

Prognostic Factors Related to Dementia with Lewy Bodies Complicated with Pneumonia: An Autopsy Study

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Abstract

Objective In patients demonstrating dementia with Lewy bodies (DLB), pneumonia is a common complication. However, the prognostic factors for the survival time in DLB with pneumonia have not been investigated by autopsy in patients with neuropathologically confirmed DLB.

Methods We conducted a retrospective study of the medical and autopsy reports of 42 patients admitted to a Japanese hospital between 2005 and 2014. The patients were neuropathologically diagnosed as having DLB by post-mortem examinations. We analyzed the effects of various factors on the time from DLB onset to death.

Results Thirty-nine of the 42 patients with DLB (92.9%) developed pneumonia during hospitalization. The median age at DLB onset was 78 years and the median time from DLB onset to death was 8 years. The Cox proportional hazard model demonstrated cerebral infarction [Hazard Ratio (HR), 2.36 (95% CI 1.12-4.96), $p=0.023$], muscle weakness [HR, 2.04 (0.95-4.39), $p=0.067$], male sex [HR, 2.84 (1.24-6.50), $p=0.014$], and age at onset (≥ 78 years.) [HR, 4.71 (1.82-12.18), $p=0.001$] to be prognostic factors for a shorter time from DLB onset to death.

Conclusion Careful treatment of cerebral infarction and muscle weakness of the lower extremities is crucial for DLB patients with pneumonia, especially for those over 78 years of age, in order to maximize the patients' life expectancies.

Key words: dementia with Lewy bodies, pneumonia, cerebral infarction, muscle weakness of the lower extremities, autonomic dysfunction, DLB

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Introduction

Dementia with Lewy bodies (DLB) is the second most common degenerative dementia disorder, after Alzheimer's disease (AD) (1). DLB is characterized neuropathologically by the presence of Lewy bodies (LB), containing α -synuclein, in the brainstem and the cerebral cortex of patients (2, 3). The core clinical features of DLB are fluctuating cognitive dysfunction, visual hallucinations, and parkin-

sonism. Pneumonia is a common complication (4, 5), and is the major cause of death in DLB patients (6, 7). Susceptibility to pneumonia in DLB patients may, in part, be caused by aspiration due to swallowing dysfunction (8). In addition, a previous report indicated that DLB patients have a decreased ventilator response to hypercapnia due to respiratory autonomic dysfunction (9). A decreased ventilator response results in the patient being more vulnerable to ventilatory failure during high-demand conditions, such as heart failure and pneumonia, possibly leading to poorer outcomes (10). It is

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plausible that decreased ventilator responses are also related to poor outcomes in DLB complicated by pneumonia. Our previous study suggested that pneumonia is the most common cause of death in patients with DLB (11). Although it is well documented that pneumonia has a significantly negative impact on the prognosis in DLB, the factors affecting life expectancy in DLB patients with pneumonia have not yet been fully evaluated. The identification of such factors is thus important to achieve an improvement in both DLB patients' life expectancies and end-of-life care.

The purpose of the present study was to investigate the disease progression of neuropathologically-diagnosed DLB patients with pneumonia and to evaluate the risk factors influencing the survival time from the onset of DLB to death.

Materials and Methods

Study design and subjects

The data in this study were obtained from an observational study in which we studied autopsy cases of confirmed AD, vascular dementia (VaD), and DLB (11). The subjects included in the present study consisted of patients who were hospitalized, deceased, and underwent post-mortem autopsy at the Choju Medical Institute, Fukushima Hospital, Toyohashi, Japan, between January 2005 and December 2014 (12). Of the eligible patients, we selected 42 patients who had been neuropathologically diagnosed with DLB, and who had developed pneumonia during hospitalization. We retrospectively reviewed the patients' charts, medical reports, and autopsy reports along with the neuropathological examination results. Data on the general and clinical backgrounds of the patients, the incidence of pneumonia, comorbidities, autonomic dysfunctions, causes of death, and neuropathological examinations results were collected. The factors associated with survival time, defined as the time from the onset of DLB to death, were analyzed in all eligible DLB patients.

This study was approved by the Institutional Review Board of the University of Tsukuba and Choju Medical Institute at Fukushima Hospital. Written informed consent was obtained from the patients' relatives.

