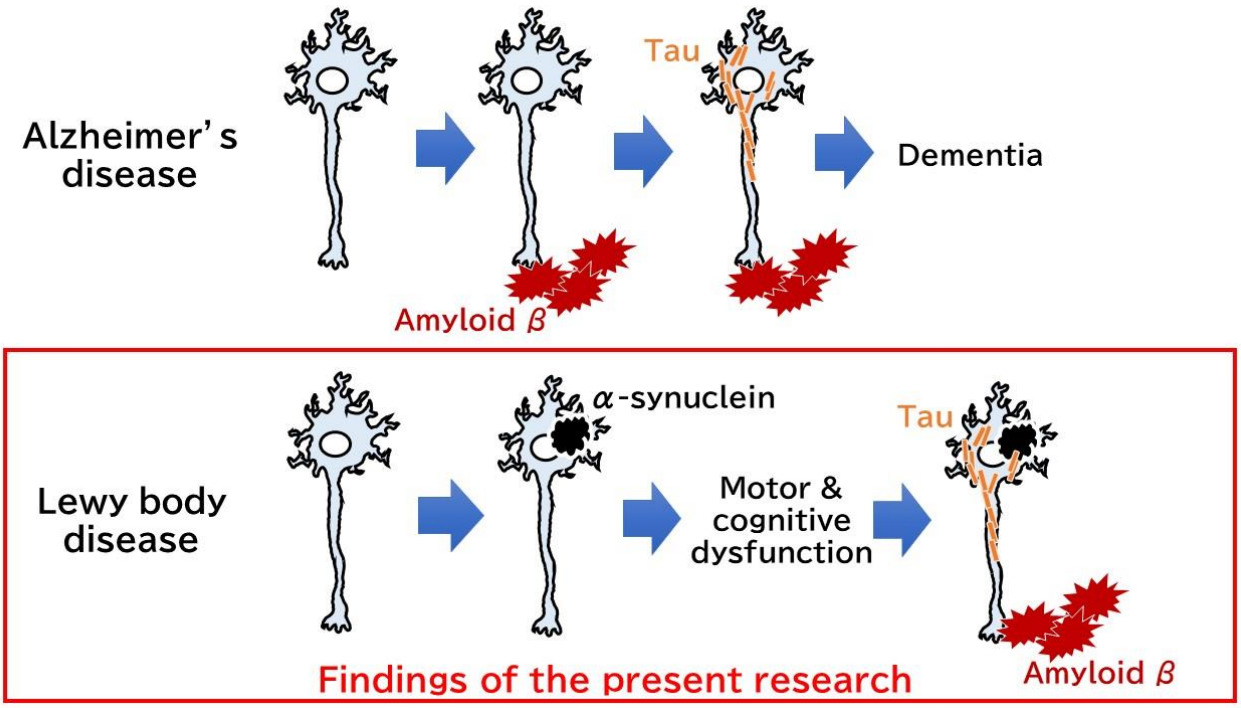
News Release

Blood-based Assessment of Comorbid Alzheimer's Disease Pathology in Lewy Body Disease: Comparative Analysis of Patients and High-risk Individuals

Key Points

- Lewy body disease includes Parkinson's disease and dementia with Lewy bodies, which are neurodegenerative disorders associated with intra-neuronal α-synuclein accumulation.
- Recent studies have shown that in addition to α-synuclein, comorbid Alzheimer's disease pathology contributes to the onset and progression of dementia in Lewy body disease, potentially serving as a treatment target.
- This study analyzed plasma biomarkers of Alzheimer's disease (amyloid-β and phosphorylated tau 181) and that of neurodegeneration (neurofilament light chain) in 84 patients with Parkinson's disease, 16 patients with dementia with Lewy bodies, 82 high-risk individuals (prodromal stage) who were identified in our previous research, and 37 low-risk individuals (healthy controls).
- Patients with Parkinson's disease and dementia with Lewy bodies showed changes related to Alzheimer's disease, while high-risk individuals did not.
- Elevated levels of the neurodegeneration marker were observed in patients with Parkinson's disease, dementia with Lewy bodies, as well as in high-risk individuals.
- The results suggest that comorbid Alzheimer's disease pathology in Lewy body disease is not present in the prodromal phase but develops after disease onset. Additionally, the neurodegeneration marker neurofilament light chain may potentially detect α-synuclein-induced neurodegeneration even in the prodromal phase.



