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ORIGINAL PAPER

Neuropathological associations of limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) differ between the oldest-old and younger-old

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Abstract

Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is most often seen in the oldest-old (≥ 90 years of age) but can also be present in the younger-old (< 90 years of age). In this study, we compared the neuropathological associations of LATE-NC and contribution of LATE-NC to cognitive impairment between the oldest-old and younger-old. We observed significant differences in the prevalence of LATE-NC and its association with other co-pathologies in these two age groups. LATE-NC was present in 30.9% (34/110) of the oldest-old but only 9.4% (19/203) of the younger-old. Participants of the oldest-old with LATE-NC were more likely to have hippocampal sclerosis (HS) (55.9% vs. 10.5%, $p < 0.001$) and moderate to severe arteriolosclerosis (82.4% vs. 50%, $p = 0.007$), but not intermediate to high Alzheimer's disease neuropathologic change (ADNC) (70.6% vs. 59.2%, $p = 0.486$) or Lewy body disease (LBD) (20.6% vs. 26.3%, $p = 0.793$). Participants of the younger-old with LATE-NC were more likely to have intermediate to high ADNC (94.7% vs. 55.4%, $p < 0.001$) and LBD (63.2% vs. 28.8%, $p = 0.013$) in addition to hippocampal sclerosis (42.1% vs. 6.5%, $p < 0.001$), and moderate to severe arteriolosclerosis (42.1% vs. 15.2%, $p = 0.020$). Of note, participants with LATE-NC and no to low ADNC were very rare in the younger-old (< 1%) but relatively common in the oldest-old (9.1%). Logistic regression modeling showed that in the oldest-old, both intermediate to high ADNC and LATE-NC were independently associated with higher odds of having dementia (OR: 5.09, 95% CI [1.99, 13.06], $p < 0.001$ for ADNC; OR: 3.28, 95% CI [1.25, 8.57], $p = 0.015$ for LATE-NC). In the younger-old, by contrast, intermediate to high ADNC and LBD were independently associated with higher odds of having dementia (OR: 4.43, 95% CI [2.27, 8.63], $p < 0.001$ for ADNC; OR: 2.55, 95% CI [1.21, 5.35], $p < 0.014$ for LBD), whereas LATE-NC did not show an independent association with dementia. Overall, LATE-NC is strongly associated with arteriolosclerosis and HS in both groups; however, in the younger-old, LATE-NC is associated with other neurodegenerative pathologies, such as ADNC and LBD; whereas in the oldest-old, LATE-NC can exist independent of significant ADNC.

Keywords Oldest-old · LATE-NC · TDP-43 · ADNC · LBD · Arteriolosclerosis · Quadruple misfolded proteins

Introduction

Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is characterized by TDP-43 inclusions present predominantly in the limbic structures, with or without co-existing hippocampal sclerosis [33]. Several large autopsy series have shown that LATE-NC is a common brain pathology present in 20–50% of older individuals [1, 6, 30, 33] and is strongly associated with amnestic dementia, independent of other known brain pathologies [8, 11, 12, 16, 18, 19, 24, 30, 32]. Mixed pathologies, including LATE-NC, Alzheimer's disease (AD) pathology, Lewy body disease (LBD), hippocampal sclerosis

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(HS), primary age-related tauopathy (PART), aging-related tau astrogliopathy (ARTAG), and cerebrovascular disease, are common in the aging brain [5, 16, 35, 37–39, 41]. The tendency for these pathologies to co-exist in the same individuals may be due to a direct causal relationship where one pathology leads to another, shared genetic risk factors, or common upstream aging-related pathogenic pathways.

Previously, we have analyzed a cohort of participants ≥ 90 years of age from the Bryan Brain Bank of the Duke/University of North Carolina AD Research Center (Duke/UNC ADRC) and observed a strong association of LATE-NC with HS and arteriolosclerosis, but not other cerebrovascular or neurodegenerative pathologies [12]. While LATE-NC occurs most often in the oldest-old (≥ 90 years of age), it can also be seen in brains of the younger-old (< 90 years of age). As differences in age at death may reflect underlying genetic and environmental risk factors affecting brain pathology, we asked whether the pattern of LATE-NC may be different between age groups. The purpose of the present study was to analyze LATE-NC phenotypes across a wide age range, and directly compare the association of LATE-NC with other co-pathologies and contribution of LATE-NC to cognitive impairment between the oldest-old and younger-old.

Participants aged 60 and above from the Duke/UNC ADRC with LATE-NC data were included in this study (including the 98 participants ≥ 90 years of age described previously [12]). We performed a comprehensive exploratory data analysis and through regression analysis determined that age 90 represents an inflection point where neuropathologic associations of LATE-NC show a significant difference. A detailed description can be found in the statistical method section. While LATE-NC was associated with HS and arteriolosclerosis, but not other neurodegenerative pathologies in the oldest-old, it was associated with ADNC and LBD in addition to HS and arteriolosclerosis in the younger-old. Further, logistic regression modeling showed that while LATE-NC and ADNC independently increased the odds of having dementia in the oldest-old, LATE-NC did not show an independent association with dementia in the younger-old. Overall, we observed a significant difference in the relationship of LATE-NC with other brain pathologies and cognitive phenotype between the oldest-old and younger-old. Further studies are warranted to elucidate whether these differences in neuropathological associations correlate with different underlying mechanisms of LATE-NC, and whether the predominant pathogenic mechanisms leading to LATE-NC may be different between the oldest-old and younger-old.

Materials and methods

Subjects

Participants were enrolled in the autopsy and brain donation program of the Joseph and Kathleen Price Bryan Alzheimer's Disease Research Center (ADRC), as previously described [14]. A total of 313 deceased participants aged 60 and above had neuropathological assessment of LATE-NC and were included in this study. Cognitive status was available for 306 participants in this cohort and was determined by annual consensus meetings based upon contemporaneous NIA-AA criteria. Apolipoprotein (APOE) genotype information was available for 294 participants in this cohort. Mini-mental status examination (MMSE) score was available for 149 participants in this cohort. All subjects gave informed consent prior to autopsy. The study was approved by the Duke Institutional Review Board.

