Lewy Body Negative Idiopathic Parkinsonism

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ABSTRACT

Objective: Pathologic Lewy body inclusions in the substantia nigra (SN) are considered the classic anatomic substrate for idiopathic Parkinsonism (iPD). The present study was designed to investigate the pathologic substrate in LB negative iPD.

Methods: Thirty-eight cases with a clinical diagnosis of iPD proximal to death were identified in the University of Kentucky Alzheimer disease brainbank (n=523), with (LBP+, n=19) and without Lewy body pathology (LBP-, n=19). Cases were analyzed for differences in semiquantitative pathological variables including LB, atherosclerosis, micro/lacunar/macro-infarcts, ApoE, cerebral amyloid angiopathy, CERAD and BRAAK staging, and quantitative differences in neuronal density and pigmentary incontinence.

Results: Half the cases with clinically diagnosed iPD/DLB did not have evidence for LBP+. There were no differences between LBP-and LBP+ cases across demographic variables (age, gender, education and ApoE). Vascular pathology did not differ between groups.. Further analysis of SN neuronal loss using stereologic quantitative techniques failed to reveal differences between LBP+ and LBP- cases (p= 0.39; t-test).

Conclusion: Pathologically-unexplained, clinically-diagnosed Parkinsonism is prevalent in this community-based sample. While idiopathic substantia nigral neuronal loss may explain Parkinsonian symptoms in this group, the etiologic cause and pathological substrate for such clinical and pathological features in LBP-, iPD remains unknown and warrants further investigation.

BACKGROUND & HYPOTHESIS

- **The neuropathologic substrate of idiopathic PD is presumed to be a-synulcein pathology in the majority of cases although alternative substrates (i.e. vascular disease and FTD) are well recognized**
- **We sought to define alternative pathologic substrates for idiopathic PD in a community-based sample of elderly subjects enrolled in an autopsy cohort**

METHODS

THE UK ADC BRAIN BANK: The UKADC brain bank has been collecting neurpathological specimens and data on subjects spanning the cognitive continuum that have participated in the longitudinal cohort of the ADC since its inception in 1985 as one of the original 10 NIA-funded ADCs. Detailed clinical and pathological data are collected on each subject allowing for significant contribution to our understanding of clinico-pathological correlations that have advanced the field over the last several decades.

SUBJECTS: Inclusion criteria includes 1) all forms of dementia or 2) subjects a minimum age 65 years; cognitive and neurological normality by enrollment examination; designated informant for structured interviews; willingness to undergo annual cognitive testing, and physical and neurological examinations. Excluded are individuals with a history of substance abuse (including alcohol); major head injury; major psychiatric illness; medical illnesses that are nonstable, impairing, or that have an effect on the CNS; chronic infectious diseases; stroke or TIA; encephalitis; meningitis; or epilepsy. All subjects enrolled agree to brain donation at death to support the UK ADC brain bank.

NEUROPATHOLOGICAL ANALYSES: Our rapid autopsy protocol provides ideal specimens for analysis with minimum PMI. Extensive dissections result in detailed bilateral quantitative and semi quantitative analyses of 34 standard regions. Sections are stained with H&E, Bielschowsky, Gallyas, and immunostains for β-amyloid, phospho-tau, α-synuclein, and TDP-43. Additional stains may be emploiyed in cases where our standard procedures fail to identify the pathological substrate for dementia.

STEREOLOGICAL ANALYSIS: Tissue sections were evaluated using an Olympus BX51 microscope, digital DP70 camera, automated Proscan II microscope stage, and the CAST stereology software system (Olympus, Danmark A/S). Each section was visualized at 4x magnification and regions of interest were generated by digitally mapping areas of inclusion and exclusion in the tissue field. Automated uniform random (meander) sampling was performed at 200x magnification.

STATISTICAL ANALYSES: Simple descriptive statistics were used for analyses of demographic, clinical, genetic, and pathological variables in the UK ADC brain bank where appropriate.

