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RESEARCH ARTICLE

Clinico-pathological comparison of patients with autopsy-confirmed Alzheimer's disease, dementia with Lewy bodies, and mixed pathology

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Abstract

Introduction: Patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) frequently demonstrate coexistent AD neuropathological change (ADNC) and Lewy body pathology (LBP) at autopsy. We investigated the effects of ADNC and LBP on the clinical presentation of these patients.

Methods: We retrospectively compared clinical and pathological features of patients with different severity of ADNC and LBP. We also compared the burden of medullary LBP between patients with and without autonomic dysfunction.

Results: Compared to pure ADNC, patients with AD/LBP have higher prevalence of DLB symptoms. Autonomic dysfunction strongly predicted the presence of LBP in patients with clinically diagnosed AD, but was not associated with increased LBP burden in the medulla. Severity of ADNC, but not LBP, was associated with cerebral atrophy.

Discussion: Clinical presentation of patients with AD/LBP differs from patients with pure ADNC or LBP. Autonomic dysfunction is a useful marker of otherwise unsuspected LBP.

KEYWORDS
Alzheimer's disease, autonomic dysfunction, dementia with Lewy bodies, Lewy body disease, mixed dementia

1 | INTRODUCTION

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are the two most common clinical forms of late-onset neurodegenerative dementias.[1] At autopsy, brains of DLB patients demonstrate Lewy bodies (LB) and Lewy neurites, collectively termed Lewy body pathology (LBP), in brainstem, limbic, and neocortical areas. Brains of AD patients exhibit senile plaques formed by the extracellular deposition of amyloid beta (Aβ) and intraneuronal neurofibrillary tangles (NFT) composed of abnormally phosphorylated tau protein.

Historically, it has been difficult to differentiate AD and DLB due to significant clinical overlap. In the early stages of dementia, both conditions may present with prominent memory symptoms.[2] In the later stages of dementia, AD patients may develop symptoms of visual hallucinations and Parkinsonism, mimicking DLB.[2] A recent article estimated that approximately 50% of patients with underlying Lewy body

pathology (LBP) may be clinically indistinguishable from AD.[3] Pathologically, there is significant overlap between AD and DLB, as 60% of sporadic AD patients have LBP in the brain.[4,5] Conversely, 66% percent of patients with DLB have amyloid plaques and 10% of patients with DLB also show NFTs.[6,7] Cognitive test scores of patients with concomitant AD neurological change (ADNC) and LBP decline faster compared to patients with pure ADNC.[6] Furthermore, the presence of severe ADNC masks typical features of DLB, making correct diagnosis even more difficult.[8]

We hypothesized that the clinical phenotype and the clinical course of patients with coexisting ADNC and LBP depend on the relative contribution of each pathology. We investigated with a retrospective study an autopsy-confirmed cohort of patients with varying severity of ADNC and LBP. We also examined the clinico-pathological correlation of autonomic dysfunction in this cohort, which emerged as a distinguishing feature for underlying LBP.

RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed the literature using traditional databases (e.g., PubMed) for articles and presentation at meetings. Although a significant proportion of patients with diagnosis of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) have mixed AD neurological change (ADNC) and Lewy body pathology (LBP), the effect of coexistence of both pathologies on the clinical course of dementia is not clear. Several studies suggest that patients with AD/LBP have a different cognitive and clinical profile compared to patients with pure ADNC or LBP.
2. **Interpretation:** Our findings suggest that patients with AD/LBP have a slower course with increased frequency of clinical features classically associated with LBP. Autonomic dysfunction in particular is useful in predicting the presence of AD/LBP. Severity of ADNC is correlated to increased severity of cerebral atrophy and severity of LBP is related to shortened survival.
3. **Future directions:** As our study is a retrospective study, it is difficult to attribute causal relationships between pathological changes and clinical manifestations. However, this provides a framework for developing hypotheses on the clinical manifestation and course of coexistent pathologies. Prospective studies with biomarkers of AD and DLB can be designed to evaluate clinical features and course of dementia in patients with mixed pathology.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were identified from the neuropathology database of the Clinic for Alzheimer's Disease and Related Disorders at the University of British Columbia, Canada. All participants had earlier consented to research participation and autopsy. Criteria for inclusion in the study were (1) presence of ADNC, (2) presence of LBP, or (3) a combination of both pathologies on neuropathological evaluation (AD/LBP). Out of a total of 259 participants between 2004 and 2017, inclusive, 181 met the inclusion criteria. Exclusion criteria were (1) heavy burden of other degenerative dementia pathology, for example, frontotemporal lobar degeneration meeting the current pathological diagnostic criteria; (2) presence of medial temporal lobe-only transactive response DNA binding protein 43 KDa (TDP43) pathology; (3) presence of significant cerebrovascular disease such as chronic infarct(s) and/or hemorrhage(s); and (4) incomplete medical information. One hundred patients were excluded, and we included 37 patients with pure ADNC, 7 patients with pure LBP, and 37 patients with AD/LBP (Table 1) in the final sample.

2.2 | Clinical information

During life, patients were followed in the clinic semi-annually or annually by specialist neurologists or geriatricians with expertise in diagnosis and management of dementia. During assessments, clinicians asked patients about domains of cognitive impairment and corroborated the symptoms with appropriate cognitive tests. For patients with a clinical diagnosis of DLB, clinicians enquired about symptoms included in the diagnostic criteria.[4] Patients were also asked about autonomic symptoms, for example, new onset of constipation, urinary incontinence, and postural symptoms suggestive of orthostatic hypotension. If autonomic symptoms were present, blood pressure was measured in the clinic to look for postural hypotension. All clinical information is stored in paper and electronic charts, which were reviewed for the current analysis. Information on affected cognitive domains and presence of clinical symptoms including Parkinsonism, visual hallucinations, cognitive fluctuations, REM sleep behavior disorder (RBD), neuroleptic sensitivity, and gait disturbance or falls were obtained from chart review, and recorded as either present or absent. Demographic information was obtained from chart review, which included sex, age at onset of cognitive symptoms, age at onset of dementia, and age at death. Age at onset of cognitive symptoms was based on patient and caregiver reports. For patients who first presented with mild cognitive impairment (MCI), age at onset of dementia was calculated from the time when they first fulfilled the criteria for dementia. We also obtained longitudinal Mini-Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores administered during clinic visits. MoCA scores were converted to MMSE scores for statistical analysis according to methods published by Roalf et al.[9]

2.3 | Pathological evaluation and classification

All participants underwent a standardized neuropathological examination. Formalin-fixed, paraffin-embedded brain tissue blocks were cut at 5 microns and stained with hematoxylin and eosin (HE), HE combined

TABLE 1 Classification of severity of AD and Lewy body pathology

	AD pathology		Lewy body pathology
Severity	CERAD staging	Braak staging	Severity
Severe	Frequent	V/VI	Neocortical
Moderate	Moderate	III/IV	Limbic system
Mild	Sparse	I/II	Brainstem only

Abbreviations: AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

with Luxol fast blue (HE/LFB), modified Bielschowsky silver, Gallyas silver, and Congo red stains. Standard immunohistochemistry (IHC) was performed using the Dako Omnis automated staining system with primary antibodies against alpha-synuclein (α- syn; Thermo Scientific; 1:10,000 after microwave antigen retrieval), Aβ (DAKO; 1:100 with initial incubation for 3 hours at room temperature), hyperphosphorylated tau (clone AT-8; Innogenetics; 1:2000 after microwave antigen retrieval), phosphorylation-independent TDP-43 (ProteinTech; 1:1000 after microwave antigen retrieval), and ubiquitin (DAKO; 1:500 after microwave antigen retrieval).