Neuropathological assessment

After death, the brains were processed and banked according to published protocols [13]. Immunohistochemistry was performed using the following primary antibodies: β-amyloid (4G8 clone; BioLegend Cat#: 800702; 1:1000), tau (AT8 clone; Thermofisher Cat#: MN1020; 1:500), α-synuclein (BD Biosciences Cat#: 610787; 1:100), and TDP-43 (ProteinTech Cat#: 12892-1-AP; 1:200). LATE-NC was assessed by TDP-43 immunostaining of the amygdala, hippocampus with entorhinal cortex and adjacent temporal lobe, and mid frontal lobe following the LATE consensus working group report [33]. Participants with LATE-NC stage 1 had TDP-43 lesions confined to the amygdala, those with stage 2 had TDP-43 lesions in the entorhinal cortex and/or hippocampus, and those with stage 3 had TDP-43 lesions in the neocortex. Of note, neocortical TDP-43 lesions were sparse and focal in LATE-NC stage 3 (Fig. 1). Neuropathologic assessment of ADNC, LBD, HS, PART, ARTAG, arteriolosclerosis, and cerebral amyloid angiopathy (CAA) were performed according to published guidelines [9, 10, 15, 23, 26–29, 34, 42, 44, 45].

Statistical methods

To determine the inflection point for age, we first performed an exploratory analysis by presenting the histogram of LATE-NC frequency over different ages (Fig. 2). We additionally utilized ages 75, 80, 85, 90, and 95 as cut-offs and performed logistic regression analysis with

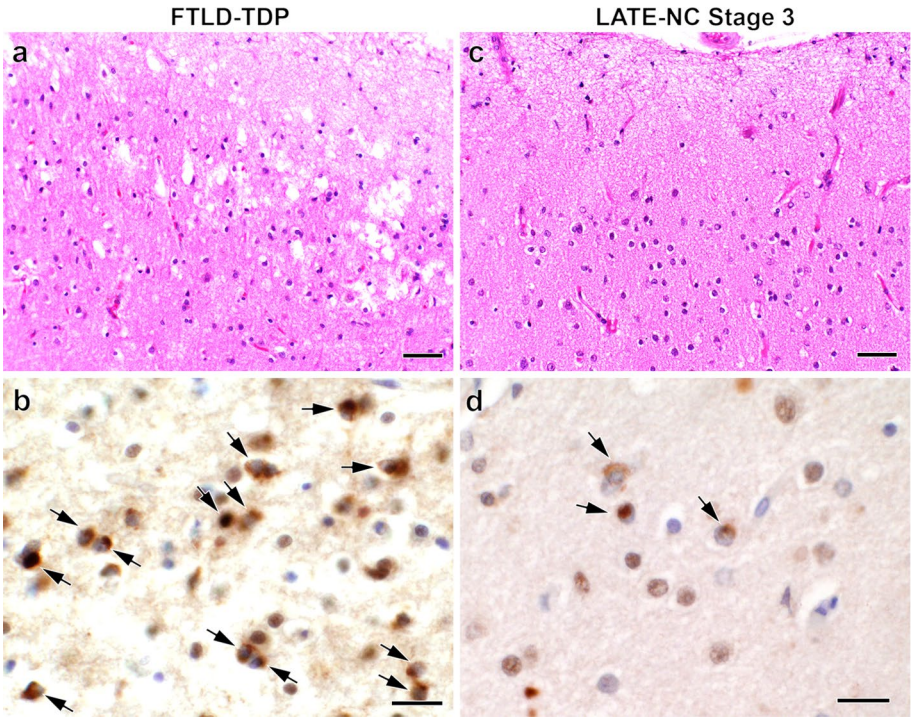

Fig. 1 Representative images of the mid frontal cortex from participants with FTLD-TDP (**a**, **b**) and LATE-NC stage 3 (**c**, **d**). Sections were stained for hematoxylin and eosin (**a**, **c**) and TDP-43 (**b**, **d**). Participants with LATE-NC stage 3 do not show cortical microvacuolation characteristic of FTLD-TDP (**a**, **c**), and the density of TDP-43 lesions is sparser than in FTLD-TDP (black arrows in **b**, **d**). Scale bar = 50 µm in (**a**, **c**), and scale bar = 20 µm in (**b**, **d**)

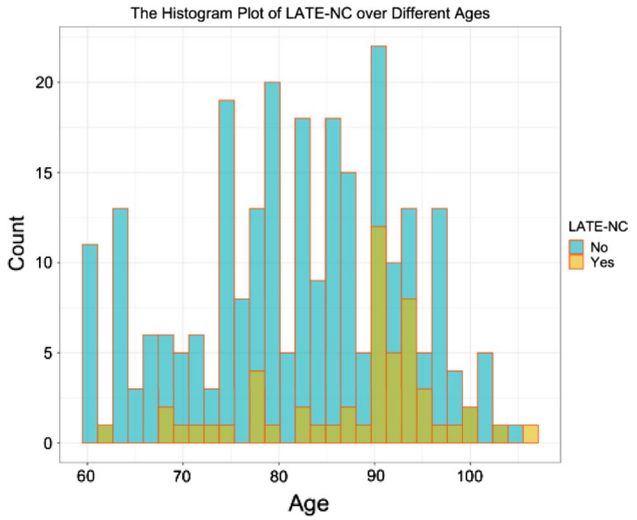

Fig. 2 Histogram plot showing number of participants with and without LATE-NC across different ages. There is a sharp increase in the number of participants with LATE-NC at age 90

interaction terms and compared the model performance by the Akaike information criterion (AIC).

Demographic and clinical characteristics were summarized using mean, standard deviation (SD), median, and range for continuous variables and frequency counts and percentages for non-missing categorical values. The association of LATE-NC with APOE genotype and various brain pathologies was evaluated using Fisher's exact test, while the Mann–Whitney test was adopted to compare two unpaired groups of data: for example, to test if ages are different over quadruple misfolded protein (QMP) vs non-QMP groups. Categories were combined to create binary variables (yes/no) for statistical tests due to the small sample size in each category. The Benjamini–Hochberg method was utilized to adjust *p*-values to account for multiple testing. Multivariable logistic regression models were used to evaluate responses of binary variables. Linear regression analysis was used to predict a continuous dependent variable from a number of independent variables. Alpha was set at 0.05 for two-sided tests.

