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Associations among Braak stage, Parkinsonian Gait, Cognition and Functional Status in Autopsy-confirmed Dementia with Lewy Bodies

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Abstract

Objective: Compromised functional abilities in older adults with dementia with Lewy bodies (DLB) represent a significant burden to families and frequently lead to institutionalization. Contributing factors to this compromise are poorly understood.

Methods: Using data collected at a first study visit, multiple regression modeling was used to examine the associations between Braak staged Alzheimer's disease (AD) pathology, Apolipoprotein E (ApoE) status, Parkinsonian gait, cognition and functional status from a cohort of 102 cases with an autopsy-confirmed diagnosis of dementia stemming from combined Lewy body and AD pathology.

Results: On average, 60% of functional activities were compromised per case. Worse functional status was associated with older age at first study visit, compromised cognitive status, and Parkinsonian gait after controlling for gender, mental status and other covariates. Worse cognitive status predicted worse functional status in both the low and high Braak groups.

Conclusions: Older persons with DLB presenting with moderately compromised cognition and Parkinsonian gait should be expected to have impaired functional abilities. Providing these patients with supportive environments may help them to remain independent for longer periods of time.

Keywords

Functional status; dementia with Lewy bodies; Alzheimer's disease

1 INTRODUCTION

Functional status is an important factor to consider over the course of aging, especially for those older adults with dementia, because currently there are no disease modifying therapies.

¹ As dementia progresses, impaired functional status diminishes the level of independence of older adults.²

Historically, disease burden such as functional impairment has been examined using single diagnostic dementia subtypes often based on clinical presentations. Most recently, neuropathological evidence obtained at autopsy is demonstrating multiple co-existing pathologies.³ However, research to understand the clinical presentation, level and progression of functional impairment in the context of any combination of these neuropathologies is limited. None the less, clinicians should consider the possibility of more than one pathology when examining a patient presenting with a single diagnosis.

Two of the most common single occurring dementia subtypes include Alzheimer's disease (AD), the most prevalent neurodegenerative dementia, and dementia with Lewy bodies (DLB) accounting for 4.2% to 7.5% of all dementias.⁴ Both are forms of dementia and different diseases. Lewy bodies are present in DLB, while amyloid-beta (A β) plaques and neurofibrillary tangles (NTF) constitute the primary neuropathology of AD. In AD, Braak staging is used to classify neurofibrillary tangle load.⁵ Research to date has demonstrated that identifying co-occurring DLB and AD is difficult for clinicians.⁴ The identification of specific risk factors, including biomarkers, are needed.

In addition to the neuropathological underpinnings associated with subtypes of dementia, attention to factors determining risk for these subtypes has increased. Particularly important among these are age and genetic variants. These have proven to be important risk factors for a number of dementia subtypes. The most important genetic risk factor for AD, the most common age-related dementia, is Apolipoprotein E (ApoE) status. Located on chromosome 19, three possible alleles (e2, e3, e4) are associated with a differing level of AD risk.⁶ For example, possession of one or two ApoE-e4 alleles confers a higher risk for developing AD than the presence of other ApoE allele pairs.⁷ Apart from its association with AD, Dickson and colleagues⁸ reported an association of the APOE-e4 allele with risk of diffuse Lewy body disease with low AD pathology.

Older adults with DLB are known to be more functionally impaired when compared to those with other neurodegenerative dementias.^{9,10} Dementia with Lewy bodies is related pathologically to Parkinson's disease (PD). Found in both DLB and PD, aggregated alpha synuclein (α -syn) protein make up the Lewy body and Lewy neurite pathology found on autopsy. In DLB, increasing amounts of α -syn in the brainstem, limbic, neocortical, midbrain and ventral forebrain regions of the brain cause increasing, but sometimes fluctuating, cognitive and physical symptoms that compromise normal functioning.¹¹

While older adults with DLB are known to be more functionally impaired^{9,10} only a few studies have provided evidence that worse cognitive impairment,⁹ specific age ranges² and extrapyramidal motor dysfunction¹⁰ may be contributing factors. For example, when compared to older adults with AD, those with DLB between the ages of 67 and 81 are 1.5 to 2 times more at risk of faster decline in function.² However, reasons for this more impaired functional status among older adults with DLB are largely unknown.