The severity of senile neuritic plaque pathology was staged according to Consortium to Establish a Registry for Alzheimer's Disease (CERAD) recommendations.[10] Extent of tau pathology was staged according to Braak et al.[11,12] The severity of ADNC was semi-quantitatively categorized as mild, moderate, and severe as described in Table 1. LBP was assessed according to the recommendations of the third report of the DLB consortium consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies.[13] The severity of LBP was classified into brainstem, limbic, and neocortical pathology, in increasing order of severity. We classified the patients in five groups depending on the combined pathological severity of ADNC and LBP, namely (1) severe ADNC with neocortical LBP, (2) severe ADNC with limbic LBP, (3) severe ADNC with brainstem to no LBP, 4) neocortical LBP with moderate ADNC, and (5) neocortical with mild to no ADNC (Table 1). Brain weight at the time of autopsy was used as a marker of cerebral atrophy.

In addition, we compared the pathological burden of LBP and α-syn between patients with and without autonomic dysfunction. Dorsal motor nucleus (DMN) and nucleus ambiguous (NA) are affected by α-syn pathology in patients with LBP, which may be correlated with symptomatic autonomic dysfunction.[14,15] Sections of medulla from selected patients with clinical features of autonomic dysfunction and matched controls were evaluated for α-syn pathology burden using IHC. The amount of pathology was evaluated semi-quantitatively as none (0, no staining), mild (1, scattered neurites or a single LB), moderate (2, several neurites and two or more LB), severe (3, numerous neurites and LBs), or very severe (4, the entire nucleus with abundant staining) in the DMN, the NA, and the nucleus tractus solitaires (NTS) on each stain. The severity of α-syn pathology was compared between patients with and without autonomic dysfunction using a *t* test. The prevalence of LBP was compared between the two groups with Chi-square test.

2.4 | Statistical analysis

We performed statistical analysis with R software, version 3.6.0 (www.R-project.org). We compared the demographic variables between the groups, which included sex, age at onset of cognitive symptoms, and age at onset of dementia. We compared the frequency of clinical symptoms and affected cognitive domains between the groups. We used analysis of variance (ANOVA) to compare continuous variables and Pearson's Chi-square test to compare categorical variables. MMSE scores at presentation were compared using analysis of covariance (ANCOVA) with the age of onset of cognitive symptoms as a covariate. For ANOVA and ANCOVA analyses, we used Bonferroni correction for multiple comparisons. We performed pairwise comparisons with Tukey's post hoc test. We used multivariate logistic regression to analyze the association between clinical features and underlying pathology. The regression models used pure ADNC, pure LBP, and AD/LBP as dependent variables. Clinical features, domains of cognitive impairment, and age of onset of symptoms were used as independent variables. We calculated the odds ratio, confidence interval, and significance levels for each clinical feature. We compared brain weight at autopsy between the groups using ANCOVA with survival from dementia onset as a covariate. Kaplan-Meier analysis was performed to compare survival from the onset of cognitive symptoms and survival from the onset of dementia among the pathological groups. Pairwise comparisons of survival between groups were performed using log-rank test with Bonferroni correction for multiple comparisons. We compared the survival of patients with and without autonomic dysfunction. We also performed multivariate Cox proportional hazard analyses to evaluate the effect severity of individual pathologies, for example, Lewy bodies, neuritic plaques, and NFTs, on survival of patients.

We compared the frequency of LBP and the severity of α-syn deposition in brainstem nuclei between patients with autonomic dysfunction and matched controls using Pearson's Chi-square test and unpaired *t* test.