Results

To determine the data inflection point, we first performed an exploratory analysis by presenting the histogram plot of LATE-NC over different ages and observed that LATE-NC distribution increased substantially near age 90 (Fig. 2). Furthermore, considering the interaction effects between age and ADNC, Lewy Body disease, and arteriolosclerosis, AIC values were calculated using age at 75, 80, 85, 90, and 95 as cutoff. The model with age at 90 as the cutoff had the smallest AIC value (AIC: 249.17 for age 75, AIC: 247.20 for age 80. AIC: 241.42 for age 85, AIC: 236.45 for age 90, and AIC: 249.11 for age 95). These results confirmed the rationality of using age 90 as the cutoff.

To evaluate the normality of our data, we plotted the age distribution of participants between 60 and 90 and those ≥ 90 and observed that both cohorts deviated from normal

distribution (Supplemental Fig. 1, online resource). This is not unexpected, as the age at death of most participants of our brain donation program range from their mid-80s to early 90s. We adopted the Shapiro–Wilk's test to check for normality. *p*-values for both age groups (60–90, > 90) were both smaller than 0.001, confirming that the data deviated from a normal distribution. We further calculated the skewness of the two age distributions; the results were − 0.479 and 1.078, which shows the data were moderately skewed. However, since we adopted Fisher's exact test for our analysis, which is a nonparametric test that does not depend on any parametric assumption, the results would still be valid regardless of the data distribution.

Demographic, clinical, and neuropathologic characteristics of the cohort are summarized in Supplemental Table 1, online resource. The mean age at death was 82.9 ± 10.8 years, 203 participants were < 90 (mean = 76.8 ± 8.2 years), and 110 participants were ≥ 90 (mean = 94.0 ± 3.8 years). The younger-old group had fewer female participants (49.8% vs. 67.3% of the oldest-old, $p = 0.006$). Cognitive status also differed between the two groups (in the younger-old, 35.3% were normal, 11.0% had MCI, and 53.7% had dementia; while in the oldest-old, 27.6% were normal, 24.8% had MCI, and 47.6% had dementia; $p = 0.016$). There was a higher proportion of *APOE4* carriers in the younger-old, but the difference was not statistically significant (36.8% vs. 28.8%, $p = 0.212$).

LATE-NC was much more prevalent in the oldest-old (30.9% vs. 9.4%, $p < 0.001$). Overall, the oldest-old showed more brain pathology, including intermediate to high ADNC (62.7% vs. 49.3%, $p = 0.045$), HS (24.5% vs. 9.9%, $p = 0.003$), ARTAG (34.5% vs. 10.8%, $p < 0.001$), moderate to severe arteriolosclerosis (60.0% vs. 17.7%, $p < 0.001$), and moderate to severe atherosclerosis (35.5% vs. 18.2%, $p = 0.002$). There was no significant difference in the prevalence of LBD, PART, microinfarcts, and CAA between the two age groups.

LATE-NC can co-exist with a variety of brain pathologies, ranging from relatively moderate (Fig. 3a–d) to severe co-pathologies (Fig. 3e–h). Previous studies have shown a strong association between LATE-NC and HS, ADNC, LBD, as well as arteriolosclerosis [1–4, 6, 22, 25, 36, 39]. Given the significant difference in prevalence of several brain pathologies between the oldest-old and younger-old, particularly that of LATE-NC, HS, and arteriolosclerosis, we investigated whether the neuropathological associations of LATE-NC in these two age groups also differed (Tables 1 and 2, Supplemental Fig. 2, online resource). Consistent with our previous observations [12], oldest-old participants with LATE-NC have a higher likelihood of having HS (55.9% vs. 10.5%, $p < 0.001$) and moderate to severe arteriolosclerosis (82.4% vs. 50%, $p = 0.007$), but not intermediate to high ADNC (70.6% vs. 59.2%, $p = 0.486$) or LBD (20.6% vs. 26.3%, $p = 0.793$). In contrast, younger-old participants with LATE-NC were more likely to have hippocampal sclerosis (42.1% vs. 6.5%, $p < 0.001$) and moderate to severe arteriolosclerosis (42.1% vs. 15.2%, $p = 0.020$), as well as intermediate to high ADNC (94.7% vs. 55.4%, $p < 0.001$) and LBD (63.2% vs. 28.8%, $p = 0.013$). Of note, whereas younger-old participants with LATE-NC almost invariably had intermediate to high ADNC, oldest-old participants with LATE-NC but no to low ADNC were quite common (29.4% of those with LATE-NC, representing 9.1% of the entire oldest-old cohort). LATE-NC was not associated with CAA, atherosclerosis, microinfarcts, *APOE4* status, and ARTAG in either the oldest-old or younger-old; LATE-NC was negatively associated with PART in the younger-old, but not the oldest-old (Tables 3 and 4, Supplemental Fig. 3, online resource).

We next performed logistic regression analysis to study the association between LATE-NC and ADNC, LBD, and arteriolosclerosis in the oldest-old and younger-old (Table 5). In the oldest-old, only moderate to severe arteriolosclerosis was associated with increased odds of having LATE-NC (OR: 4.54, 95% CI [1.74, 13.49], $p = 0.003$), whereas in the younger-old, both moderate to severe arteriolosclerosis and intermediate to high ADNC were associated with increased odds of having LATE-NC (OR: 4.52, 95% CI [1.49, 13.7], $p = 0.008$ for arteriolosclerosis; OR: 20.09, 95% CI [2.50, 161.60], $p = 0.005$ for ADNC). Given the difference in proportion of females and *APOE4* carriers in these two age groups, we performed additional logistic regression analysis to address the same potential predictors, while adjusting for sex and *APOE4* genotype as covariates. Again, only moderate to severe arteriolosclerosis was associated with LATE-NC in the oldest-old (OR: 4.71, 95% CI [1.67, 15.73], $p = 0.006$), whereas both moderate to severe arteriolosclerosis and intermediate to high ADNC were associated with LATE-NC in the younger-old (OR: 4.98, 95% CI [1.51, 16.42], $p = 0.008$ for arteriolosclerosis; OR: 17.16, 95% CI [2.06, 142.98], $p = 0.009$ for ADNC).