As with all forms of neurodegenerative dementia, DLB is considered a possible or probable diagnosis until autopsy. A primary issue has been the use of heterogeneous samples where misdiagnosis is high.¹² Increasing evidence is demonstrating that for some individuals, multiple neuropathologies are present upon autopsy. For example, AD pathology can co-occur with DLB pathology,^{13,14} however, the synergistic effects these multiple pathologies are unknown. Therefore, many study reports may be missing the contribution a secondary disease process may have upon functional status.

To address the changing focus of dementia research, we sought to investigate to what degree AD pathology was associated with and might account for the variance seen in functional status among older adults with a definitive diagnosis of DLB. Additional variables included cognition and Parkinsonian gait, as well as other risk factors (i. e., age, ApoE status) associated with both DLB and AD.

2 METHODS AND MATERIALS

A retrospective cross-sectional design was used to address the study purpose. Data were obtained from the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center (ADRC). All cases (N=104) were consented and enrolled in a longitudinal study designed to characterize AD and related dementias. Each had a pathological diagnosis of dementia with Lewy bodies at autopsy. Consent for autopsy was obtained from subjects prior to death or from next of kin at the time of death. Study oversight was provided by the UCSD Human Research Protections Program.

Case data were extracted from the Center's database (demographics, medical history, physical/neurological evaluations, neuropsychological testing, genetic testing, autopsy). Only baseline visit data and neuropathology data from autopsy were utilized for this study. One case missing Dementia Rating Scale (DRS) data and one with severe cognitive impairment were excluded leaving a final sample of 102.

2.1 Case characteristics

Demographic data were obtained from Center research charts (nursing and neurology) and the research data base. Chart extraction was completed by investigators and RN research assistants with good reliability demonstrated at 84% agreement and a Cohen's Kappa at 0.65. Demographic data included education, age at first visit and other variables such as duration of disease to death and age at death that were used to control for variance in years from onset to first visit. Additional characteristics included Parkinsonian gait (yes/no).

2.2 Neuropathology

All cases met 1996 diagnostic pathological consensus criteria for DLB.¹⁵ Braak staging was determined by examining the entorhinal cortex and counting the NFT in at least five neuronal clusters. Lower Braak stages indicated less AD pathology. Center pathology and histology processes are described in more detail elsewhere.¹⁴ Braak staging (0–3 versus 4–6) was used to determine burden of AD pathology¹⁶, then to classify and compare DLB- LB (minimal AD load; Braak 0–3) and DLB-AD (significant AD pathology; Braak 4–6) cases. The decision to divide cases based on specific Braak stage ranges (i.e., 0-3 versus 4-6) was

based on our experience that individuals age 70 and older who are cognitively normal have neuropathology consistent with Braak stages 1 or 2.¹⁴ The few subjects with stage 3 typically have no clinically detectable dementia or MCI. However, every case with Braak stage 4 or higher has a diagnosis of dementia, or at least MCI. As a result, we made a decision to separate cases into groups divided into Braak stage 0–3 and Braak stage 4–6.

2.3 Clinical biomarkers

Because the ApoE alleles occur in pairs, the pairs for all cases are classified into groupings: e2/e2, e2/e3, e3/e3, e2/e4, e3/e4, and e4/e4. For data analyses, we coded the ApoE pairs into a binomial variable based on whether the pair included at least one e4 allele. For analysis, we excluded the 2/4 pair because the e4 allele is associated with increased risk while the e2 allele with reduced risk.⁷

We also used Parkinsonian gait (yes/no obtained from research chart) as a clinical biomarker. Recently, this clinical biomarker has been found to be a predictor of both cognitive decline and dementia in persons with PD.^{17,18}