Diagnosis and definitions

The details of the neuropathological diagnosis of DLB and cause of death have been described in our previous study (11). For ensuring the accuracy of the cause of death, including sudden death, two investigators independently reviewed the data with masked clinical diagnoses written by the physician in charge (11).

The occurrence of pneumonia was defined as pneumonia during hospitalization, once or more times, based on the diagnostic criteria established by the guidelines for the management of hospital-acquired pneumonia in adults by the Japanese Respiratory Society (13).

The time of dementia onset was defined as year when pa-

tients first experienced forgetfulness, disorientation, abnormal behavior, delusions, or visual hallucinations, according to the Guidelines for Dementia 2010 (14). The duration of hospitalization was defined as the time from hospital admission until the patient's death.

Sleep disorders were diagnosed by physicians in charge if patients had sleeplessness complaints, reversed sleep-wake cycles, demonstrated confusion or other nursing problems at night time during hospitalization. Urinary incontinence, constipation, increased sputum production, and swallowing dysfunction were all clinically diagnosed by physicians specializing in geriatric medicine during the hospitalization.

Statistical analysis

General and clinical patient background data, the clinical time course (including survival time), and cause of death were summarized. As the median onset age of the patients was 78, they were divided into two groups according to their age (≤ 78 or ≥ 79 years of age) to analyze the effects in younger and older patients with DLB. For the patients with DLB complicated by pneumonia, survival curves of the time from DLB onset to death were analyzed by the Kaplan-Meier method, and comparisons were made using the log-rank test. To evaluate independent factors for the time from DLB onset to death, the step-wise method was used for the Cox proportional hazard model. Data analyses were conducted using the SPSS Statistics 22.0 software program (IBM, Armonk, USA). For all analyses, significance levels were two tailed, and $p < 0.05$ was considered to be significant.

Results

General characteristics of study patients with DLB

During the observation period, a total of 261 patients died and were autopsied at the study site. Of these, a total of 42 patients (30 females, 68.2%) were neuropathologically-diagnosed with DLB, and 39 (92.9%) of whom acquired pneumonia during hospitalization. The demographic and clinical characteristics of the DLB patients are shown in Table 1.

The median age of DLB onset was 78 years of age. Although the body mass index was unable to be measured in all patients owing to their physical conditions, this was low in most of the DLB patients at hospital admission. Cerebral infarction was pathologically observed in 35.7% of the DLB patients. Over 60% of the DLB patients had swallowing dysfunction. Sleeping disorders were observed in 52.4% of the patients, as were other common autonomic dysfunctions including constipation (81.0%), repeated falls (35.7%), and urinary incontinence (90.5%). The underlying conditions of hypertension, respiratory emphysema, and fractures of the femur were observed in more than 20% of the DLB patients.

Table 1. General Characteristics of Patients with Dementia with Lewy Bodies.

		n=42
		Total - n (%)
Sex - n (%)		
Male		14 (31.8)
Female		30 (68.2)
Age - median (IQR)		
Time of death		87 (81-92)
Time of dementia onset		78 (72-85)
Incidence of pneumonia		39 (92.9)
Neuropathological condition		
Weight of brain - median (IQR)	(n=35)	1,050 (1,000-1,140)
Type of DLB		
Limbic		14 (33.3)
Neocortical diffuse		13 (31.0)
Cerebral infarction		15 (35.7)
Clinical condition- n (%)		
BMI at admission- median (IQR)	(n=20)	17.8 (13.8-20.8)
Muscle weakness of the lower extremities		14 (33.3)
Increased sputum		12 (28.6)
Swallowing dysfunction		26 (61.9)
PEG		20 (47.6)
Autonomic dysfunction		
Sleep disorder		22 (52.4)
Urinary incontinence		38 (90.5)
Constipation		34 (81.0)
Comorbidity- n (%)		
Hypertension		12 (28.6)
Heart failure		3 (7.1)
Respiratory emphysema		9 (21.4)
Diabetes mellitus		2 (4.8)
Malignant neoplasm		6 (14.3)
Repeated falls		15 (35.7)
Fracture of femur		12 (28.6)
Tuberculosis		3 (7.1)

DLB: dementia with Lewy bodies, PEG: percutaneous endoscopic gastrostomy, IQR: interquartile range

Clinical conditions of DLB patients at death

Of the 39 DLB patients with pneumonia, the median age at death was 86 years [interquartile range (IQR), 81-91] with female patients on average older than male patients (Table 2). The median time from DLB onset to death was 8 years (IQR, 5-14). Male patients had a shorter period from the time of DLB onset to death than females.

