CI 1.6–4.3), and orientation (OR 3.5, 95% CI 2.1–5.9). The association with impaired orientation was unique to LATE-NC, and the strength and significance of the other associations were comparable to ADNC. Furthermore, we found that history of osteoarthritis (OR 0.37, adjusted 95% CI 0.21–0.66) and hypertension (OR 0.52, adjusted 95% CI 0.28–0.98) were associated with a reduced likelihood of LATE-NC, but not ADNC.

Discussion

Our results suggest that LATE-NC is a prevalent degenerative pathology in the oldest-old and has significant associations with dementia and impairment in cognitive domains with magnitudes that are comparable to ADNC. We also found that past medical histories of hypertension and osteoarthritis were associated with a lower likelihood of LATE-NC. This might help identify upstream mechanisms leading to this important pathology.

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From the University of California (S.A.S., K.A.S., R.Y., C.K., M.M.C.), Irvine; and Stanford University (S.B., T.J.M.), CA.

Glossary

ADNC = Alzheimer disease neuropathologic change; **CAA** = cerebral amyloid angiopathy; **FTD** = frontotemporal dementia; **HS** = hippocampal sclerosis of aging; **LATE** = limbic predominant age-related TDP-43 encephalopathy; **LATE-NC** = LATE neuropathologic change; **LWCS** = Leisure World Cohort Study; **MMSE** = Mini Mental State Examination; **MVL** = microvascular lesion; **TDP-43** = TAR DNA binding protein 43; **UC** = University of California.

Cognitive impairment in older individuals is commonly due to the presence of multiple pathologies.[1] A significant proportion of these pathologies do not have reliable blood-based or imaging biomarkers making clinicopathologic studies necessary to study their effect on outcomes such as dementia and impairment in various cognitive domains. Limbic predominant age-related TAR DNA binding protein 43 (TDP-43) encephalopathy (LATE) is a recently defined clinicopathologic construct to denote the presence of phosphorylated TDP-43 inclusions in limbic and isocortical neurons in older individuals.[2] Limbic TDP-43 inclusions are a common neurodegenerative change in older individuals reported in more than 20% of old age autopsy cohorts with its prevalence particularly increasing after age 90 years.[3,4] Given the recent consensus on LATE neuropathologic change (LATE-NC), its relationship with cognitive outcomes such as dementia, its cognitive signature, and potential upstream risk factors require further investigation, and therefore, there is a pressing need to explore these issues in well-characterized cohorts. Leveraging data obtained from one of the largest single-center oldest-old cohorts, The 90+ Study, we aimed to examine the relationship of LATE-NC with a diagnosis of dementia and impairment in various cognitive domains. We also aimed to characterize potential risk and protective factors of this important neurodegenerative change in the oldest-old segment of the population.

Methods

Participants

Participants from The 90+ Study who had agreed to longitudinal in-person assessments and postmortem brain examination were included. The 90+ Study is a community-based cohort in Southern California that studies the physical and mental health of the fastest-growing age group in the United States.[5] Initially, participants in The 90+ Study were survivors from the Leisure World Cohort Study (LWCS), an epidemiologic investigation of a retirement community in Orange County, CA, in the early 1980s. The 90+ Study was initiated in 2003 when the surviving participants from the original LWCS who were aged 90 years and older on January 1, 2003, were invited to join. We also extended a similar invitation on January 1, 2008, and every year thereafter to those turning 90 years old. More recently, open recruitment of volunteers aged 90 years and older beyond the LWCS was initiated using a variety of recruitment methods including mailing lists of residences believed to have people aged 90 years and older, talks at local communities, talks to primary doctors, ads in local newspapers, and relatives or friends of participants. Participants from the LWCS were recruited regardless of cognitive diagnosis, whereas noncohort volunteers had no or mild dementia. The inclusion criteria for the present study were the availability of (1) brain autopsy results and (2) clinical and neuropsychological diagnosis from a multidisciplinary case conference as described below.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants or their designated surrogates provided consent to participate in the study. Procedures were reviewed and approved by the Institutional Review Board at the University of California (UC), Irvine.