Next, we compared our cohort to a cohort collated by the National Alzheimer's Coordinating Center (NACC). The analytic sample from NACC was restricted to participants who: (i) have neuropathology data; (ii) were > 60 years old at the time of the last assessment; (iii) had no indication of frontotemporal lobar degeneration and other tauopathies; and (iv) were not missing data on the presence of TDP-43 inclusions in the spinal cord, amygdala, hippocampus, entorhinal/inferior temporal cortex, and neocortex. LATE-NC was defined as present if TDP-43 lesions were found in any of the following regions: amygdala, hippocampus, entorhinal/inferior temporal cortex, or neocortex. Basic characteristics of the participants ($N = 1440$) included in this analysis are summarized in Supplemental Table 2, online resource. Of note, compared to our cohort, the NACC cohort

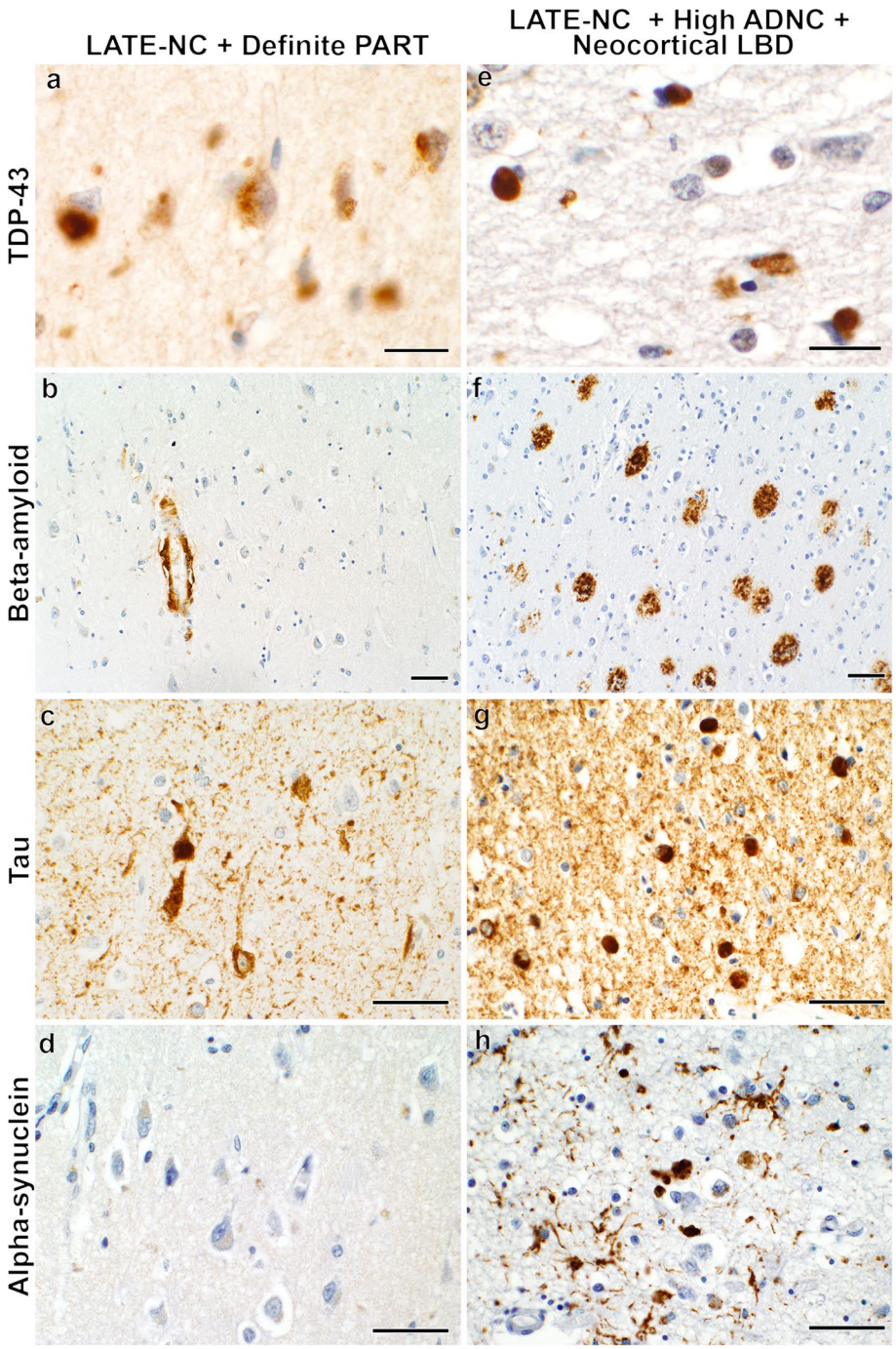

Fig. 3 LATE-NC can co-exist with a variety of brain pathologies. Representative images of the entorhinal cortex from a participant with definite PART (Braak stage III, Thal phase 0), LATE-NC stage 2, and moderate CAA (**a**–**d**). Immunostaining for TDP-43 highlights cytoplasmic inclusions (**a**), beta-amyloid highlights CAA but no plaques (**b**), tau highlights a few neurofibrillary tangles (**c**), and alpha-synuclein shows no Lewy bodies or neurites (**d**). Representative images of the entorhinal cortex from a participant with high ADNC (Thal phase 5, Braak stage V, CERAD score frequent), neocortical LBD, and LATE-NC stage 2 (**e**–**h**). Immunostaining for TDP-43 highlights cytoplasmic inclusions (**e**), beta-amyloid highlights many plaques (**f**), tau highlights many neurofibrillary tangles and dense neuropil threads (**g**), and alpha-synuclein highlights many Lewy bodies (**h**). Scale bar = 20 µm in (**a**) and (**e**), and scale bar = 50 µm in (**b**–**d**) and (**f**–**h**)

showed a higher percentage of *APOE4* carriers and higher percentage of participants with intermediate to high ADNC.