Although the causes of death in the DLB patients varied, pneumonia was the most common (53.8%), followed by renal failure (15.4%) and respiratory failure (12.8%). Sudden death was observed in 10.3% of the DLB patients.

Evaluation of the factors associated with the time from DLB onset to death

The Kaplan-Meier curve in Figure shows the influence of age of onset, cerebral infarction, muscle weakness of the lower extremities, age at DLB onset, sleep disorder, and comorbidities including hypertension and respiratory emphysema, from the time of DLB onset to death. There were significant differences between the patients with and without

cerebral infarction ($p=0.007$), with and without muscle weakness of the lower extremities ($p=0.037$), and according to age ≤ 78 years or ≥ 79 years ($p<0.001$). No significant differences were observed between the patients with and without sleep disorder, or between those with and without the comorbidities investigated in this study.

In the DLB patients with pneumonia, the Cox proportional hazard model revealed a male sex (HR, 2.83), age of onset ≥ 78 years (HR, 4.71), cerebral infarction (HR, 2.36), and muscle weakness of the lower extremities (HR, 2.04) to be factors associated with the time from DLB onset to death (Table 3).

Discussion

We found that the prognostic factors identified in autopsy-confirmed DLB patients with pneumonia were pathologically-confirmed cerebral infarction, muscle weakness of the lower extremities, a male sex, and older age at onset (≥ 78 years).

Of the patients with DLB in this study, only three did not develop pneumonia during hospitalization (Table 1), and pneumonia was the most common cause of death (Table 2) in those who were affected. Our results are consistent with those of previous studies, such as those reporting a high incidence of pneumonia (4, 5) and a high frequency of pneumonia-associated mortality in patients with DLB (6).

In the present study, the median time to death from DLB onset was 8 years (Table 2), while the reported survival-times of DLB were various and ranged from 1.8 to 9.5 (15). One of the independent factors associated with disease progression in this study was cerebral infarction (Table 3). We confirmed cerebral infarction by autopsy, and included asymptomatic and old cerebral infarctions. Although only a few studies have so far reported an association between the clinical features and cerebrovascular lesions in DLB, a previous report indicated no greater susceptibility to death from stroke (16). Although our data did not include any neuroimaging findings, our results indicated the possibility of the long-term influence of cerebral infarction, including asymptomatic cerebral infarction and a history of small cerebral infarctions, on the progression of DLB.

Muscle weakness of the lower extremities was observed in 33.3% of DLB patients (Table 1). Muscle weakness was also evaluated as a potential prognostic factor of DLB by the Cox proportional hazard model (Table 3). Although muscle weakness of the lower extremities is regarded as a risk factor for falls and fractures, in the present study, neither of these were associated with a shortened life expectancy in our study participants. It is important to bear in mind that previous studies indicated an association between muscle strength of the extremities and the risk of death in older adults, as well as a risk of lung function deterioration (17, 18). In addition, a low pulmonary function was found to be associated with a low muscle mass in community-dwelling elderly people (19). Similar to these

Table 2. Clinical Condition of Death among DLB Patients with Pneumonia.

	n=39
Age at time of death - median (IQR)	Total - n (%)
Male	86 (81 - 91)
Female	80 (76 - 87)
Number of years to death from DLB onset- median, yr. (IQR)	88 (85 - 93)
Male	8 (5 - 14)
Female	7 (1 - 15)
Age of onset ≤ 78 yr.	8 (5 - 13)
Age of onset ≥ 79 yr.	13 (8 - 16)
Immediate cause of death - n (%)	5 (3 - 7)
Pneumonia	21 (53.8)
Respiratory failure	5 (12.8)
Heart failure	1 (2.6)
Sepsis	3 (7.7)
Renal failure	6 (15.4)
Sudden death	4 (10.3)