Assessments

Participants underwent evaluations every 6 months. Clinical evaluations included a battery of neuropsychological tests, neurologic examination, and self- or informant-completed questionnaires for demographics and medical history. Furthermore, after a participant's death, additional information was obtained from informants regarding cognition and function since the last evaluation. In addition, medical history information from the obtained medical records was incorporated into self- or informant-provided medical history.

Determination of Dementia and Impaired Cognitive Domains

The clinical diagnosis of dementia was made using the Diagnostic and Statistical Manual of Mental Disorders 4th edition; criteria in a multidisciplinary consensus diagnostic conference completed after a participant's death, with conferees blinded to pathologic findings. All available information on the participant was used in determination of dementia. This included neuropsychological test scores, neurologic examination, information collected from informants, available medical records, videos containing semistructured interviews about their daily life and questions to test their memory and brief examination of their gait from the time of visits, and death certificates. Similarly, identification of the impaired cognitive domains was based on consideration of participants' scores in longitudinal neuropsychological tests, information obtained from their informants, and their conduct in recorded semistructured interviews that were reviewed at postmortem conferences. Specifically, determination of memory impairment is based on participants' longitudinal performance in the short (9 item) version of the California Verbal Learning Test, their performance in memory subdomains of Mini Mental State Examination (MMSE)

Table 1 Demographic and Neuropathologic Characteristics of the Participants

	Whole group (N = 328)	No dementia (N = 177, 54%)	Dementia (N = 151, 46%)	*p* Value
Age at death (SD)	97.7 (3.6)	97.6 (3.5)	97.9 (3.6)	0.3
Female	237 (72%)	123 (70%)	114 (76%)	0.2
College graduate	167 (51%)	103 (58%)	64 (42%)	0.004[a]
ADNC	125 (38%)	52 (29%)	73 (48%)	<0.001[a]
LATE-NC	105 (32%)	39 (22%)	66 (44%)	<0.001[a]
Lewy body	40 (12%)	15 (9%)	25 (17%)	0.03[a]
CAA	139 (42%)	65 (37%)	74 (49%)	0.02[a]
Arteriolosclerosis	195 (59%)	100 (57%)	95 (63%)	0.2
MVL	31 (9%)	16 (9%)	15 (10%)	0.8

Abbreviations: ADNC = Alzheimer disease neuropathologic change; CAA = cerebral amyloid angiopathy; LATE-NC = limbic predominant age-related TAR DNA binding protein 43 encephalopathy neuropathologic change; MVL = microvascular lesion.
[a] Denotes significant difference (*p* < 0.05) between dementia and no dementia groups.

and modified MMSE (3MS), and their conduct in the semistructured interviews. Language impairment is diagnosed based on the performance in the 15-item version of the Boston Naming Test, category fluency, and performance in semistructured interviews. Visuospatial function is mainly assigned based on systematically collected information about participants' problems with finding way indoor or outdoor. Orientation is considered impaired when participants struggle with the temporal and spatial orientation items from MMSE. Specifically, participants are asked questions about date, day of the week, and season (temporal orientation) and the address of the place of assessment to include state, county, city, building, and floor (spatial orientation). Finally, executive function impairment is diagnosed when there is abnormal performance in Trails B and clock-drawing tests and reduced letter fluency or when there is informant report of problems with complex tasks. Performance in neuropsychological tests is typically depicted against standard norms of age-matched counterparts[6] to aid determination of whether the performance is within the normal range at each visit.