Summary

A research group led by Professor Masahisa Katsuno and Dr. Keita Hiraga (lead author) from the Department of Neurology, Nagoya University Graduate School of Medicine, in collaboration with the National Center for Geriatrics and Gerontology and National Institutes for Quantum Science and Technology, analyzed the coexistence of Alzheimer's disease in the pre- and post- onset stages of Lewy body disease using plasma biomarkers from patients and high-risk individuals.

Lewy body disease is a neurodegenerative disorder characterized by intra-neuronal accumulation of α-synuclein. Recent post-mortem brain studies have reported that in addition to α-synuclein, comorbid Alzheimer's disease pathology (amyloid-β and tau) contributes to the onset and progression of dementia in Lewy body disease. However, it was unclear when these Alzheimer's disease-related changes emerge in Lewy body disease.

This study measured plasma biomarkers of Alzheimer's disease (amyloid-β and phosphorylated tau 181) and that of neurodegeneration (neurofilament light chain) in 84 patients with Parkinson's disease, 16 patients with dementia with Lewy bodies, 82 high-risk individuals (prodromal stage) who were identified using a questionnaire-based screening developed by Professor Katsuno's research group (Hattori et al. ***J Neurol*** 267(5):1516-1526, 2020, Hattori et al. ***NPJ Parkinsons Dis*** 9:1-9, 2023), and 37 low-risk individuals (healthy controls). The results showed that patients with Parkinson's disease and dementia with Lewy bodies exhibited changes related to Alzheimer's disease, while high-risk individuals did not show changes in plasma biomarkers of Alzheimer's disease.

However, the neurodegeneration marker was elevated in high-risk individuals, as well as patients with Parkinson's disease and dementia with Lewy bodies.
These findings suggest that comorbid Alzheimer's disease pathology in Parkinson's disease and dementia with Lewy bodies is not present in the prodromal phase but begins to develop after the onset. Furthermore, the results indicate that the neurodegeneration marker neurofilament light chain may potentially detect α-synuclein-induced neurodegeneration from the prodromal phase.
This research will be published in the U.S. scientific journal "npj Parkinson's Disease" on July 31, 2024.

Research Background

Recent research has shown that in neurodegenerative diseases, including dementia, the accumulation of abnormal proteins precedes clinical symptoms by more than 20 years, highlighting the importance of suppressing pathology before symptom onset (Figure 1). Lewy body disease is a neurodegenerative disorder characterized by intra-neuronal accumulation of α-synuclein, encompassing Parkinson's disease and dementia with Lewy bodies. Parkinson's disease, affecting an estimated 200,000 people in Japan, presents with motor symptoms such as bradykinesia and cognitive impairment. Dementia with Lewy bodies, the second most common form of dementia after Alzheimer's disease, affects an estimated 600,000-900,000 people in Japan and is characterized by cognitive impairment with visual hallucinations and Parkinsonism. Recent attention has focused on prodromal symptoms of Lewy body disease, such as autonomic dysfunction (e.g., constipation), olfactory dysfunction, and REM sleep behavior disorder, which appear 10-20 years before the onset of motor or cognitive symptoms.