2.3 Cognitive status

The Mini Mental State Examination (MMSE) is routinely administered and reported in research and clinical settings and is a brief screen for global cognition (orientation, delayed recall, attention, language, construction). Scores range from 0–30 points, with lower scores indicating possible cognitive problems. Validity is questionable for persons in early stages of DLB and mild to moderate AD.^{19–21}

The Mattis Dementia Rating Scale (MDRS) is a lengthier and more comprehensive measure of cognition and is composed of five subscales [attention (37 points), initiation and perseveration (37 points), construction (6 points), conceptualization (39 points), and memory (25 points)] for a total of 144. Lower scores indicate greater cognitive impairment. The MDRS is reliable and valid for staging DLB and AD dementia.^{22–26}

2.4 Functional status

For the purpose of this study, functional status was determined by the score on a measure of instrumental activities of daily living. Examples include shopping, preparing balanced meals and managing personal finances. Over the history of the Center, two related functional status instruments [Pfeffer Outpatient Disability Scale (PODS) and Functional Activities Questionnaire (FAQ)] were administered to participants' study partners. Each had the same 10 items (e. g., shopping, cooking a balanced meal), with higher scores indicating greater dependence and scales that included a 'not applicable' scoring option. Both versions have demonstrated reliability and validity.^{25,26,27,28} In 2005 the FAQ replaced the PODS, and the scoring criteria were changed. As has been done in previous published studies in order to maintain our sample size, the FAQ scores were re-calculated to align with the PODS scoring schema and scoring details are described elsewhere.¹⁴

3 DATA ANALYSIS

Descriptive statistics were used to report case characteristics, Braak staging, cognition, and functional status. To compare case characteristics by Braak staging, two-sample t-tests and chi-square tests were used. Fischer's exact test was used for nominal variables when cell sample sizes were less than 5 and Eta for associations between nominal and interval level data.²⁹

To address the primary study purpose, Pearson correlation coefficients were used to examine linear associations between functional status and cognition as well as between case characteristics (continuous variables) and functional status and cognition. Next, prediction models using stepwise regression were run for three separate samples (total, low Braak stage, high Braak stage). The DRS total score was used as the measure of cognition for the regression analysis. To determine if certain levels of cognition mediated the relationship between other independent variables and functional status, independent variables were grand-mean centered for interpretation of any predictive association. A calculated recommended sample size of 61 was obtained for an anticipated effect size of 0.30, power level 0.8 and probability level of 0.05 for the regression modeling.

4 RESULTS

The case characteristics are displayed in Table 1. In summary, male gender accounted for 64.7% (n= 66) of the total sample of 102 DLB cases. Of the total, more cases were classified as high Braak stage (n= 55) compared to low (n= 47). Two cases were missing ApoE allele measures. Of the 100 cases concerning ApoE pair status, 44% were 3/3, 40% were 3/4, 7% were 4/4, 6% were 2/3, and 3% were 2/4. There were no subjects with an ApoE status of 2/2. Forty six percent (46.1%) of the cases (n=47) had at least one ApoE-e4 allele. Those cases with at least one ApoE-e4 allele had a higher Braak stage [X^2 (1, N=97) = 591, p 0.02].

There were no significant differences between high versus low Braak stage groups in age at first study visit, years of education, age at onset, gender, years of symptoms from onset to baseline (first) study visit, total MMSE and DRS scores, or functional status (Table 1). However, those with higher Braak stage showed a longer mean duration of illness from estimated onset of symptoms to first study visit than those in the lower Braak stage group. For those cases with Parkinsonian gait (n=29), most (n=19) had a low Braak stage (chi sq 5.892, p = .015) indicating less AD pathology. Pearson correlations are displayed for the entire sample across characteristic variables in Table 2.