We performed logistic regression analysis to study the association between LATE-NC and ADNC, LBD, and arteriolosclerosis in the oldest-old and younger-old from the NACC cohort (Supplemental Table 3, online resource). Similar to our cohort, in the oldest-old, only moderate to severe arteriolosclerosis was associated with increased odds of having LATE-NC (OR: 1.83, 95% CI [1.01, 3.33], $p = 0.047$); whereas in the younger-old, both moderate to severe arteriolosclerosis and intermediate to high ADNC were associated with increased odds of having LATE-NC (OR: 1.54, 95% CI [1.21, 1.97], $p = 0 < 0.001$ for arteriolosclerosis; OR: 2.95, 95% CI [2.06, 4.22], $p < 0.001$ for ADNC). We also performed additional logistic regression analysis to address the same potential predictors, while adjusting for sex and *APOE4* genotype as covariates. Again, only moderate to severe arteriolosclerosis was associated with LATE-NC in the oldest-old (OR: 1.80, 95% CI [1.01, 3.30], $p = 0.049$), whereas moderate to severe arteriolosclerosis, intermediate

Table 1 ADNC, LBD, arteriolosclerosis, and HS by LATE-NC status in participants < 90

	LATE-NC		
	No ($N=184$)	Yes ($N=19$)	Adjusted p-value
ADNC			< 0.001*
None–Low	82 (44.6%)	1 (5.3%)	
Intermediate–High	102 (55.4%)	18 (94.7%)	
LBD			0.013*
No	131 (71.2%)	7 (36.8%)	
Yes	53 (28.8%)	12 (63.2%)	
Arteriolosclerosis			0.020*
No–mild	156 (84.8%)	11 (57.9%)	
Moderate–severe	28 (15.2%)	8 (42.1%)	
Hippocampal sclerosis			< 0.001*
No	172 (93.5%)	11 (57.9%)	
Yes	12 (6.5%)	8 (42.1%)	

*Statistical significance ($p < 0.05$)

Table 2 ADNC, LBD, arteriolosclerosis, and HS by LATE-NC status in participants ≥ 90

	LATE-NC		
	No ($N=76$)	Yes ($N=34$)	Adjusted p-value
ADNC			0.486
None–Low	31 (40.8%)	10 (29.4%)	
Intermediate–High	45 (59.2%)	24 (70.6%)	
Lewy body			0.793
No	56 (73.7%)	27 (79.4%)	
Yes	20 (26.3%)	7 (20.6%)	
Arteriolosclerosis			0.007*
No–mild	38 (50%)	6 (17.6%)	
Moderate–severe	38 (50%)	28 (82.4%)	
Hippocampal sclerosis			< 0.001*
No	68 (89.5%)	15 (44.1%)	
Yes	8 (10.5%)	19 (55.9%)	

*Statistical significance ($p < 0.05$)

to high ADNC, and *APOE4* carrier status were associated with LATE-NC in the younger-old (OR: 1.51, 95% CI [1.18, 1.93], $p < 0.001$ for arteriolosclerosis; OR: 2.42, 95% CI [1.66, 3.53], $p < 0.001$ for ADNC; OR: 1.54, 95% CI [1.19, 2.00], $p = 0.001$ for *APOE4*).

In recent years, there has been an increasing interest in the quadruple misfolded protein (QMP) phenotype (i.e., brains with co-existing ADNC, LBD, and LATE-NC). We stratified our cohort by the combination of misfolded proteins (Supplemental Table 4, online resource) and identified 18 participants with QMP. Participants with no neurodegenerative pathology, multiple systems atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) were excluded from this analysis. Overall, participants showed increased percentage of dementia and lower final MMSE scores with increased number of misfolded protein species. Participants with tau and/or amyloid and LATE-NC were the oldest age group (90.5 ± 7.2 years), suggesting that LATE-NC primarily affects the oldest-old. However, the presence of Lewy bodies in participants with QMP substantially lowers the age at death (82.7 ± 10.9 years) to levels similar to those without LATE-NC.

Next, we focused our comparison on participants with LATE-NC and co-existing ADNC and LBD (QMP) and those with LATE-NC and ADNC or PART but no LBD (Tau and/or amyloid + TDP-43) (Table 6). Participants with QMP showed younger age at death (82.7 vs. 90.5 years, $p = 0.014$), lower LATE-NC stage (stage 1: 27.8% vs. 17.1%, stage 2: 55.6% vs. 54.3%, stage 3: 16.7% vs. 28.6%, $p = 0.014$), were less likely to have moderate to severe arteriolosclerosis (50% vs. 77.1%, $p = 0.014$) and more likely to have higher Thal phase (94.4% vs. 71.4%, $p = 0.014$). Participants with QMP were also more likely to be *APOE4* carriers, more likely to have intermediate to high ADNC, higher Braak stage, higher CERAD score, and less likely to have HS; however, these differences were not statistically significant.

To study the effect of mixed pathologies on cognitive status in the oldest-old vs. younger-old, we performed logistic regression using dementia as independent variable and LATE-NC, ADNC, LBD, and arteriolosclerosis as dependent variables (Table 7). In the oldest-old, both LATE-NC and intermediate to high ADNC independently increased the odds of having dementia (OR: 3.28, 95% CI [1.25, 8.57], $p = 0.015$ for LATE-NC; OR: 5.09, 95% CI [1.99, 13.06], $p < 0.001$ for ADNC), whereas the effect of LBD and arteriolosclerosis was not statistically significant. In the younger-old, however, intermediate to high ADNC and LBD increased the odds of having dementia (OR: 4.43, 95% CI [2.27, 8.63], $p < 0.001$ for ADNC; OR: 2.55, 95% CI [1.21, 5.35], $p = 0.014$ for LBD); the effect of LATE-NC and arteriolosclerosis did not reach statistical significance.

We performed additional analysis on the 149 participants with replete MMSE data (Table 8), and showed that participants with LATE-NC, intermediate to high ADNC, and LBD had lower final MMSE scores (19.4 ± 6.47 vs. 23.9 ± 7.32, $p = 0.003$ for LATE-NC; 20.0 ± 8.22 vs. 26.5 ± 4.70, $p < 0.001$ for ADNC; 20.8 ± 8.96 vs. 24.3 ± 6.53, $p = 0.011$ for LBD). Next, we performed logistic regression using final MMSE score as independent variable and LATE-NC, ADNC, and LBD as dependent variables (Table 9). In the oldest-old, ADNC was associated with lower MMSE scores (OR: − 3.74, 95% CI [− 6.53, − 0.95], $p = 0.011$); the effect of LATE-NC was marginal (OR: − 3.18, 95% CI [− 6.31, − 0.05], $p = 0.052$). In the younger-old, both ADNC and