Pathologic Evaluations

All postmortem brain procurements were performed at the UC, Irvine, between 2003 and 2020 using Alzheimer's Disease Research Center protocols. Before dissection, the whole brain was weighed, and then, one hemisphere was selected based on the clinician's impression of any asymmetry in clinical features. The selected hemisphere and contralateral hippocampus were fixed with 4% paraformaldehyde for at least 2 weeks before dissection. Beginning in January 2017, all pathologic evaluations were performed at Stanford University using state-of-the-art neuropathologic methods according to the current National Institute on Aging- Alzheimer's Association neuropathologic guidelines.[7] To unify the pathologic evaluations across the samples procured over 2 decades, and to implement the recommendations for pathologic evaluation of LATE-NC,[2] all brains procured before 2017 were shipped to Stanford University to be reevaluated, resampled, and resectioned followed by histochemical and immunohistochemical stains exactly according to the protocols used in cases collected after 2016. We considered the following pathologic changes for analysis: Alzheimer disease neuropathologic change (ADNC), TAR-DNA binding protein 43 inclusions (LATE-NC), Lewy bodies (LBs), arteriolosclerosis, microvascular lesions (MVLs), and cerebral amyloid angiopathy (CAA).

Demographics and Medical History Variables

Demographics and medical history variables were obtained from participants or their informants at the first visit and were updated at every follow-up visit. Medical history variables included hypertension, hypercholesterolemia, heart disease, chronic obstructive pulmonary disease, diabetes, stroke, transient ischemic attack, seizure, rheumatologic disease, osteoarthritis, macular degeneration, glaucoma, thyroid

Table 2 Association Between Individual Neuropathologies and the Outcome of Dementia

	OR	95% CI	*p* Value
ADNC	2.32	1.46–3.70	<0.001[a]
LATE-NC (TDP-43)	2.85	1.74–4.67	<0.001[a]
Lewy body	2.29	1.14–4.56	0.02[a]
CAA	1.59	1.01–2.50	0.04[a]
Arteriolosclerosis	1.17	0.74–1.86	0.49
MVL	1.05	0.49–2.23	0.89

Abbreviations: ADNC = Alzheimer disease neuropathologic change; CAA = cerebral amyloid angiopathy; LATE = limbic predominant age-related TAR DNA binding protein 43 encephalopathy neuropathologic change; MVL = microvascular lesion.
All regressions are adjusted for age at death, sex, and education status.
[a] Denotes significant associations (*p* < 0.05).

Table 3 Association Between Neuropathologies and the Outcome of Impairment in Cognitive Domains

	ADNC OR (95% CI)	LATE-NC OR (95% CI)	LB OR (95% CI)	CAA OR (95% CI)	AS OR (95% CI)	MVL OR (95% CI)
Memory	**1.86 (1.1–3.1)**	**3.0 (1.8–5.1)**	1.51 (0.7–3.3)	1.08 (0.7–1.8)	0.87 (0.53–1.4)	1.87 (0.8–4.5)
Language	**2.15 (1.3–3.6)**	**2.6 (1.6–4.3)**	1.5 (0.7–3.1)	1.5 (0.9–2.4)	0.6 (0.4–1.1)	1.1 (0.5–2.6)
Visuospatial function	**3.3 (1.8–6.1)**	1.8 (0.97–3.2)	**2.4 (1.1–5.2)**	1.2 (0.6–2.2)	0.6 (0.3–1.1)	0.7 (0.2–2.0)
Orientation	1.5 (0.9–2.5)	**3.5 (2.1–5.9)**	1.9 (0.9–4.0)	1.2 (0.7–1.9)	0.9 (0.5–1.5)	0.8 (0.4–2.0)
Executive function	1.5 (0.9–2.4)	1.6 (0.95–2.6)	1.9 (0.9–3.8)	1.3 (0.8–2.1)	1.3 (0.8–2.0)	1.4 (0.6–3.1)

Abbreviations: ADNC = Alzheimer disease neuropathologic change; AS = arteriolosclerosis; CAA = cerebral amyloid angiopathy; LATE = limbic predominant age related TAR DNA binding protein 43 encephalopathy neuropathologic change; LB = lewy body; MVL = microvascular lesion.
Significant associations are in bold. All regressions are adjusted for age at death, sex, and education status.

disease, depression, and anxiety. Heart disease and rheumatologic illness were composite variables. Heart disease was considered present if the patient had a history of any of the following: coronary artery disease, atrial fibrillation and other arrhythmia, congestive heart failure, and myocardial infarction. Rheumatologic disease history was established based on the reported history of lupus, or scleroderma, or rheumatoid arthritis.