DLB: dementia with Lewy bodies, IQR: interquartile range

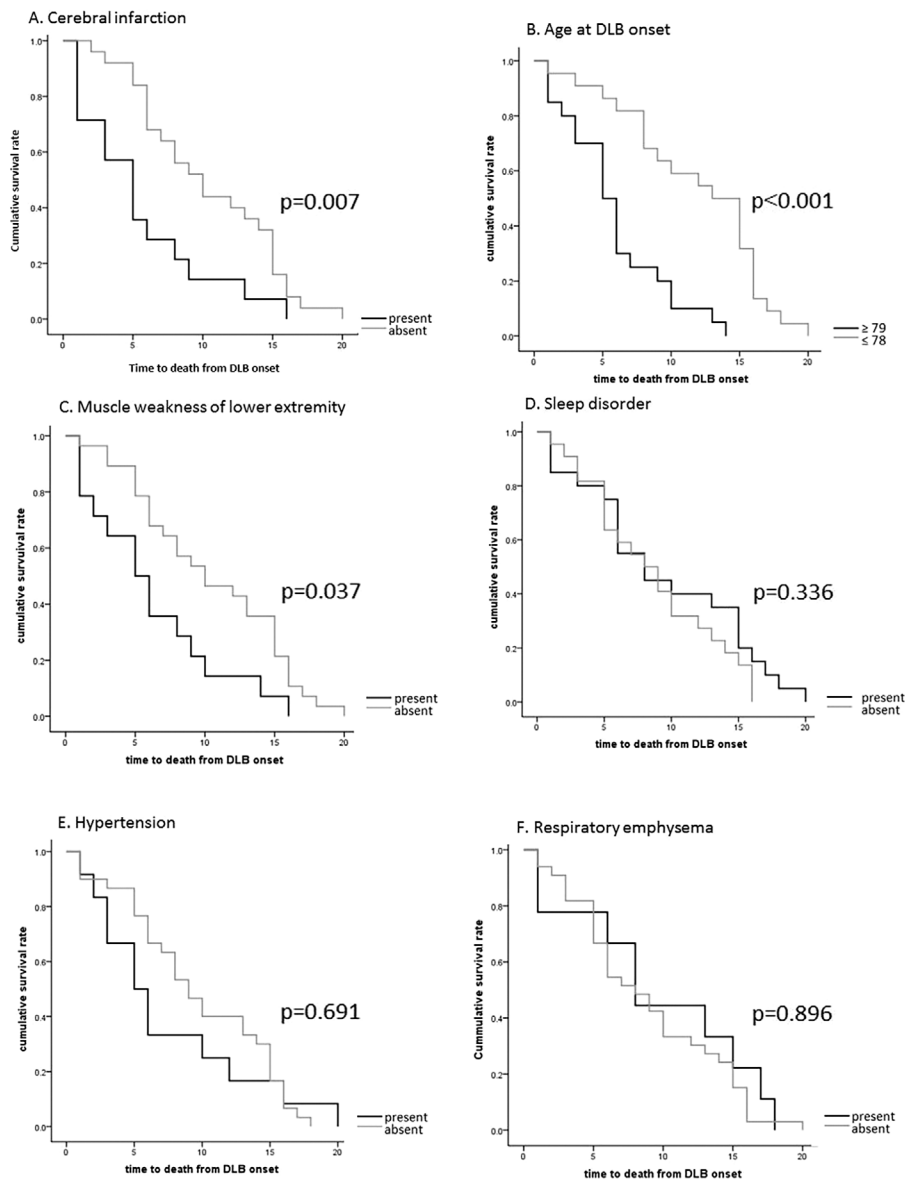


Figure. Kaplan-Meier curves showing the number of years from the onset of dementia with Lewy bodies to death. Comparisons of each covariance were tested using the log-rank test.

Table 3. Risk Factors for Survival Time of Dementia with Lewy Bodies by Cox Hazard Model.