3 | RESULTS

The study included 45 male and 36 female patients. There was no significant difference in the male:female ratio among the groups. At the time of onset of cognitive symptoms, the average age of the patients was 65.3 years. The age of onset of cognitive symptoms, as shown in

TABLE 2 Demographic, clinical, and pathological features of patients

	Severe ADNC	Severe ADNC Limbic LBP	Severe ADNC Neocortical LBP	Moderate ADNC Neocortical LBP	Neocortical LBP	*P*
N	31	10	18	15	7	
M:F	16:15	3:7	8:10	12:3	6:1	.041
Age of symptom onset (y)[a]	63.7 ± 8.3	65.7 ± 9.0	62.2 ± 10.0	65.1 ± 7.9	65.3 ± 9.0	.016
Age of dementia onset (y)[a]	66.7 ± 8.8	67.7 ± 9.3	64.3 ± 9.3	74.6 ± 6.7	67.3 ± 8.8	.018
Survival from symptom onset (y)[a]	9.8 ± 3.3	9.6 ± 3.6	10.5 ± 4.9	7.2 ± 2.4	7.0 ±1.8	.001
Survival from dementia onset (y)[a]	6.9 ± 2.8	7.6 ± 3.4	8.4 ± 4.7	4.6 ± 2.0	4.9 ± 2.2	.009
MMSE score at presentation[a]	23.6 ± 4.6	19.7 ± 6.3	20.6 ± 6.8	23.0 ± 4.9	22.0 ± 5.7	.2
Memory symptoms (%)	96.8	90	100	100	71.4	.03
Visuospatial deficit (%)	34.3	14.3	8.6	28.6	14.3	.02
Parkinsonism (%)	9.7	20	16.7	40	71.4	.005
Visual hallucinations (%)	3.2	10	11.1	40	14.3	.02
Cognitive fluctuation (%)	3.2	0	0	40	0	.001
RBD (%)	0	0	25	50	25	.02
Autonomic dysfunction (%)	12.9	10	61	73.3	85.7	.0001
Neuroleptic sensitivity (%)	3.2	0	0	13.3	14.3	.267
Brain weight (gms)[a]	1178±157	1193±112	1173±113	1340±150	1435±155	.007

[a]Values are expressed as mean ± SD.

Abbreviations: ADNC, Alzheimer's disease neuropathological change; LBP, Lewy body pathology; MMSE, Mini-Mental State Examination; RBD, REM sleep behavior disorder; SD, standard deviation.

Table 2, was significantly different between the subgroups ($P = .016$). Pairwise comparisons revealed that patients with severe ADNC and neocortical LBP developed cognitive symptoms at an earlier age than patients with moderate ADNC and neocortical LBP. On the other hand, there was no difference in age of onset between patients with severe ADNC and neocortical LBP and patients with severe AD and limbic LBP. The average age at the time of diagnosis of dementia was 67.8 years, which differed significantly among the subgroups ($P = .018$). Pairwise comparisons again revealed that patients with severe ADNC and neocortical LBP had a younger age of onset of dementia compared to patients with moderate ADNC and neocortical LBP.

Analysis of clinical features revealed significant differences among the groups. Patients with AD/LBP had higher frequency of memory symptoms compared to patients with pure LBP. Patients with moderate to severe ADNC, with or without LBP, had a higher frequency of visuospatial deficits as well. Patients with AD/LBP had a higher frequency of Parkinsonism, visual hallucinations, RBD, and cognitive fluctuations compared to patients with pure ADNC. Patients with AD/LBP had lower frequency of symptoms diagnostic of DLB compared to patients with pure LBP. Autonomic dysfunction was more frequent in patients with LBP. On multivariate logistic regression analysis, we noted a significant association of memory impairment with pure AD pathology (odds ratio [OR] 39.1, confidence interval [CI] 1.28–2456.87, $P = .04$). Autonomic dysfunction was strongly associated with both pure LBP (OR 4.13, CI 1.21–16.04, $P = .03$) and with AD/LBP (OR 7.87, CI 2.35–31.19, $P = .002$). MMSE scores at presentation, adjusted for age, were not significantly different between the groups.