Statistical Analyses

We compared characteristics between the groups with and without dementia using *t* tests for continuous variables and Fisher exact tests for categorical variables. Each pathologic change was dichotomized as follows: ADNC was considered present in those with high likelihood of Alzheimer disease neuropathology according to National Institute on Aging- Alzheimer's Association guidelines.[8] LATE-NC was defined as present in those with involvement of the hippocampus and/or neocortex (stage 2 or 3 according to the consensus paper[2]). Lewy body disease was considered present in those with involvement of limbic structures and/or the neocortex in accordance with NIA-AA[8] and consensus guidelines.[9] MVLs were remote focal ischemic lesions found only on microscopic examination of standardized screening sections.[10] MVLs were scored positive if there were 2 or more MVLs in the screening sections.[8] Finally, arteriolosclerosis and CAA were scored positive in those with moderate to severe pathologic change of each according to the published criteria.

We first used separate logistic regressions to estimate the odds of dementia in relation to each of the dichotomized pathologies. We then estimated the independent contribution of each of the pathologies to the odds of dementia in a logistic regression that included all pathologies. In addition, we performed a similar logistic regression including all pathologic changes to investigate the independent relationship of each pathology with impairment of each cognitive domain as outcome. Finally, we investigated the relationship of LATE-NC as outcome with each of the past medical histories in separate logistic regressions.

Given the high number of comparisons for the association between individual pathologies and between pathologies and

past medical history variables, and to avoid reporting false-positive associations, adjustment for multiple comparisons was performed based on Benjamini-Hochberg adjustment for false discovery rate.[11,12] *p* Values <0.05 were considered statistically significant.

Data Availability

Data for all the analyses and results reported in this article were acquired from The 90+ Study. Data not published within the article will be shared by request from any qualified investigator.

Results

As of May 2020, of 433 participants enrolled in the autopsy program who had died, 405 (94%) had their brains procured. Of these, full pathology assessment was available for 328 participants. We included all 328 participants in the analysis. Table 1 summarizes the demographic and neuropathologic characteristics of the study participants as a whole and stratified by dementia status. In line with the demographics of the oldest-old, most participants were female (72%). They were also highly educated, with more than 50% having a college degree or more. Ninety-eight percent of participants were White. Age at death and sex were not significantly different between those with and without dementia, but those without dementia were more likely to be a college graduate (58% vs 42%, *p* = 0.004). Among the examined pathologic changes, ADNC, LATE-NC, LB, and CAA were significantly more prevalent in the dementia group. Fifty participants (15%) had both ADNC and LATE-NC. Of these, 35 (70%) had dementia at death. Examining the association between each individual pathologic change and the odds of dementia adjusting for age at death, sex, and education (Table 2), we found that ADNC (OR 2.32, 95% CI 1.46–3.70), LATE-NC (OR 2.85, 95% CI 1.74–4.67), LB (OR 2.29, 95% CI 1.14–4.56), and CAA (OR 1.59, 95% CI 1.01–2.50) were the neuropathologic variables significantly associated with dementia. In a model including all pathologic variables, however, ADNC (OR 1.9, 95% CI 1.1–3.1) and LATE-NC (OR 2.7, 95% CI 1.6–4.5) were the only lesions that remained