4.1 Functional Status

Functional status scores for the entire sample at first visit demonstrated a moderate amount of functional impairment with PODS/FAQ mean of 0.62 (SD=0.29). Functional status was worse when age was older at first study visit (r 0.25, p<0.01), there were fewer years of education (r -0.18; p<0.05), and global cognition (DRS total score) was worse (r -.53; p<0.05) (Table 2). Those cases with APOE 2/3 and 2/4 had better functional status (Eta 0.427). While not significant, worse functional status at first visit was demonstrated for

those cases with high Braak stage ($M = 0.60$; $SD 0.301$) compared to low Braak ($M = 0.64$; $SD 0.288$) stage ($p = 0.43$) (Table 1).

For the entire sample for which complete data were available ($n = 97$), functional status was associated with three independent variables after controlling for age decline began, gender, education, mental status and ApoE-e4 (yes/no). Older age at first study visit, worse cognition, and having a Parkinsonian gait predicted worse functional status (Table 3). These three independent variables accounted for 49% of the variance in functional status ($F 7.808$; $p < 0.001$). There was no effect of an interaction of the cognition and functional status scores ($p = .852$).

Also displayed in Table 3 are results broken down by Braak stage. For those cases with low Braak stage, functional status was only associated with cognition, accounting for 46% of the variance ($F 2.978$; $p = 0.011$). For the high Braak stage cases, functional status was associated with cognition and Parkinsonian gait accounting for 64% of the variance ($F 7.751$; $p < 0.001$).

5 DISCUSSION

An increasing population of older adults with dementia, including those with more than one form of neuropathology, is rapidly becoming a problem of critical proportions for the scientific and healthcare communities. The cumulative and interactive effects of multiple forms of neuropathology increase the complexity of disease processes as well as the symptoms seen by clinicians.⁴ However, much of the research to date has assumed the samples to be homogenous, therefore not considering the possibility of co-occurring dementia pathologies. This study adds to the current growing body of knowledge by using a sample of cases with autopsy-confirmed DLB diagnoses and further identifying those cases with additional AD neuropathology.

Across the entire sample, this data-based study demonstrated that functional status, as measured by IADLs, was compromised. Study participants at their first visit were already dependent on others for an average of six out of 10 activities. Being approximately 4 years into the disease at the time of the first study visit was associated with worse functional status; however, this did not explain the moderate level of compromise among the sample. We also examined gender, years of education, age when decline began, age at death, presence of at least one ApoE-e4, and Braak stage (low versus high). However, none of these were useful in predicting functional status in the regression model. For our model using the entire sample, it was older age, compromised cognition, and Parkinsonian gait that predicted worse functional status.

5.1 Older Age

Age at first study visit was positively associated with functional status while controlling for a number of temporal covariates such as age when decline began and number of years from symptom onset. This suggests that older the age at first study visit, regardless of age at initial decline or years from symptom onset to first study visit, predicted worsening functioning. Therefore, age at first study visit was more important than the duration of illness in

explaining the functional status of these participants. Explanations from other research indicate that it is cumulative effects that make age the top risk factor for dementia.³⁰

There are substantiated theories on aging as well as numerous studies to support the notion that older age contributes to declining functional status.^{31–34} Aging is complex and the biological,^{35,36} social,^{31,37} and psychological³⁸ aspects of aging not only have individual effects upon function, but additive effects as well.³⁰ Therefore, it is not surprising that the variable of age was a predictor of functional status.

Implications for clinicians may be that older patients with DLB may have more memory related problems such as remembering appointments that might compromise their functioning. For older patients who appear to be conflating their functional status (and without a reliable partner to verify their status), clinicians may want to follow up with a more comprehensive functional status assessment that includes an observational in-home visit.

5.2 Compromised Cognition

Not surprising, worse cognition predicted worse functioning. These results are aligned with findings from other studies.^{9,14,39} In fact, cognition has been identified as a primary predictor as well as a moderator variable when examining different types of functioning.^{9,40} Compromised attention, frontal dysfunction (i.e., initiation, perseveration, conceptualization), poor construction abilities, and impaired memory, all cognitive abilities measured in this study, would explain worsening abilities to accomplish many IADLs. New important scientific work in brain network connectivity for persons with dementia,⁴¹ and specifically among persons with DLB,⁴² may hold structural and functional explanations for the association between worsening cognition and function. However, this work is limited at this point, having neither specifically focused upon IADLs or been conducted among populations with co-occurring dementia pathologies.

