Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC), Alzheimer's disease neuropathologic changes (ADNC), and FTLD-TDP: associated clinical symptoms

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Background

TDP-43 is a key protein in age-related dementia. Analogous to Aβ and tau in AD. TDP-43 pathology develops in a hypothetical, hierarchical, and stereotypical pattern. TDP-43 deposition seems to first appear in the amygdala, then progresses to limbic areas, and finally develops in frontal neocortex and other brain structures. A working group has recently suggested a classification system for limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC). In the present study, we examined the clinical features associated with autopsy-confirmed LATE-NC including cognitive functions, motor disturbances, language problems, and neuropsychiatric symptoms (NPS) in older people.

Methods

Data were derived from the National Alzheimer's Coordinating Center Neuropathology (NACC NP) Form v10. After applying inclusion and exclusion criteria, we split the subjects into two groups: non FTLD-TDP and FTLD-TDP groups (Figure 1).

Based on this staging system, we assigned a TDP-43 stage (0 to 3) to each individual and defined LATE as Stage 1 to 3 (inclusive) in the non FTLD-TDP group.

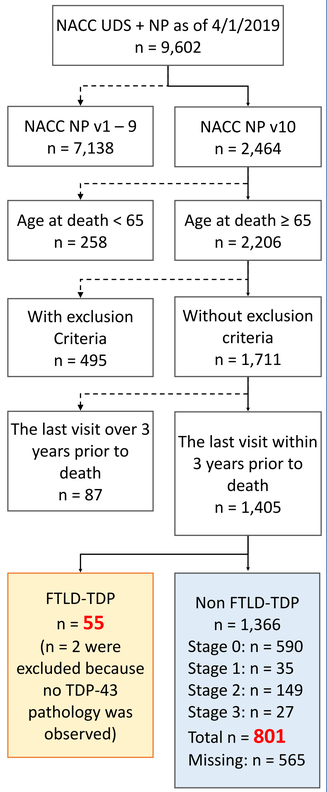

Figure 1. Study Flow Diagram

Table 1. Characteristics of non-FTLD-TDP and FTLD-TDP cases

Variable	Non FTLD-TDP subjects			FTLD-TDP	P-value
	Overall (n = 801)	Stage 0 (n = 590)	LATE-NC (n = 211)	(n = 55)	
Age at death, mean ± SD	82.7 ± 8.7	82.2 ± 8.8	84.0 ± 8.5	76.6 ± 8.9	2.0×10^{-7}
Gender, n (%)					
Men	440 (54.9)	326 (55.3)	114 (54.0)	32 (58.2)	0.85
Women	361 (45.1)	264 (44.7)	97 (46.0)	23 (41.8)	
Years of education, mean ± SD	15.7 ± 3.1	15.6 ± 3.1	16.0 ± 3.0	16.2 ± 2.7	0.24
Cognitive status, n (%)					
Normal cognition	97 (12.1)	92 (15.6)	5 (2.4)	0 (0)	2.1×10^{-11}
MCI/Impaired-not-MCI	92 (11.5)	81 (13.7)	11 (5.2)	2 (3.6)	
Dementia	612 (76.4)	417 (70.7)	195 (92.4)	53 (96.4)	
Braak NFT stage (B score), n (%)					
B0—B4	307 (38.4)	260 (44.1)	47 (22.4)	45 (81.8)	5.8×10^{-16}
B5—B6	493 (61.6)	330 (55.9)	163 (77.6)	10 (18.2)	
APOE genotype, n (%)					
ε4 negative	354 (49.6)	276 (52.6)	78 (41.3)	31 (67.4)	0.0018
ε4 positive	360 (50.4)	249 (47.4)	111 (58.7)	15 (32.6)	

Results

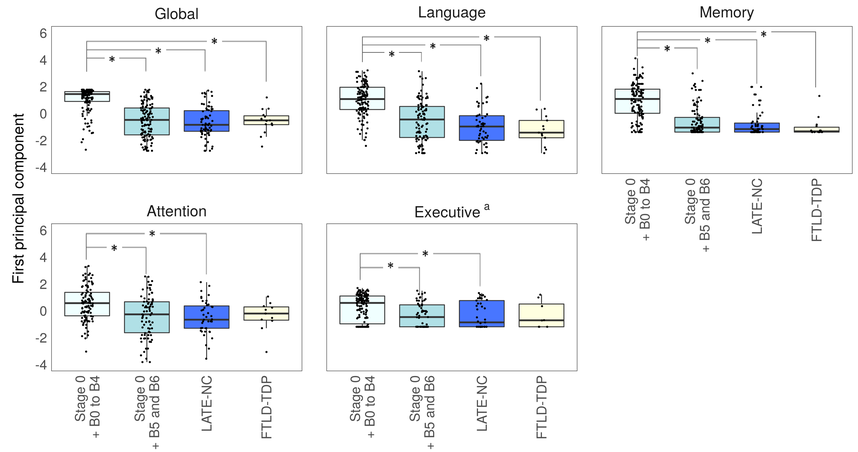

Figure 2. Boxplot of first principal components for cognitive domains by TDP-43 pathology groups. Stage 0 groups are separated by Braak NFT stages.

[a] Executive domain comprises Trail Making B only; thus the y-axis represents the scaled score.

* indicates statistical significance after applying Bonferroni multiple comparison adjustment.