**Figure 1** Association of Pathologies With Dementia as the Outcome
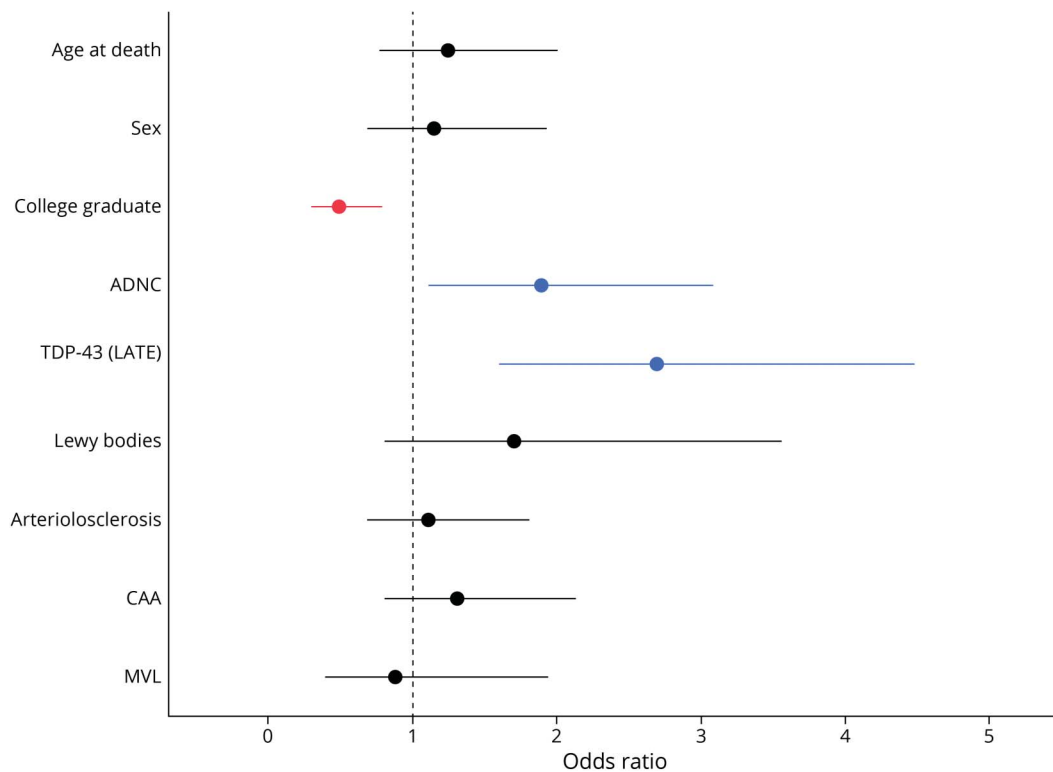
OR less than 1 indicates lower odds of dementia, and odds ratios greater than 1 represent higher odds. ADNC = Alzheimer disease neuropathologic change; CAA = cerebral amyloid angiopathy; LATE = limbic predominant age-related TAR DNA binding protein 43 encephalopathy; MVL = microvascular lesion.

significantly associated with dementia (Figure 1). We also examined the association between the pathologies with separate regression analyses adjusting for age at death and sex. LATE-NC was associated with ADNC and MVL in unadjusted models, but these associations did not survive adjustment for multiple comparisons (for LATE-NC and ADNC: OR 1.8, adjusted 95% CI 0.95–3.5; for LATE-NC and MVL: OR 2.17, adjusted 95% CI 0.70–6.7). Among all the examined associations, the relationship between ADNC

and LB (OR 3.3, adjusted 95% CI 1.4–7.4) was the only association that survived adjustment for multiple comparisons. In addition, LB frequency was almost 3 times more in those with ADNC (20%) compared with ADNC-negative participants (7%). LATE-NC was present in 26% of ADNC-negative and 40% of ADNC-positive participants.