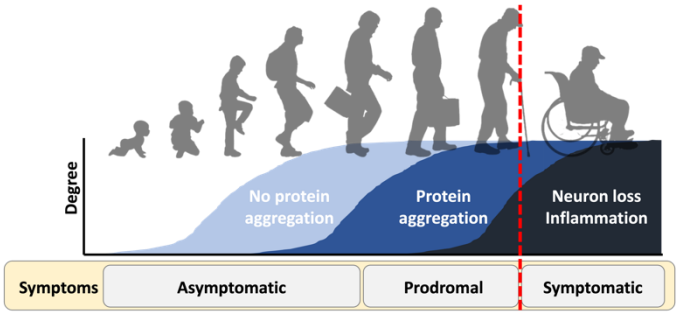


Figure 1. Time-course of neurodegeneration

Our previous research identified that 5.7% of healthy individuals over 50 years old have two or more prodromal symptoms, defining this group as high risk for developing Lewy body disease (Hattori et al. ***J Neurol*** 267(5):1516-1526, 2020). High-risk individuals had mild cognitive decline and hyposmia compared with low-risk individuals with no prodromal symptoms. Approximately one-third of the high-risk individuals had deficits in DaT-SPECT or cardiac MIBG scintigraphy, and the prevalence of abnormalities on DaT-SPECT was 4 times higher in the high-risk individuals than that in the low-risk individuals (Hattori et al. ***NPJ Parkinsons Dis*** 9:1-9, 2023) (Figure 2).

While α-synuclein pathology is known to contribute to dementia in Parkinson's disease and dementia with Lewy bodies, previous post-mortem studies have shown that over 70% of patients with dementia with Lewy bodies and 50% of patients with Parkinson's disease dementia also have comorbid Alzheimer's disease pathology. Given the recent approval of antibody treatments for Alzheimer's disease, understanding the comorbid Alzheimer's pathology in Lewy body disease is crucial as it may serve as a potential treatment target.

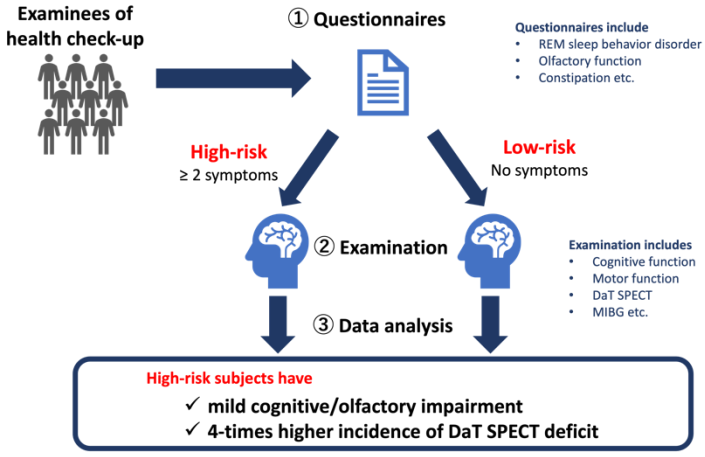
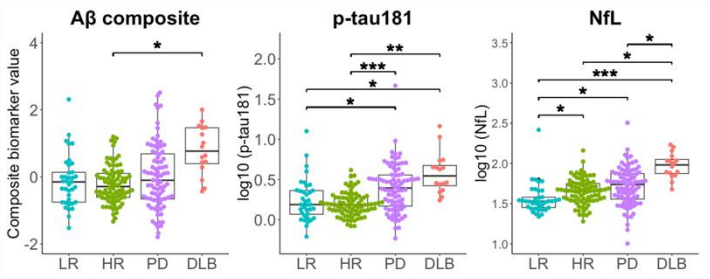


Figure 2. High-risk cohort study of Lewy body disease

This study aimed to elucidate the comorbid Alzheimer's disease pathology in the pre- and post-onset stages of Lewy body disease by measuring plasma biomarkers for Alzheimer's disease (amyloid-β and phosphorylated tau 181) and neurodegeneration (neurofilament light chain) in 84 patients with Parkinson's disease, 16 patients with dementia with Lewy bodies, 82 high-risk individuals, and 37 low-risk individuals.