Table 3 CAA, atherosclerosis, microinfarcts, *APOE4*, PART, and ARTAG by LATE-NC status in participants < 90

	LATE-NC		
	No ($N=184$)	Yes ($N=19$)	Adjusted p-value
Cerebral amyloid angiopathy			0.239
Moderate–Severe	27 (14,7%)	5 (26.3%)	
None–Mild	157 (85.3%)	14 (73.7%)	
Atherosclerosis			0.391
Moderate–Severe	32 (17.4%)	5 (26.3%)	
None–Mild	152 (82.6%)	14 (73.7%)	
Microinfarcts			0.164
No	154 (83.7%)	13 (68.4%)	
Yes	30 (16.3%)	6 (31.6%)	
***APOE4* allele**	($N=190$)		0.164
No	113 (64.9%)	7 (43.8%)	
Yes	61 (35.1%)	9 (56.3%)	
PART			0.031*
No	125 (67.9%)	18 (94.7%)	
Yes	59 (32.1%)	1 (5.3%)	
ARTAG			0.440
No	165 (89.7%)	16 (84.2%)	
Yes	19 (10.3%)	3 (15.8%)	

*Statistical significance ($p < 0.05$)

Table 4 CAA, atherosclerosis, microinfarcts, *APOE4*, PART, and ARTAG by LATE-NC status in participants ≥ 90

	LATE-NC		
	No ($N=76$)	Yes ($N=34$)	Adjusted p-value
Cerebral amyloid angiopathy			
Moderate–Severe	17 (22.4%)	10 (29.4%)	0.680
None–Mild	59 (77.6%)	24 (70.6%)	
Atherosclerosis			
Moderate–Severe	27 (35.5%)	12 (35.3%)	1
None–Mild	49 (64.5%)	22 (64.7%)	
Microinfarcts			
No	51 (67.1%)	29 (85.3%)	0.160
Yes	25 (32.9%)	5 (14.7%)	
***APOE4* allele**	($N=104$)		0.106
No	57 (78.1%)	17 (54.8%)	
Yes	16 (21.9%)	14 (45.2%)	
PART			0.486
No	49 (64.5%)	26 (76.5%)	
Yes	27 (35.5%)	8 (23.5%)	
ARTAG			1
No	50 (65.8%)	22 (64.7%)	
Yes	26 (34.2%)	12 (35.3%)	

LBD were associated with lower MMSE scores (OR: − 6.58, 95% CI [− 9.53, − 3.63], $p < 0.001$ for ADNC; OR: − 3.80, 95% CI [− 7.15, − 0.44], $p = 0.029$ for LBD); the effect of LATE-NC was not statistically significant.

Discussion

While LATE-NC is most often seen in individuals over 85, it can also be present in younger individuals. Whether LATE-NC shows different patterns of neuropathological

Table 5 Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression

	OR (95% CI)	*p*-value
Association between LATE-NC and ADNC, Lewy body and arteriolosclerosis for subjects < 90		
ADNC (Intermediate–High vs None–Low)	20.09 [2.50, 161.60]	0.005*
Lewy body (Yes vs. No)	1.97 [0.69, 5.96]	0.212
Arteriolosclerosis (Moderate–Severe vs. No–Mild)	4.52 [1.49,13.70]	0.008*
Association between LATE-NC and ADNC, Lewy body and arteriolosclerosis for subjects ≥ 90		
ADNC (Intermediate–High vs None–Low)	1.27 [0.51, 3.28]	0.609
Lewy body (Yes vs. No)	0.66 [0.23, 1.78]	0.426
Arteriolosclerosis (Moderate–Severe vs. No–Mild)	4.54 [1.74, 13.49]	0.003*
Association between LATE-NC and ADNC, Lewy body and arteriolosclerosis for subjects < 90, account for APOE4 and Sex		
ADNC (Intermediate-High vs None-Low)	17.16 [2.06, 142.98]	0.009*
Lewy body (Yes vs. No)	2.04 [0.63, 6.58]	0.232
Arteriolosclerosis (Moderate–Severe vs. No–Mild)	4.98 [1.51, 16.42]	0.008*
APOE4 (Yes vs. No)	0.96 [0.41, 2.27]	0.924
Sex (Female vs. Male)	0.57 [0.18, 1.81]	0.342
Association between LATE-NC and ADNC, Lewy body and arteriolosclerosis for subjects ≥ 90, account for APOE4 and Sex		
ADNC (Intermediate–High vs None–Low)	0.67 [0.21, 2.00]	0.472
Lewy body (Yes vs. No)	0.63 [0.19, 1.87]	0.420
Arteriolosclerosis (Moderate–Severe vs. No–Mild)	4.71 [1.67, 15.73]	0.006*
APOE4 (Yes vs. No)	2.34 [0.97, 5.96]	0.062
Sex (Female vs. Male)	1.29 [0.48, 3.63]	0.621

*Statistical significance ($p < 0.05$)

associations in different age groups remains understudied. In this study, we observed significant differences in the prevalence and neuropathological associations of LATE-NC in the oldest-old (≥ 90 years of age) vs. younger-old (< 90 years of age). LATE-NC was present in 30.9% of the oldest-old and only 9.4% of the younger-old. Further, LATE-NC was associated with arteriolosclerosis and HS, but not ADNC or LBD in the oldest-old, whereas in the younger-old, LATE-NC was associated with ADNC and LBD in addition to arteriolosclerosis and HS (Fig. 4). Our findings show that younger-old participants with LATE-NC almost invariably (94.7%) have intermediate to high ADNC and a large proportion (63.2%) of them also have LBD. In contrast, a substantial proportion of oldest-old participants with LATE-NC (29.4%) have no or low ADNC. Participants with LATE-NC but no or low ADNC represent 9.1% (10/110) of the oldest-old cohort, comparable to a recent report [31]. Our findings are also in line with a recent study that showed stronger association between LATE-NC and neocortical LBD in participants less than 90 years of age compared to those 90 and above [2]. We also performed similar analysis on a cohort of participants above 60 years of age collated by NACC. Overall, the NACC cohort showed a higher percentage of APOE4 carriers and higher percentage of participants with intermediate to high ADNC. Nevertheless, there was a similar difference in neuropathologic associations of LATE-NC between the oldest-old and younger-old.