We performed another logistic regression analysis including all pathologic changes in the same model to investigate the

Figure 2 Association of Medical Histories With LATE-NC
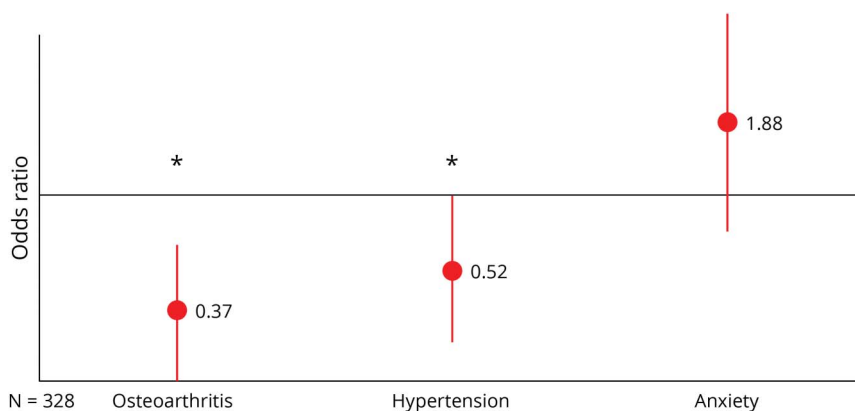
OR less than 1 indicates lower odds of LATE pathology, and odds ratios greater than 1 represent higher odds of LATE pathology in individuals with a particular medical history. Only the associations with asterisks survived adjustment for multiple comparisons. All associations are adjusted for age at death, sex, and education. LATE-NC = limbic predominant age-related TAR DNA binding protein 43 encephalopathy neuropathologic change.

relationship of different lesions with different cognitive domains as outcome (Table 3). We found that memory impairment was only associated with ADNC (OR 1.86, 95% CI 1.1–3.1) and LATE-NC (OR 3.0, 95% CI 1.8–5.1). Similarly, language impairment was only associated with ADNC (OR 2.15, 95% CI 1.3–3.6) and LATE-NC (OR 2.6, 95% CI 1.6–4.3). Visuospatial impairment, on the other hand, was significantly associated with ADNC (OR 3.3, 95% CI 1.8–6.1) and LB (OR 2.4, 95% CI 1.1–5.2) but not with LATE-NC (OR 1.8, 95% CI 0.97–3.2). Orientation impairment was only significantly associated with LATE-NC (OR 3.5, 95% CI 2.1–5.9). Executive function impairment was not significantly associated with any of the neuropathologic changes.

Subsequently, we investigated the association of LATE pathology as outcome with the reported medical histories through regression models adjusted for sex, age at death, education, and multiple comparisons (Figure 2). Histories of hypertension (OR 0.52, adjusted 95% CI 0.28–0.98) and osteoarthritis (OR 0.37, adjusted 95% CI 0.21–0.66) were significantly associated with a lower likelihood of LATE-NC. In contrast, history of anxiety was associated with a higher likelihood of LATE-NC in unadjusted models, but the relationship did not survive correction for multiple comparisons (OR 1.88, adjusted 95% CI 0.74–4.8). Examining the association of medical histories and ADNC, hypertension was the only PMH variable that was associated with a lower likelihood of ADNC in unadjusted models, but the association did not survive correction for multiple comparisons (OR 0.58, adjusted 95% CI 0.32–1.14). Neither heart disease nor rheumatologic disease composite measure was associated with LATE-NC or ADNC.

Discussion

In this study, we investigated the association of LATE-NC with outcomes of dementia and impairment in various cognitive domains in comparison with other common neurodegenerative diseases, particularly Alzheimer disease. In a regression analysis including all common pathologic changes, LATE-NC and ADNC were the only diseases that had a significant association with dementia, and LATE-NC was associated with higher odds of dementia than ADNC. We also found that LATE-NC was the strongest predictor of impairment in 3 of the 5 examined cognitive domains and that its association with memory impairment had a higher OR than ADNC in this age group. We also examined the association of medical histories with LATE-NC as outcome and found that histories of hypertension and osteoarthritis were associated with decreased likelihood of LATE-NC. We performed these analyses in a cohort exclusively comprising oldest-old individuals. This is important since, by definition, LATE-NC is a pathology that is especially prevalent in the oldest-old.[2] This age epoch is the fastest-growing segment of our population with around 50% of those having dementia in the United States by year 2050, projected to belong to this group.[13]