5.3 Parkinsonian Gait

Parkinsonian gait present at first study visit was also a predictor of worse functioning. The mechanics of the Parkinsonian gait could likely hamper the performance ability of a number of the IADLs that were measured by the PODS and FAQ (e.g., shopping alone, driving). Previous studies found mild Parkinsonian features including bradykinesia in similar samples; however, did not specifically identify Parkinsonian gait^{4,43} which can be easily assessed by clinicians.

5.4 Braak Staging

At the outset of the analysis, Braak stage was not associated with functional status while controlling for other covariates. Therefore, we reanalyzed the data using the two Braak stages (Low and High) separately to identify any significant associations with functional status. Cognition remained a significant predictor of functional status for each of the new groups. Having used a global measure for cognition (the DRS) may have diminished the sensitivity of the cognition variable to differentiate between the different neuropathologies. When looking for differences between Braak stages among subjects suspected of co-

occurring DLB and AD neuropathology, instruments specifically measuring both visuospatial abilities and episodic memory may perform better than a measure of global cognition when attempting to differentiate the two Braak groups.¹⁴

In the low Braak group, only worse cognition predicted worse functional status, an outcome that was not surprising at all. However, in this low Braak group, one might have expected more concentrated aggregated α -syn protein, and, therefore more of an effect from Parkinsonian motor symptoms upon functioning. This was not the case in this study. Therefore, additional research is warranted examining functional status and the role clinical symptoms such as Parkinsonian gait may have in moderating functional status relative to both low and high Braak stages.

In the high Braak group, both worse cognition and Parkinsonian gait predicted worse functional status. Again, it is not surprising that compromised cognition would predict worse functional status. Seemingly contradictory to our findings, however; increased AD pathology is known to mask the presence of DLB clinical symptoms (e. g., Parkinsonian features).⁴⁴ Therefore, one might have expected that Parkinsonian gait would have had less of an effect upon functional status in this higher Braak group. Our study findings did not support this, suggesting further research is indicated.

5.6 Study Limitations

This study has some limitations to consider when interpreting the results. Rescaling of the FAQ from four response options down to three options compressed the scale. This may have resulted in the possible loss of scoring variability and the introduction of bias, underestimating some functional difficulty among the sample. Next, because the two Braak groups were under powered for regression modeling, a larger sample size for each Braak group would be necessary for more precise model estimates. Other studies examining co-existing neuropathologies have had the burden of small sample sizes as well^{3,4,43,45,46} indicating the need for more study volunteers and collaboration across study settings.

In summary, for the larger study group (Braak low plus high groups), older age, compromised cognition and Parkinsonian gait predicted worse functioning. Clinicians seeing older adults with features of cognitive decline and Parkinsonian gait should suspect that these patients will have compromised independent functioning. At a minimum, a supportive services evaluation should be completed to determine how best to allocate resources to support these patients.

When examining low versus high Braak stages separately, cognition remained a predictor of worse functioning for both groups. Additionally, Parkinsonian gait predicted worse functional status in the high Braak group. With emerging evidence supporting multiple pathologies among patients with dementia, these Braak group findings have clinical and research implications. Among persons with DLB having moderately compromised cognition, clinicians and researchers may be able to use Parkinsonian gait as an indicator of more AD pathology.

6 CONCLUSION

This study demonstrates that there are important relationships between specific demographic characteristics, cognition, biomarkers, and functional status for clinicians to consider when caring for patients with DLB. As one of the few studies to have been conducted using a sample of autopsy confirmed DLB cases, this study identified that older age, impaired cognition, and Parkinsonian gait make significant contributions to predicting functional status. Additionally, it was demonstrated that AD neuropathology was co-occurring in the sample of all DLB cases providing additional support to the growing body of evidence that dementia in older adults is often the result of more than one type of neuropathology.