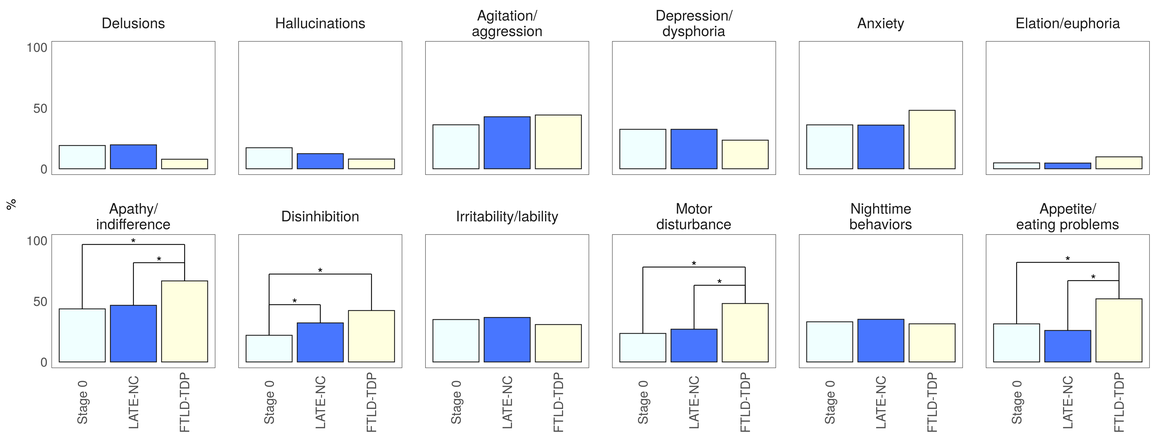

Figure 3. Prevalence of neuropsychiatric and other symptoms by TDP-43 pathology-defined case groups.

* indicates statistical significance after applying Bonferroni multiple comparison adjustment

Table 2. Adjusted and inverse probability (IP) weighted odds ratios of neuropsychiatric and other symptoms between Braak NFT stages in the subjects with TDP-43 pathology Stage 0 and between LATE and Stage 0 in the subjects with Braak NFT stage B0—B4

Symptoms	Braak NFT stage B5 – B6 vs. B0 – B4 in people with Stage 0		LATE-NC vs. Stage 0 in people with Braak NFT stage B0 – B4	
	Adjusted OR [a] (95% CI)	IP weighted OR [a,b] (95% CI)	Adjusted OR [a] (95% CI)	IP weighted OR [a,b] (95% CI)
Delusions	**2.70 (1.52 – 4.72)**	1.67 (0.73 – 3.81)	1.39 (0.46 – 3.51)	1.18 (0.43 – 3.23)
Hallucinations	1.55 (0.87 – 3.49)	1.03 (0.50 – 2.12)	1.01 (0.30 – 2.81)	0.97 (0.33 – 2.84)
Agitation or aggression	**2.44 (1.56 – 3.85)**	**2.45 (1.48 – 4.04)**	1.83 (0.84 – 3.30)	1.94 (0.88 – 4.28)
Depression or dysphoria	1.03 (0.66 – 1.71)	1.06 (0.66 – 1.70)	1.22 (0.58 – 2.36)	1.26 (0.58 – 2.74)
Anxiety	**1.58 (1.02 – 2.54)**	1.56 (0.96 – 2.52)	1.16 (0.53 – 2.30)	1.13 (0.50 – 2.54)
Elation or euphoria	1.05 (0.40 – 4.40)	1.20 (0.46 – 3.09)	1.19 (0.17 – 8.07)	0.99 (0.19 – 5.05)
Apathy or indifference	**2.01 (1.32 – 3.40)**	**1.95 (1.22 – 3.12)**	1.88 (0.90 – 2.97)	2.04 (0.96 – 4.35)
Disinhibition	**1.93 (1.17 – 3.50)**	**1.86 (1.02 – 3.36)**	2.33 (0.99 – 5.69)	**2.36 (1.02 – 5.45)**
Irritability or lability	**2.48 (1.59 – 3.11)**	**2.23 (1.35 – 3.70)**	1.29 (0.58 – 2.48)	1.31 (0.58 – 2.98)
Motor disturbance	**2.75 (1.59 – 6.31)**	**2.39 (1.24 – 4.60)**	2.34 (0.84 – 4.45)	**2.72 (1.05 – 7.06)**
Nighttime behaviors	**1.59 (1.03 – 2.35)**	1.36 (0.84 – 2.20)	1.16 (0.52 – 2.36)	1.54 (0.68 – 3.50)
Appetite and eating problems	1.28 (0.82 – 2.28)	1.33 (0.83 – 2.13)	0.74 (0.30 – 1.51)	0.96 (0.38 – 2.45)

[a] The covariates included in the model are age at death, gender, years of education, and APOE genotype.

[b] IP weighted ORs were computed by weighted logistic regression model with stabilized inverse probability to take into account selection bias and missing data.

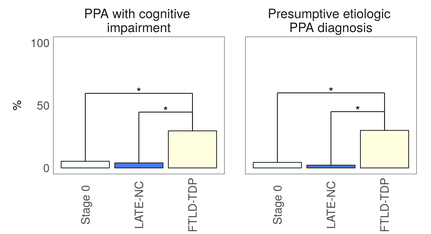

Figure 4. Prevalence of primary progressive aphasia (PPA) in TDP-43 pathology-related diseases

* indicates statistical significance after applying Bonferroni multiple comparison adjustment.

Discussion

Global cognitive impairment, memory disorders, and language deficits were all seen in association with ADNC, LATE-NC, and FTLD-TDP. Some other stereotypical clinical features, including primary progressive aphasia, were associated with FTLD-TDP pathology. However, our results highlight the importance of including multiple different controls to establish a disease-specific clinical phenomenon. Agitation/aggression, apathy/indifference, disinhibition, irritability/lability, and motor disturbance were all increased (versus low-pathology controls) in subjects with severe ADNC but lacking TDP-43 proteinopathy. In summary, this relatively large cohort of well-worked up research subjects did not reveal a specific clinical feature that was shared between LATE-NC and FTLD-TDP.

Acknowledgements

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