Previous studies have reported the association of TDP-43 pathology with memory impairment[2,14,15] and a similarity in clinical presentation of LATE-NC and ADNC.[14,16] Here, we performed a head-to-head comparison of the 2 neuropathologic changes in terms of their association with important outcomes of dementia and impairment in various cognitive domains. We believe that our approach in using postmortem multidisciplinary assigned diagnoses was particularly robust because we use all the available information from clinical and neuropsychological assessments, informant questionnaires, and medical charts to determine impairment in cognition and various cognitive domains blind to outcomes of neuropathologic evaluation. It is rather striking that LATE-NC had a stronger association with the very aspect of cognitive function that is almost universally ascribed to Alzheimer disease, that is, memory impairment. The other interesting finding was that LATE-NC was the only pathologic change significantly associated with impaired orientation. Impaired orientation in our cohort is determined by answers participants provide to temporal and spatial orientation questions from MMSE and 3MS cognitive tests. The unique contribution of LATE-NC to this aspect of cognitive function might be useful in prediction of its presence given the current challenges in the differentiation between cognitive signature of LATE-NC and ADNC. On the other hand, visuospatial impairment defined as participants' inability to navigate their environment, ascertained mainly from informants' accounts, was significantly associated with ADNC and LB, but not LATE-NC. In conjunction with orientation impairment seemingly specific to LATE-NC, this might be another useful pointer for differentiating LATE-NC from ADNC and Lewy body disease. Language impairment, on the other hand, was a common feature between ADNC and LATE-NC, and similar to memory impairment, LATE-NC was associated with higher odds of language impairment in our cohort. Future studies examining the language impairment in greater detail might provide insight into what specific language function is affected in each pathology.

Investigating the association of LATE-NC with medical histories ascertained from patients and their informants revealed intriguing associations. Osteoarthritis was significantly associated with lower odds of LATE-NC in our cohort (OR 0.37, adjusted 95% CI 0.21–0.66), an association that was not seen with ADNC (OR 0.79, adjusted 95% CI 0.35–1.33). The direction of this association was rather unexpected given the degenerative nature of both conditions. One possible mechanism for the observed strong association comes from a study that found that the serum level of progranulin is higher in those with osteo- and rheumatoid arthritis compared with control groups.[17] Progranulin is a highly conserved protein encoded by the granulin gene.[18] It is found in both CNS and peripheral tissues and is considered a growth factor regulating cell growth and survival, wound repair, and inflammation.[19] Variation in the progranulin gene, leading to haploinsufficiency, leads to frontotemporal lobar degeneration associated with TDP-43 accumulation.[20] Therefore, it is conceivable that the observed association between

osteoarthritis and reduced likelihood of LATE-NC might be through the progranulin link. Further mechanistic studies will be important to explore this potential link in further detail. We did not observe any association between LATE-NC and history of autoimmune conditions comprising rheumatoid arthritis, lupus, and scleroderma. This is noteworthy because we had previously reported a significant association between history of the same autoimmune conditions and hippocampal sclerosis of aging (HS) pathology.[21] Given the notion of the close relationship between pathologic TDP-43 accumulation and HS, lack of similar relationship in those with LATE-NC is intriguing. There are, however, important differences between the 2 conditions in that LATE-NC is far more prevalent than HS in the oldest-old (32% vs 12% in our cohort, HS data not shown), and almost half of those with HS in our cohort do not harbor TDP-43 pathology (unpublished data). Therefore, it is conceivable that the 2 diseases might be associated with different upstream mechanisms and risk factors.

