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Relationships between Lewy and tau pathologies in 375 consecutive non-Alzheimer olfactory bulbs

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Letter to editors

The olfactory bulb is highly susceptible to Lewy-related pathology (i.e. Lewy bodies and Lewy neurites).¹ We herein report the frequency of Lewy-related pathology in a range of non-Alzheimer disorders and the factors that might contribute to risk for Lewy-related pathology using multiple logistic regression methods.

Excluding Alzheimer disease and overt Lewy body disease, olfactory bulbs from 375 consecutive elderly brains were studied with α -synuclein immunohistochemistry. We scored

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Author Contributions

KK: Acquisition, analysis and interpretation of data; drafting of manuscript; execution of the statistical analysis; writing of the first draft

OAR: Review and critique; interpretation of data

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1) the density and distribution of olfactory Lewy-related pathology 2) Lewy-related pathology in additional brain regions vulnerable for Lewy-related pathology and 3) phospho-tau immunoreactivity. Genotyping for APOE and MAPT was performed in progressive supranuclear palsy (PSP) and corticobasal degeneration cases.

Olfactory Lewy-related pathology was detected in 43 cases (11%) (Table 1). The distribution and the morphology of Lewy-related pathology were similar to previous reports (Supplemental Figure). Twenty-one out of 43 cases (49%) were discovered to have Lewy-related pathology in the olfactory bulb, and in six cases (14%) it was restricted to the olfactory bulb (Supplemental Table), further supporting the value of olfactory bulb for screening for Lewy-related pathology.² Subjects with Lewy-related pathology were older and had greater Braak neurofibrillary tangle (NFT) stage for both the overall cohort and for the PSP subgroup. Logistic regression modeling revealed Braak NFT stage (odds ratio: 4.4, $p = 0.003$) as an independent variable for Lewy-related pathology in PSP, and both Braak NFT stage (odds ratio: 1.8, $p = 0.01$) and age (odds ratio: 1.1, $p = 0.04$) were significant for the overall cohort. Within the olfactory bulb, no correlation was found between tau burden and Lewy-related pathology ($r = 0.08$, $p = 0.60$). Neither APOE nor MAPT genotypes were associated olfactory bulb Lewy-related pathology.

Regarding Lewy-related pathology among other neurodegenerative disorders, we confirm that Lewy-related pathology appears to be associated with aging, which is in line with previous report in multicenter elderly cohort;^{3, 4} however, the underlying mechanism of Lewy-related pathology in aging remains to be determined. In contrast, it has been reported that subjects with Lewy bodies in the setting of advanced AD had both younger age at death and age of dementia onset, compared with those without Lewy-related pathology.⁵ In a hospital-based cohort, Jellinger reported an association between concurrent Lewy-related pathology and Alzheimer pathology regardless of age at death in the 7th to 10th decade.⁶ These findings suggest that disease-specific factors accelerate Lewy-related pathology in the olfactory bulb in AD. The current study is the largest series of pathologically confirmed PSP to undergo screening for olfactory bulb Lewy-related pathology. It is noteworthy that Alzheimer-type tau pathology quadruples the risk for Lewy-related pathology in PSP even though cases with advanced Alzheimer pathology were specifically excluded.

In this study, we confirm that olfactory bulb screening identifies Lewy-related pathology in a range of non-AD neurological conditions in which this pathology was not previously suspected; moreover, in some cases this is the only brain region affected. The pathogenesis of olfactory bulb Lewy-related pathology might be different from that found in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Demographic, pathologic and olfactory screening characteristics across various neurological conditions

Demographic and pathologic characteristics of various disorders.

	N	Age		Female		Braak NFT		Thal amyloid		Brain Weight	
		LRP (%)	LRP	No LRP	LRP	No LRP	LRP	No LRP	LRP	No LRP	No LRP
Overall	375	43 (11%)	80 (71, 85) *	75 (70, 83)	51%	47%	II (I, III) **	1 (0, 3)	1 (0, 2)	1160 (1020, 1260)	1140 (1040, 1260)
PSP	161	18 (11%)	79 (73, 82) *	74 (70, 78)	44%	43%	II (II, III) **	0 (0, 3)	0 (0, 2)	1210 (1020, 1300)	1160 (1080, 1260)
CBD	35	6 (17%)	75 (71, 81)	72 (67, 76)	33%	59%	II (0, III)	0 (0, 2)	0 (0, 2)	1165 (1080, 1220)	1080 (960, 1220)
FTLD	29	2 (7%)	81 (73, 88)	77 (72, 84)	0%	41%	0 (0, 0)	1 (1, 1)	0 (0, 1)	1150 (940, 1360)	1000 (890, 1090)
ALS	18	2 (11%)	71 (70, 71)	70 (68, 78)	100%	63%	II (II, III)	2 (2, 2)	0 (0, 2)	1160 (1120, 1200)	1140 (1010, 1280)
AGD	7	2 (29%)	94 (89, 98)	87 (74, 91)	100%	80%	III (III, IV)	1 (1, 1)	0 (0, 1)	1040 (1010, 1070)	1055 (983, 1090)
HpScl	8	0 (0%)	NA	91 (90, 95)	NA	68%	NA	II (I, II)	NA	NA	1220 (1190, 1235)
PA	21	3 (14%)	90 (86, 92) *	81 (77, 84)	33%	33%	III (III, III)	3 (2, 3)	3 (3, 3)	1120	1110 (1048, 1210)
PART	19	4 (21%)	88 (79, 94)	86 (81, 92)	75%	40%	III (II, III)	2 (0, 4)	0 (0, 2)	930 (880, 1150)	1175 (1020, 1330)
MSA	8	0 (0%)	NA	66 (65, 71)	NA	25%	NA	II (II, III)	NA	NA	1120 (980, 1400)
CVD	34	3 (10%)	81 (73, 83)	82 (76, 87)	33%	45%	II (0, III)	1 (1, 1)	0 (0, 1)	1120 (95, 1150)	1240 (967, 1260)
Normal	35	3 (9%)	69 (58, 83)	75 (67, 84)	100%	59%	II (0, III)	1 (0, 1)	0 (0, 1)	1135 (1090, 1180)	1080 (1020, 1275)

* indicates $p < 0.05$ and

** indicates $p < 0.01$.

Abbreviations: N = number of cases; LRP = Lewy-related pathology; No LRP = no Lewy-related pathology; Age = age at death; Female = frequency of women; Braak NFT = neurofibrillary tangle stage; Thal amyloid = amyloid phase. ALS = amyotrophic lateral sclerosis; AGD = argyrophilic grain disease; HpScl = hippocampal sclerosis; CBD = corticobasal degeneration; FTLD = frontotemporal lobar degeneration; MSA = multiple system atrophy; PA = pathological aging; PART = primary age-related tauopathy; PSP = progressive supranuclear palsy; CVD = cerebrovascular dementia; Normal = neurologically normal; NA = not available.