	HR	95% CI	p value
Sex - Male	2.84	1.24 – 6.50	0.014
Age of onset - \geq 78 yr.	4.71	1.82 - 12.18	0.001
Cerebral infarction	2.36	1.12 – 4.96	0.023
Muscle weakness of the lower extremities	2.04	0.95 - 4.39	0.067

n=39

HR: hazard ratio, CI: confidence interval. p value: chi-squared test

Baseline adjustment covariates: sex, pneumonia occurrence, pathologically identified cerebral infarction, hypertension, heart failure, malignant neoplasm pulmonary emphysema, fracture of femur, sleep disorder, urinary incontinence, repeated falls, swallowing dysfunction, muscle weakness of the lower extremities, increased sputum, and percutaneous endoscopic gastrostomy. Only items of $p < 0.1$ are shown.

Interactions between sex and age of onset, or cerebral infarction and muscle weakness of the lower extremities were not significant ($p = 0.712$ or $p = 0.449$, respectively).

observations, the results of the present study suggest that weakness of the extremities in DLB patients may be associated with a low respiratory function and thus aggravate the poor prognosis for patients with pneumonia. Along with decreasing physical activity, the daily activities of a patient would decrease gradually and this might shorten the patients' life.

Although the smoking history of our patients was difficult to collect, quite a high incidence of respiratory emphysema was observed (Table 1). Liao et al. reported that in COPD patients with dementia, the incidence rate of hospital mortality was higher than those of dementia patients without COPD (20). In the present study, the Kaplan-Meier method failed to indicate any significant difference between patients with and without respiratory emphysema of the time from DLB onset to death (Figure). This difference may be due to the fact that the deterioration of lung function in very older patients with DLB progresses regardless of a history of COPD.

Although the data on dysphagia was mostly collected from the observations of the clinicians in charge due to the difficulty to conduct conventional swallowing assessments (21, 22) on this kind of group of patients, swallowing dysfunction was observed in 61.9% of the DLB patients (Table 1). It has been reported that susceptibility to pneumonia in DLB may be attributed to swallowing dysfunction (23). Despite the possibility that swallowing dysfunction may induce pneumonia, in the present study, this was not associated with a shortened life expectancy in DLB patients with pneumonia, and it also was not identified as a prognostic factor in DLB with pneumonia (Table 3). Although the use of a percutaneous endoscopic gastrostomy tube (PEG) has been considered for the management of dysphagia, a meta-analysis concluded that PEG placement provided no evidence for an improvement in the long-term survival rates in patients with advanced dementia (24). The results of the present study are therefore compatible with the previous studies.

We observed the available data for other factors related to autonomic dysfunction, including sleeping disorders, urinary incontinence, and constipation. However, these symptoms

were not identified as useful prognostic factors in DLB (Table 3). A previous study in Sweden observing the 36-month survival of patients with DLB concluded that autonomic dysfunction, including orthostatic hypotension, incontinence, and constipation, were related to the survival time in patients with DLB (25). This discrepancy may also be due to the fact that the majority of patients presented with a high incidence of urinary incontinence and constipation during the course of the illness among the patients with DLB which and these frequencies were compatible with the findings of a previous report in Japan (7).

The present study is associated with some limitations. The time of DLB onset was retrospectively estimated from the patients' medical records relying on reports from patients, patients' families, and/or caregivers about the commencement of the symptoms and initial signs of DLB. Thus, there may be a discrepancy between this and the actual time of onset. As the subjects of present study were pathologically confirmed DLB patients at a single center, the number of patients was thus quite small. Further studies are therefore required in alternative and larger populations before the results can be generalized and any definitive conclusions can be made. The diagnosis of pneumonia in this age group is often delayed because of the frequent absence of fever, the paucity or absence of cough, and changes in mental status (delirium) (26). Therefore, it was not possible to examine the precise time from the occurrence of pneumonia to mortality. Due to the nature of this retrospective study, additional factors that may be related to disease progression in patients with DLB, such as orthostatic hypotension (27), parkinsonism, nutrition support, and the reasons for hospital admission might exist, but they were not included in the analysis in the present study.

In conclusion, careful management and the prevention of cerebral infarction and muscle weakness in DLB patients with respiratory tract infection are crucial factors for maximizing the patients' life expectancy, as well as for improving the patients' end-of-life care. The results of the present study warrant further prospective cohort studies with a larger group of patients.

The authors state that they have no Conflict of Interest (COI).

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