We found that history of hypertension was associated with a lower likelihood of both ADNC and LATE-NC. The association between hypertension and ADNC, however, did not survive adjustment for multiple comparisons (OR 0.58, adjusted 95% CI 0.32–1.14). Previous work by our group has shown a lower risk of dementia in those who develop hypertension after age 80 years.[22] In addition, evidence from other population-based studies suggests that late-life hypertension might be associated with improved survival in the very old.[23,24] We hypothesize that this effect could be due to maintenance of brain perfusion in those who develop hypertension at the later stages of their lives. The observation that those with a history of hypertension had a reduced likelihood of both LATE-NC and ADNC (ADNC association did not survive correction for multiple comparisons) supports the notion that the maintenance of perfusion is important in protecting the brain against degenerative pathologies irrespective of the pathology type. It is noteworthy that this association has only been studied in cohorts of mostly White individuals and generalizing findings to other ethnicities requires further studies on diverse populations.

We found that LATE-NC was associated with history of anxiety, but this association did not survive correction for multiple comparisons (OR 1.89, adjusted 95% CI 0.74–4.8). Despite this, the putative mechanisms underlying the association between LATE-NC and mood disorders are worth further attention and investigation. The causal relationship between the so-called mood disorders and dementia has been the subject of long-standing debate.[25-28] Most literature on the subject, however, has been centered around the clinical dementia syndromes rather than the relationship of mood disorders with degenerative neuropathologies. Given the recent introduction of LATE-NC construct, there is a paucity of research on its relationship with depression and anxiety. A recent study of participants of the National Alzheimer's Coordinating Center found an association between TDP-43 neuronal cytoplasmic inclusions and apathy in a subset of the TDP-43–positive group who were almost exclusively older than 85 years at the time of death.[29] Another line of evidence for the relationship between TDP-43 and mood disorders comes from frontotemporal dementia (FTD). TDP-43 pathology is one of the 2 main proteinopathies associated with behavioral variant FTD that has apathy as one of its core diagnostic features.[30] In addition, patients with FTD frequently demonstrate obsessive traits and anxiety.[31] Perry syndrome, a rare genetic form of TDP-43 pathologic change, also presents with apathy and atypical depression.[32] Furthermore, a relationship between anxiety and LATE-NC is conceivable given the significance of amygdala in both conditions. Previous imaging[33,34] and animal studies have shown the relevance of amygdala structures to anxiety. In addition, based on the LATE-NC progression framework, amygdala involvement is the first stage of LATE-NC.[2] Further work to investigate the longitudinal relationship between measures of depression, anxiety, and LATE-NC will help investigate their potential causal relationship.

Strengths of this study include the relatively large sample size, focus on the oldest-old individuals who are purported to bear the brunt of LATE-NC, significant majority of women in the study population that is representative of the demographic distribution in this age group, use of uniform diagnostic criteria for assignment of dementia diagnosis and impairment in various cognitive domains throughout the study period by the same group of investigators, and consistent pathologic assessments for all study samples. On the other hand, the lack of ethnic and racial diversity in the study population restricts interpretation of the findings.

In conclusion, we here report the results from an exclusively oldest-old cohort where we found that LATE-NC had significant associations with dementia and impairment in cognitive domains commonly ascribed to Alzheimer disease, with magnitudes that were comparable to ADNC. We also found that history of osteoarthritis and hypertension were associated with a reduced likelihood of LATE-NC. Furthermore, we compared the neuropsychological characteristics and risk factors of LATE-NC with ADNC. Our results highlight the importance of LATE-NC in an age epoch that is the fastest-growing segment of our population with the highest rates of dementia and suggest that there are potentially important associations between certain past medical histories and LATE-NC that warrant further investigation.

Disclosure
The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Appendix Authors

Name	Location	Contribution
Seyed Ahmad Sajjadi, MD, PhD	University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Syed Bukhari, MS	Stanford University	Major role in the acquisition of data
Kiana Scambray, BA	University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content
Rui Yan, MS	University of California, Irvine	Analysis or interpretation of data
Claudia Kawas, MD	University of California, Irvine	Major role in the acquisition of data and analysis or interpretation of data
Thomas J. Montine, MD, PhD	Stanford University	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Maria M. Corrada, ScD	University of California, Irvine	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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