On Kaplan-Meier analysis, we noted a significant difference between the groups in survival from symptom onset ($P = .001$) and also after diagnosis of dementia ($P = .009$). Patients with severe ADNC survived longer than patients with neocortical LBP after the onset of dementia. Patients with severe ADNC and neocortical LBP also survived longer than patients with neocortical LBP only. There was no significant difference in survival between patients with severe ADNC and patients with severe ADNC and neocortical LBP. However, when we analyzed possible factors contributing to the difference, the Cox proportional hazard model did not reveal a significant effect of the age of onset or the severity of neuropathology on survival of the patients. There was no difference in survival between patients with and without autonomic dysfunction.

TABLE 3 Pathological comparison of patients with and without autonomic dysfunction

	Autonomic dysfunction		
	Present	Absent	*P*
Lewy bodies			
Dorsal nucleus	33.3%	27.3%	.72
Nucleus ambiguous	16.7%	0%	.15
α- synuclein deposition			
Dorsal nucleus[a]	1.3 ± 1.3	0.9 ± 0.8	.77
Nucleus ambiguous[a]	2.0 ± 1.7	1.9 ± 1.3	.4
NTS[a]	0.96 ± 0.84	0.86 ± 0.81	.78

[a]Values are expressed as mean ± SD.
Abbreviations: NTS, nucleus tractus solitaires; SD, standard deviation.

Comparison of brain weight at autopsy revealed significant difference between the groups when adjusted for age at the time of dementia diagnosis and survival ($P = .007$). Tukey's post hoc test revealed significantly lower brain weights in patients with severe ADNC. Longer survival from diagnosis of dementia was associated with lower brain weight at autopsy ($P = .002$).

The pathologic changes in brainstem nuclei of patients with and without autonomic dysfunction are described in Table 3. We did not observe significant differences in either presence of LBP on HE stain or the severity of α-syn deposition between the two groups. Interestingly, in patients with pure ADNC, there was no increase in tau burden in those with autonomic dysfunction (data not shown).

4 | DISCUSSION

Classically, each dementia syndrome has been attributed to a particular species of misfolded protein. In clinical settings, however, a considerable proportion of dementia patients have coexisting pathologies. As ADNC and LBP are commonly coexistent pathologies at autopsy, we examined the characteristics of a cohort of patients with different severities of ADNC and LBP. More than 50% of patients in our cohort had AD/LBP, whom we stratified according to the combined severity of neuropathology. We observed that the groups significantly differed from each other in several aspects: (1) patients with an earlier age of onset and longer survival demonstrated more severe ADNC at autopsy, (2) presence of autonomic dysfunction was associated with underlying synucleinopathy, and (3) patients with severe ADNC had significantly more brain atrophy compared to patients with LBP. It is possible that ADNC is driving the earlier age of onset in this cohort, or alternatively, patients with ADNC may be surviving longer and therefore demonstrated more severe pathology at the time of autopsy. Interestingly, a recent study demonstrated that DLB patients have an earlier age of onset of symptoms and more severe clinical features when there is evidence of amyloid deposition on positron emission tomography imaging.[16] This suggests that coexisting ADNC and LBP is associated with an earlier age of onset of dementia.

