Inclusion Of Axial Rigidity May Improve Diagnostic Accuracy For Dementia With Lewy Bodies

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ABSTRACT

Objective: The diagnostic accuracy of dementia with Lewy bodies (DLB) is poor. The present study examined demographic and clinical features that may improve diagnostic accuracy for the prediction of underlying Lewy body pathology (LBP).

Methods: Eighty cases with pathological and/or clinical diagnosis of DLB were identified in the University of Kentucky Alzheimer's Disease Center Brain Bank (n=523), including 13 cases positive for DLB clinically and pathologically, 14 cases with DLB were showed no Lewy body pathology (LBP), and 52 cases negative for clinical DLB but positive for LBP. Demographic, clinical, and genetic were analyzed between groups to identify variables that might lead to improved diagnostic accuracy in DLB.

Results: Only axial (p= 0.017; t-test) and lower extremity rigidity (p= 0.034; t-test) differed between true positive and false positives cases.

Conclusion: Including assessment of axial or lower limb rigidity as a component of diagnostic criteria for DLB would improve the positive predictive value from 48% currently to 82% without a significant trade off in negative predictive value (10.5% currently to 11% with inclusion of axial and lower limb rigidity specifically). The diagnostic criteria for DLB need to be revised to detect underlying pathology based on this and further findings from similar studies in large pathologic series.

BACKGROUND & HYPOTHESIS

- **Work from our center and others have demonstrated poor diagnostic accuracy for Dementia with Lewy Bodies (DLB)**
- **We sought to explore the clinical signs & symptoms of DLB and determine their predictive value for autopsy proven DLB**
- **We hypothesized that specific clinical variables might be able to enhance diagnostic accuracy for underlying α-synuclein pathology given the overlap in symptoms with other degnerative disease states**

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.

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. Relationship of clinical vs. pathological diagnosis of DLB in the UK Brain Bank

Cases (n=79/523)	Pathology Positive for DLB	Pathology negative for DLB
Clinical DLB	13 (True positives)	14 (false positives)
Clinical Non DLB	52 (false negative)	N/A

Table 2. Relationship of clinical vs. pathological diagnosis of DLB in the UK Brain Bank

Variable	True positives	False positives	False negatives	P-value
Age (mean years)	83.0	84.2	80.3	0.27 †
Gender M F	4 9	8 6	21 31	0.35 ‡
Atherosclerosis* (mean score	1.5	1.7	1.2	0.23 ¥
Total Infarct (mean)	1.7	0.6	1.2	0.51 ¥
NIA-Reagan** (mean)	2.2	2.8	2.6	0.13 ¥
CERAD*** (mean)	3.2	3.7	3.4	0.74 ¥
Braak (mean)	4.2	5.1	5.0	0.19 ¥
ApoE (allele frequency)	0.5	0.4	0.6	0.74 ‡
CDR global (mean)	2.3	2.1	2.0	0.87 ¥
MMSE (mean)	10.2	12.6	10.8	0.85 †
UPDRS total (mean)	16.6	12.8	4.1	<0.0001

†, ANOVA; ‡, Chi-square approximation; ¥, Kruskal-Wallis ANOVA
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; ApoE, apolipoprotein E ε4; CDR, Clinical Dementia Rating scale; MMSE, Folstein Mini-mental State Examination score; UPDRS, Unified Parkinson's Disease Rating Scale
*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

Table 3. Comparison of UPDRS Items between pathologically proven DLB and DLB-negative cases (mean; Students t-test)

UPDRS Item	True positives	False positives	P-value
Total Score	16.6	12.8	0.26
Speech	1.5	1.2	0.41
Masked facies	1.7	1.3	0.34
Neck rigidity	0.9	0.2	0.02
R upper rigidity	1.7	1.2	0.21
L upper rigidity	1.7	1.1	0.18
R lower rigidity	1.7	0.9	0.07
L lower rigidity	1.7	0.8	0.03
Posture	1.7	1.5	0.65
Bradykinesia	1.7	1.8	0.75
Gait	1.1	1.9	0.07
Rest tremor (total)	0.4	0.2	0.47
AMRs (total)	1.8	1.6	0.71

CONCLUSIONS

Figure 1. Comparison of Neck tremor in True and False positives

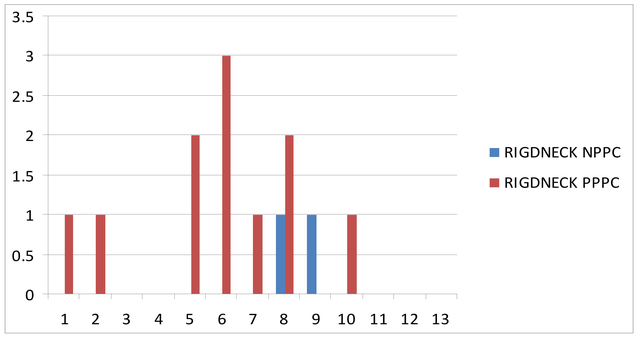
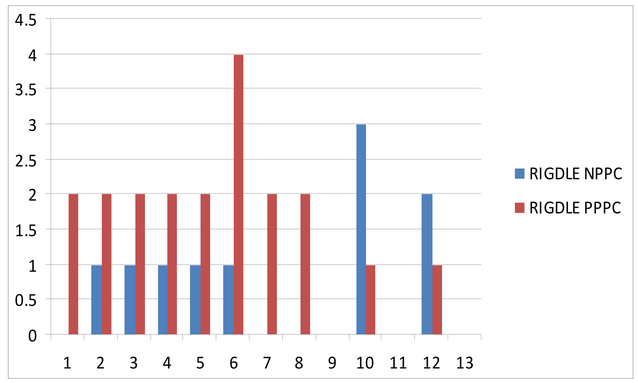


Figure 2. Comparison of Neck tremor in True and False positives



CONCLUSIONS

- **Including assessment of axial or lower limb rigidity as a component of diagnostic criteria for DLB would improve the positive predictive value from 48% currently to 82% without a significant trade off in negative predictive value (10.5% currently to 11% with inclusion of axial and lower limb rigidity specifically).**
- **The diagnostic criteria for DLB need to be revised to detect underlying pathology based on this and further findings from similar studies in large pathologic series.**

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