Research Results

The study found that patients with Parkinson's disease with cognitive impairment and patients with dementia with Lewy bodies showed elevated levels of Alzheimer's disease-related biomarkers (Aβ composite and p-tau181) compared to low-risk individuals. However, high-risk individuals did not show an increase in these biomarkers. The neurodegeneration marker neurofilament light chain (NfL) was elevated in patients with Parkinson's disease and dementia with Lewy bodies and high-risk individuals compared to low-risk individuals (Figure 3).



LR, Low-risk; HR, High-risk; PD, Parkinson's disease; DLB, Dementia with Lewy bodies

Figure 3. Levels of plasma biomarkers

Classifying the progression of Alzheimer's pathology based on the presence (+) or absence (-) of amyloid-β (A), tau (T), and neurodegeneration (N) revealed that Parkinson's disease and dementia with Lewy bodies patients had a higher proportion of A+T+(N)+, indicating comorbid Alzheimer's pathology.

In contrast, high-risk individuals showed a higher proportion of A-T-(N)+, suggesting neurodegeneration without Alzheimer's pathology (Table 1).

	Low-risk (LR)	High-risk (HR)	PD	DLB	*p*-values		
					LR vs HR	LR vs PD	LR vs DLB
A-T-(N)-, n (%)	19 (51.4)	31 (36.9)	25 (28.4)	0 (0.0)	0.195	0.039	<0.001
A+T-(N)-, n(%)	5 (13.5)	5 (6.0)	2 (2.3)	0 (0.0)	0.345	0.142	0.345
A+T+(N)-, n (%)	1 (2.7)	0 (0.0)	2 (2.3)	0 (0.0)	1.000	1.000	1.000
A+T+(N)+, n (%)	1 (2.7)	2 (2.4)	24 (27.3)	11 (64.7)	1.000	0.002	<0.001
A+T-(N)+, n(%)	1 (2.7)	5 (6.0)	3 (3.4)	2 (11.8)	0.799	1.000	0.670
A-T+(N)-, n(%)	3 (8.1)	2 (2.4)	5 (5.7)	0 (0.0)	0.832	0.832	0.832
A-T-(N)+, n(%)	4 (10.8)	34 (40.5)	13 (14.8)	2 (11.8)	0.004	1.000	1.000
A-T+(N)+, n(%)	3 (8.1)	5 (6.0)	14 (15.9)	2 (11.8)	0.839	0.783	0.839

Table 1. AT(N) classification

In patients with Parkinson's disease, Aβ composite levels were associated with cognitive function, while p-tau181 levels were associated with motor and non-motor symptoms. NfL levels were associated with cognitive function, motor symptoms, and non-motor symptoms. These findings suggested that Alzheimer's disease-related changes affect both cognitive and motor functions. High-risk individuals showed no correlation between these biomarkers and clinical symptoms, but those with higher NfL levels had a higher rate of abnormal cardiac MIBG scintigraphy images.

These results suggest that comorbid Alzheimer's disease pathology in Parkinson's disease and dementia with Lewy bodies begins to appear after the disease onset rather than in the prodromal phase. Additionally, the elevation of NfL in high-risk individuals, despite the absence of increased Alzheimer's disease-related biomarkers, suggests that NfL may potentially detect α-synuclein-induced neurodegeneration in the prodromal phase.

Research Summary and Future Perspective

This study suggests that Alzheimer's disease-related changes in Lewy body disease begin to appear after the disease onset rather than in the prodromal phase. With the recent introduction of anti-amyloid-β antibody treatments for early-stage Alzheimer's disease patients, comorbid Alzheimer's pathology in Lewy body disease may become a future treatment target. Our research group is currently conducting annual evaluations of high-risk individuals for Lewy body disease. We aim to elucidate further when comorbid Alzheimer's pathology appears in Lewy body disease and how it affects neurological prognosis by longitudinally following and evaluating both Lewy body disease patients and high-risk individuals.

Acknowledgement
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