In this study, we observed a negative association between LATE-NC and PART in the younger-old, similar to a previous report [6]. PART was defined as Thal phase 0–2 and Braak stage I–IV according to published guidelines [10], and therefore, a substantial proportion of participants with PART were also categorized as having no to low ADNC. The negative association we observe between LATE-NC and PART may in fact reflect the strong association between LATE-NC and intermediate to high ADNC in the younger-old.

Mixed pathologies are common in the aging brain. The tendency for ADNC, LBD, and LATE-NC to co-exist may be due to shared genetic risk factors or common upstream age-related changes. Alternatively, the presence of one type of pathology may predispose the cells to another type of pathology. For example, previous studies have demonstrated that TDP-43 and tau inclusions can co-exist in the same hippocampal dentate granule neurons [43]. We identified 18 participants with quadruple misfolded protein (QMP) phenotype in our cohort. Our analysis showed that participants with increased number of misfolded protein species showed increased percentage of dementia and lower final MMSE scores, consistent with a previous report [20]. Although LATE-NC appears to affect mostly the oldest-old, the presence of Lewy bodies in participants with QMP significantly lowers the age at death, suggestive of a synergistic effect between these protein misfolding pathologies. Notably, a substantial proportion of individuals with LATE-NC

Table 6 Comparison of participants with Tau and/or amyloid + TDP-43 and QMP

	All	Tau and/or amyloid + TDP-43	QMP	Adjusted *p*-value
	(*N* = 53)	(*N* = 35)	(*N* = 18)	
Demographics				
Age (years)				0.014*
Mean (SD)	87.8 (9.3)	90.5 (7.2)	82.7 (10.9)	
Median	90.0	92.0	82.5	
Range	62–106	69 – 106	62–103	
Sex				0.192
Female	33 (62.3%)	20 (57.1%)	13 (72.2%)	
Male	20 (37.7%)	15 (42.9%)	5 (27.8%)	
APOE4	(*N* = 294)			0.555
No	24 (51.1%)	18 (56.3%)	6 (40.0%)	
Yes	23 (48.9%)	14 (43.8%)	9 (60.0%)	
Neuropathologic				
LATE-NC Stage				0.014*
1	11 (20.8%)	6 (17.1%)	5 (27.8%)	
2	29 (54.7%)	19 (54.3%)	10 (55.6%)	
3	13 (24.5%)	10 (28.6%)	3 (16.7%)	
Arteriolosclerosis				0.014*
No–Mild	17 (32.1%)	8 (22.9%)	9 (50.0%)	
Moderate–Severe	36 (67.9%)	27 (77.1%)	9 (50.0%)	
Atherosclerosis				0.555
No–Mild	36 (67.9%)	21 (60.0%)	15 (83.3%)	
Moderate–Severe	17 (32.1%)	14 (40.0%)	3 (16.7%)	
ADNC				0.116
None–Low	11 (20.8%)	10 (28.6%)	1 (5.6%)	
Intermediate–High	42 (79.2%)	25 (71.4%)	17 (94.4%)	
Thal phase				0.014*
0–2	11 (20.8%)	10 (28.6%)	1 (5.6%)	
3–5	42 (79.2%)	25 (71.4%)	17 (94.4%)	
Braak stage				0.116
0–2	1 (1.9%)	1 (2.9%)	0 (0.0%)	
3–4	30 (56.6%)	22 (62.9%)	8 (44.4%)	
5–6	22 (41.5%)	12 (34.3%)	10 (56.6%)	
CERAD score				0.090
0–1	22 (41.5%)	16 (45.7%)	6 (33.3%)	
2–3	31 (58.5%)	19 (54.3%)	12 (66.7%)	
HS				0.487
No	26 (49.1%)	15 (42.9%)	11 (61.1%)	
Yes	27 (50.9%)	20 (57.1%)	7 (38.9%)	

(particularly in the oldest-old) lack significant ADNC or LBD, suggesting that there may be pathogenic mechanisms specific to LATE-NC independent of other protein misfolding pathologies.

Arteriolosclerosis, but not other cerebrovascular pathologies such as atherosclerosis, CAA, or microinfarcts, was strongly associated with LATE-NC in both the oldest-old and younger-old cohorts. Arteriolosclerosis is very common in advanced age, but the full spectrum of clinical risk factors associated with arteriolosclerosis remains understudied. Previous studies have shown that traditional cardiovascular risk factors, such as hypertension, diabetes, and hypercholesterolemia, were less predictive of arteriolosclerosis than they were of cardiac pathology [7]. Notably, recent analysis of data from the NACC did not show an association between LATE-NC and hypertension, diabetes, or hypercholesterolemia [6]. Future research is warranted to better understand the clinical risk factors that contribute to arteriolosclerosis

Table 7 Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression

	OR (95% CI)	*p*-value
Association between Dementia and LATE-NC, ADNC, Lewy body and arteriolosclerosis for subjects < 90		
LATE-NC (Yes vs No)	6.35 [0.78, 51.95]	0.084
ADNC (Intermediate–High vs None–Low)	4.43 [2.27, 8.63]	< 0.001*
Lewy body (Yes vs. No)	2.55 [1.21, 5.35]	0.014*
Arteriolosclerosis (Moderate-Severe vs. No-Mild)	2.04 [0.83, 5.05]	0.118
Association between Dementia and LATE-NC, ADNC, Lewy body and arteriolosclerosis for subjects ≥ 90		
LATE-NC (Yes vs No)	3.28 [1.25, 8.57]	0.015*
ADNC (Intermediate–High vs None–Low)	5.09 [1.99, 13.06]	< 0.001*
Lewy body (Yes vs. No)	0.56 [0.21, 1.51]	0.250
Arteriolosclerosis (Moderate–Severe vs. No–Mild)	1.56 [0.63, 3.89]	0.336

Table 8 MMSE scores, by age, LATE-NC, ADNC, and Lewy body ($N = 149$)