RESULTS

Table 1. Clinical, demographic and genetic variables in clinically diagnosed idiopathic Parkinson's disease (iPD) cases in the UK Brain Bank

Variables	LB + (n=19)	LB – (n=19)	p value
Age (mean years)	83.9	85.6	0.41
Gender M F	7 12	10 9	0.5
MMSE (mean)	9.6	12.8	0.24
UPDRS total (mean)	19.6	14.0	0.07
ApoE (n, positive cases)	8	5	0.37

Table 2. Pathologic variables in clinically diagnosed iPD cases in the UK Brain Bank

Variables (mean scores)	LB + (n=19)	LB – (n=19)	p value
Total infarct	1.3	0.5	0.20
Atherosclerosis*	1.7	1.6	0.64
NIA-Reagan Criteria**	2.3	2.4	0.52
CERAD***	2.5	2.4	0.71
Braak Stage	4.2	4.6	0.72
CAA****	0.8	0.9	0.80

Abbreviations: MMSE, Folstein Mini-mental State Examination score; UPDRS, Unified Parkinson's Disease Rating Scale; ApoE, apolipoprotein E ε4; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CAA, cerbral amyloid angiopathy
*Atherosclerosis scale: 0=no lumen blockage; 1=0-25% lumen blockage; 2=26-50% lumen blockage; 3=51-75% lumen blockage; 4=76-100% lumen blockage
**NIA-Reagan scores converted to numerical stage as follows: No=0; 1= low likelihood; 2=intermediate likelihood; 3=high likelihood
***CERAD scores converted to numerical stage as follows: No=0; 1=possible; 2=probable; 3=definite
*CAA scale: 0=no CAA; 1=mild leptomeningeal CAA; 2=moderate parenchymal CAA; 3=severe parenchymal CAA; 4=evidence for CAA-related hemorrhage

Table 3. Comparison of UPDRS Items between pathologically proven α-synuclein positive and negative cases (Students t-test)

Variables	LB+	LB-	P value
Neuron density	0.507	0.723	0.39
PI density	0.118	0.146	0.59
Total neurons	3864907	12783141	0.04
Total PI	865546	2571540	0.051

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CONCLUSIONS

Figure 1. Neuronal density (p=0.40, t-test)

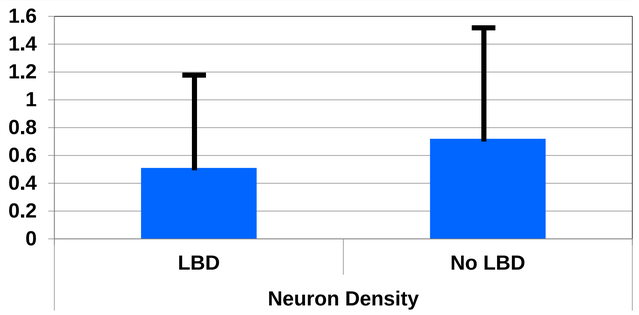


Figure 2. Density of pigmentary incontinence (PI) (p=0.60, t-test)

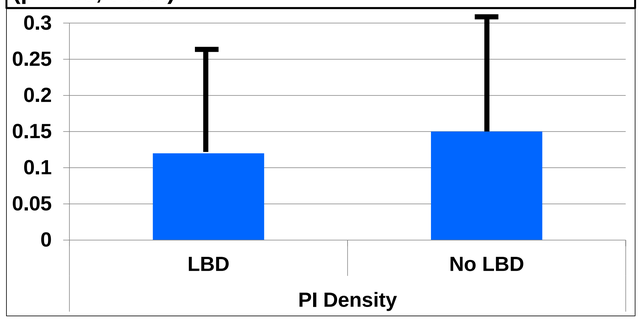
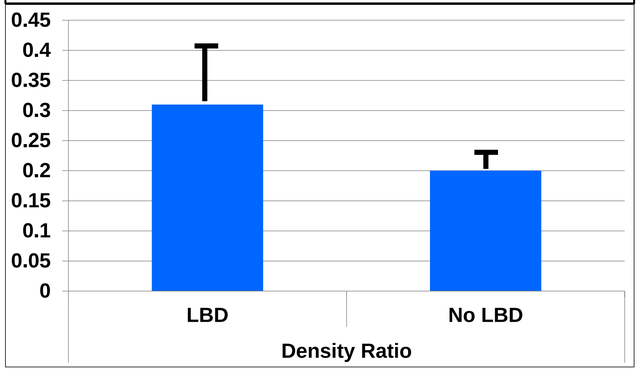


Figure 3. Density ratio of PI/Neurons (p<0.002, t-test)



CONCLUSIONS

- **Neither neuronal density, nor density of pigmentary incontinence distinguish LBD+ from LBD- parkinsonism in this autopsy series**
- **The significant PI/Neuron density ratio suggests a relative preservation of SN integrity in 50% of subjects with clinical parkinsonism**
- **The pathologic substrate for LBD-parkinsonism remains elusive**
- **Further exploration is warranted**