Possibly due in part to a longstanding research focus upon single dementia subtypes, clinical trials have offered no cure and only minimal symptom relief. Therefore, until there are effective treatments or cures for dementia, it is imperative for health care professionals to learn as much as possible about the functional status of these patients in order to design interventions, create safe environments, and promote quality of life.

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Key points:

Using a sample of autopsy confirmed dementia Lewy Body with Alzheimer's disease pathology cases, older age, impaired cognition, and Parkinsonian gait were significant contributors to predicting functional status. Parkinsonian gait differentiated those cases with lesser Alzheimer's disease pathology and older age differentiated those with more Alzheimer's disease pathology. Clinicians should consider co-occurring pathologies in patient with only one diagnosis.

TABLE 1.

Subject Characteristics

	All (N=102)	Low Braak Stage (n=47)	High Braak Stage (n=55)	
	Mean (SD)	Mean (SD)	Mean (SD)	P-value
Age (1 st visit), years	73.8 (6.29)	74.2 (5.59)	73.3 (6.71)	.45
Education, years	14.8 (3.22)	15.4 (2.93)	14.4 (3.42)	.98
Age at onset	70.7 (6.83)	72.2 (7.01)	70.1 (7.05)	.14
Years from onset to 1 st visit	3.9 (2.39)	4.0 (2.59)	3.7 (2.23)	.51
Age at death	79.0 (6.44)	79.3 (6.17)	79.4 (6.93)	.92
Disease duration (onset to death, years)	8.5 (3.71)	7.3 (2.79)	9.34 (4.18)	.01
ApoE-e4 allele frequency (%)	46.1	35.6	60.0	.02
MMSE total score	20.56 (6.03)	22.2 (5.74)	19.8 (6.33)	.05
DRS total score	106.8 (19.31)	110.7 (18.51)	105.8 (20.97)	.21
PODS total/(# items X 2)	.62 (.294)	.60 (.301)	.64 (.288)	.43

Note: DRS=Mattis Dementia Rating Scale: Range 0–144; lower scores indicate greater cognitive impairment. PODS=Pfeffer Outpatient Disability Scale: higher scores indicate greater functional impairment.

TABLE 2.

Pearson Correlations for the total sample

Variable	1.	2.	3.	4.	5.	6.	7.
1. Age at 1 st study visit	1.00						
2. Age at death	.85 ***	1.00					
3. Age at onset	.91 ***	.82 ***	1.00				
4. Symptom onset to 1 st visit (yrs)	.05	.05	-.18 *	1.00			
5. Education (yrs)	.01	-.04	-.02	.14	1.00		
6. DRS Total Score	-.53 ***	.13	-.04	.03	.24 *	1.00	
7. PODS total/(# items X 2)	.25 **	.09	.15	.10	-.18 *	-.53 ***	1.00

Note: n=97. DRS=Mattis Dementia Rating Scale. PODS=Pfeffer Outpatient Disability Scale.

*
p<.05**
p<.01***
p<.001

TABLE 3.

Functional Status at First Visit: Final Stepwise Linear Regression Models (n=97, 44 & 53)

		Age (years)			Cognition (DRS total)			Parkinsonian Gait (yes/no)		
Group	n	b	(SE)	p	b	(SE)	p	b	(SE)	p
All	97	.023	.012	.033	-.008	.001	.000	.171	.052	.002
Braak Low	44	n/a	n/a	n/a	-.006	.002	.012	n/a	n/a	n/a
Braak High	53	n/a	n/a	n/a	-.009	.002	.000	.222	.077	.006

Note: APOE 4: Present/not present; dummy variables constructed for regression. DRS=Mattis Dementia Rating Scale: Range 0–144; lower scores indicate greater cognitive impairment. Parkinsonian Gait: Present/not present; dummy variables constructed for regression.