We noted that the pathological groups differed from each other in clinical symptoms that are characteristically associated with synucleinopathy. We hypothesize that LBP affects specific brain regions in addition to the areas affected by ADNC, which results in additional symptom burden and shorter survival. In particular, autonomic dysfunction was significantly associated with underlying synucleinopathy. In DLB patients, the frequency of autonomic dysfunction, commonly presenting as urinary incontinence, constipation, or orthostatic hypotension, is very high.[17] Autonomic dysfunction is observed in all synucleinopathies and is associated with a shortened survival.[18] In our cohort, autonomic dysfunction was strongly associated with underlying LBP (pure or combined with ADNC). Our results suggest autonomic dysfunction can be an important clinical clue to *ante mortem* diagnosis of underlying syncleinopathy. However, we did not observe a significant difference in survival of patients with autonomic dysfunction. To understand the pathological basis of autonomic dysfunction, we reevaluated the severity of LBP and α-syn deposition in DMN, NA, and NTS. DMN is a key center of the autonomic nervous system that innervates the gastrointestinal system, the respiratory system, and the heart through parasympathetic neurons. In DLB, DMN is predominantly affected in contrast to multiple system atrophy (MSA), which predominantly affects the ventrolateral medulla.[19] NA innervates the sinus node of the heart and is responsible for vagal modulation of the heart rate. NTS is an important relay station for autonomic reflexes controlling cardiovascular function.[20] We hypothesized that these nuclei will be significantly affected in patients who develop clinical signs of autonomic dysfunction. However, we could not demonstrate a difference in the severity of pathological changes between patients with and without autonomic features. The result may be due to the small sample size, or the autopsy findings at time of death may not reflect the clinical symptoms when patients present at the earlier stage of disease. Autonomic symptoms, such as genitourinary symptoms, may be associated with pathological burden in the thoracic and the sacral spinal cord, which was not sampled in our study. This may also be a reason of lack of significant difference in pathological burden between patients with and without autonomic dysfunction.

Hansen et al. described Lewy body variant of AD (LBV) as a separate clinical and pathological entity, which was characterized by the presence of concomitant Lewy bodies in addition to AD pathology.[21] When patients with LBV were compared to patients with AD from the CERAD cohort, LBV patients were more likely to have more severe delayed recall deficits.[22] Visuospatial impairment has been described as a sensitive measure to distinguish DLB from AD.[23] In our cohort, visuospatial deficits were more frequent in patients with AD pathology, contrary to previous reports. This may be due to the limitation that MMSE interlocking pentagons being the only consistently available objective measure of visuospatial function in our current study.

Previous studies suggest that DLB patients have a shorter survival compared to AD, with an estimated range between 5.5 and 7.7 years from disease onset.[24] A recent study suggested that coexistence of increasing severity of ADNC with LBP is associated with shorter survival.[25] Our data revealed that patients with pure ADNC survived longer compared to patients with pure LBP, which is similar to

previously published studies. Patients with severe ADNC with neocortical LBP survived longer than patients with neocortical LBP. However, there was no significant difference in survival between patients with severe ADNC and patients with severe ADNC and neocortical LBP. It is possible that functional deficits like Parkinsonism and autonomic dysfunction, in addition to cognitive impairment in patients with LBP, result in a shorter survival.

In patients with autopsy-confirmed LBP, *ante mortem* rate of cerebral atrophy was similar to age-matched controls.[15] In patients with AD/LBP, cerebral atrophy increases markedly and the degree of atrophy correlates with Braak stage of NFT.[15] We observed that patients with severe AD pathology developed greater atrophy than patients with neocortical LBP. Among patients with mixed pathology, a similar pattern was observed, as the severity of AD pathology negatively affected the brain weight. However, patients with neocortical LBP generally have a lower burden of pathology in the neocortex compared to patients with severe AD pathology, which may explain the difference in degree of cerebral atrophy at autopsy.

Our study has a number of limitations, including a small sample size, selection bias due to recruitment from a memory clinic sample, and use of MMSE as the cognitive screening instrument. Also, the retrospective nature of our study may have missed certain clinical features during clinical assessments, leading to underreporting. Some of the strengths of our current study are the use of semi-quantitative analysis of α-syn pathology and the long duration of longitudinal follow-up.

In conclusion, we found that among patients with coexisting AD and LBP, those with more severe AD pathology present at an earlier age, and those with severe LBP have a shorter survival after onset of symptoms. Presence of severe AD pathology, rather than LBP, is associated with more severe cerebral atrophy. Presence of autonomic dysfunction correlates strongly with the presence of synucleinopathy, which may be used to identify patients with mixed AD and LBP in the clinical setting.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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