Age	All ($N = 149$)	< 90 ($N = 95$)	≥ 90 ($N = 54$)	Adjusted *p*-value
Mean (SD)	23.4 (7.35)	23.0 (8.26)	24.1 (5.41)	0.533
Median	27.0	27.0	26.0	
Range	1–30	1–30	8–30	
LATE-NC	ALL ($N = 149$)	No ($N = 131$)	Yes ($N = 18$)	Adjusted *p*-value
Mean (SD)	23.4 (7.35)	23.9 (7.32)	19.4 (6.47)	0.003*
Median	27	27	19.5	
Range	1–30	1–30	8–29	
ADNC	ALL ($N = 149$)	None–low ($N = 78$)	Intermediate–high ($N = 71$)	Adjusted *p*-value
Mean (SD)	23.4 (7.35)	26.5 (4.70)	20.0 (8.22)	< 0.001*
Median	27	28	22	
Range	1–30	7–30	1–30	
Lewy body	ALL ($N = 149$)	No ($N = 111$)	Yes ($N = 38$)	Adjusted *p*-value
Mean (SD)	23.4 (7.35)	24.3 (6.53)	20.8 (8.96)	0.011*
Median	27	27	24	
Range	1–30	7–30	1–30	

*Statistical significance ($p < 0.05$)

and the mechanistic link between arteriolosclerosis and LATE-NC.

Besides LATE-NC, TDP-43 lesions can also be seen in other brain pathologies, such as frontotemporal lobar degeneration (FTLD-TDP). The differentiation between FTLD-TDP and LATE-NC, particularly stage 3 LATE-NC, remains a topic of interest. A recent report showed that LATE-NC can be differentiated from FTLD-TDP based on the density of neocortical TDP-43 neuronal cytoplasmic inclusions [40]. Similarly, participants with stage 3 LATE-NC in our cohort lacked the dense neocortical TDP-43 lesions and microvacuolation characteristic of FTLD-TDP (Fig. 1).

Our logistic regression modeling showed that both LATE-NC and ADNC were associated with increased odds of having dementia in the oldest-old. In the younger-old however, only ADNC and LBD increased the odds of having dementia; LATE-NC did not show an independent association with dementia in this age group. Since LATE-NC almost invariably coexisted with intermediate to high ADNC in our younger-old cohort, the true contribution of LATE-NC to

Table 9 Coefficient estimation and 95% confidence intervals (CI) from linear regression

	Coefficient estimation (95% CI)	*p*-value
Association between MMSE and age, ADNC, LATE-NC, and Lewy body disease for ALL subjects		
Age indicator (≥ 90)	2.14 [– 0.15, 4.42]	0.069
LATE-NC (Yes)	– 4.39 [– 7.80, – 0.98]	0.013*
ADNC (Intermediate-high)	– 5.68 [– 7.85, – 3.51]	< 0.001*
Lewy body (Yes)	– 2.03 [– 4.49, 0.43]	0.108
Association between MMSE and ADNC, LATE-NC, and Lewy body disease for subjects < 90		
LATE-NC (Yes)	– 12.80 [– 12.80, 1.58]	0.129
ADNC (Intermediate-high)	– 6.58 [– 9.53, – 3.63]	< 0.001*
Lewy body (Yes)	– 3.80 [– 7.15, – 0.44]	0.029*
Association between MMSE and ADNC, LATE-NC, and Lewy body disease for subjects ≥ 90		
LATE-NC (Yes)	– 3.18 [– 6.31, – 0.05]	0.052
ADNC (Intermediate-high)	– 3.74 [– 6.53, – 0.95]	0.011*
Lewy body (Yes)	1.38 [– 1.79, 4.55]	0.398

cognitive impairment may be difficult to model statistically. We also may have failed to detect an association between LBD and dementia in the oldest-old due to a low percentage of neocortical LBD (4/27) in our oldest-old cohort.

This study had important limitations. Due to the relatively small sample size, many categories were combined to create binary variables for statistical analysis, precluding discovery of more granular associations. For example, recent studies have observed association of LATE-NC only with specific subtypes of LBD in larger cohorts [2, 6]. Further, the lack of association we observe in many instances may be due to insufficient sample size or low event rate of predictor variables. Lastly, the younger-old and oldest-old cohorts had different demographic and genetic characteristics. The younger-old cohort had fewer females and more *APOE4* carriers (not statistically significant), which is not unexpected. We accounted for these differences by adjusting for sex and *APOE4* status when appropriate in our analysis and observed similar results (Table 5).

Overall, despite these limitations, we observed a significant difference in the relationship of LATE-NC with other brain pathologies between the oldest-old and younger-old (summarized in Fig. 4). The relative contribution of LATE-NC to cognitive impairment also appears to differ between the two groups. Previous studies have demonstrated that participants with LATE-NC can be clustered into subgroups with distinct clinical, neuropathologic, and genetic features [17, 21], suggestive of distinct LATE-NC subtypes. Further studies are warranted to elucidate whether the different associations we observe correlate with different underlying pathogenic mechanisms and whether the predominant mechanisms leading to LATE-NC differ between the oldest-old and younger-old.

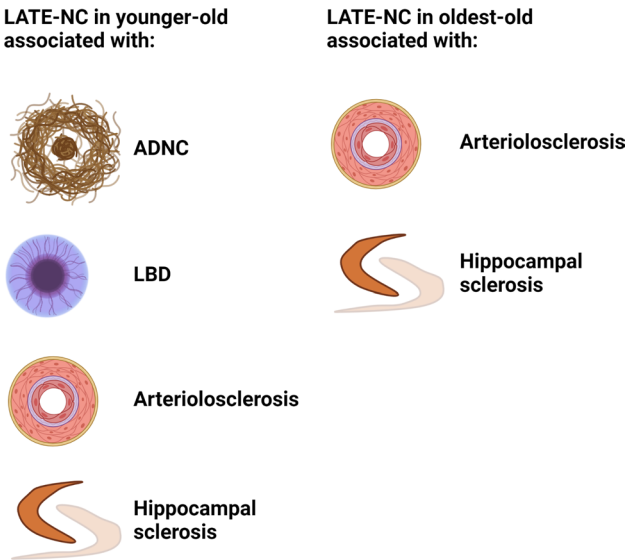

Fig. 4 LATE-NC is associated with intermediate to high ADNC, LBD, moderate to severe arteriolosclerosis, and hippocampal sclerosis in the younger-old. LATE-NC is associated with moderate to severe arteriolosclerosis and hippocampal sclerosis, but not intermediate to high ADNC or LBD in the oldest-old. Graphics were created with BioRender.com

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