News Release

Title

Clinico-imaging features of subjects at risk of Lewy body disease in NaT-PROBE baseline analysis

Key Points

• Lewy body disease (LBD) is a group of neurodegenerative disorders associated with intra-neuronal accumulation of alpha-synuclein, including Parkinson's disease and dementia with Lewy bodies (DLB).

• Prodromal symptoms, such as dysautonomia, REM sleep behavior disorder (RBD), and hyposmia, antecede the onset of motor of cognitive dysfunction by 10-20 years.

• We examined motor function, cognitive function, dopamine transporter scintigraphy (DaT-SPECT), and cardiac MIBG scintigraphy in 69 high-risk subjects with two or more prodromal symptoms (dysautonomia, RBD, and hyposmia) and 32 low-risk subjects without prodromal symptoms, whom were identified through a questionnaire survey of health checkup.

• The high-risk subjects had significantly worse scores on Stroop test, line orientation test, and the Odor Stick Identification Test for Japanese than the low-risk subjects.

• The prevalence of abnormalities on DaT-SPECT was higher in the high-risk group than in the low-risk group (24.6% vs. 6.3%, p=0.030).

• A decrease uptake on DaT-SPECT was associated with motor impairment, and MIBG scintigraphy defects were associated with hyposmia.

• Our results indicate that a combination of a simple questionnaire survey and imaging tests, such as DaT-SPECT and MIBG scintigraphy, was feasible for assessing the risk of Lewy body disease in a healthy population.

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine have revealed that a combination of a simple questionnaire survey of health checkup examinees and imaging tests, such as DaT-SPECT and MIBG scintigraphy, was feasible for assessing the risk of Lewy body disease.

Lewy body disease (LBD) is a group of neurodegenerative disorders associated with intra-neuronal accumulation of alpha-synuclein. LBD includes Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Prodromal symptoms, such as dysautonomia, hyposmia, and RBD, antecede the onset of motor or cognitive

dysfunction by 10–20 years. To date, many risk factors and prodromal markers of LBD have been reported, but little has been reported on appropriate methods for identifying high-risk individuals before developing neurological symptoms. The research team headed by Prof. Katsuno conducted a survey of prodromal symptoms in healthy individuals who visited Kumiai Kosei Hospital (Takayama, Gifu) or Daido Clinic (Nagoya, Aichi) for their annual health checkup. In our previous study, approximately 8% of health checkup examinees with ≥50 years old had ≥2 prodromal symptoms (dysautonomia, hyposmia, and RBD), and we defined them as high-risk subjects (Hattori et al. ***J Neurol*** 267(5):1516-1526, 2020). Here we examined neurological and imaging indices, including DaT-SPECT and MIBG scintigraphy, in the 69 high-risk individuals and 32 low-risk individuals without prodromal symptoms, to clarify the manifest LBD-related changes at possible prodromal subjects and to verify the plausibility of our screening methods using questionnaires. The present study revealed that high-risk subjects had mild cognitive decline and hyposmia compared to low-risk subjects, and the prevalence of abnormalities on DaT-SPECT was higher in the high-risk group, indicating progressive dopamine neurodegeneration in the brain.

Although it is difficult to identify high-risk subjects without neurological symptoms in daily medical practice, our study showed that a registry linked to a health checkup system and detailed imaging tests such as DaT-SPECT and MIBG scintigraphy can be used to assess the risk of developing neurodegenerative diseases and dementia.

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Research Background

Molecular pathological changes precede the onset of neurological symptoms by more than 20 years in various neurodegenerative diseases (Fig. 1). Lewy body disease (LBD) is a group of neurodegenerative disorders associated with intra-neuronal accumulation of alpha-synuclein. LBD includes Parkinson's disease (PD) and dementia with Lewy bodies (DLB). In Japan, number of patients with PD and DLB are estimated to be 200,000 and 600,000-900,000, respectively. Patients with LBD have a progressive motor and cognitive decline, and various medicines have been used in the treatment

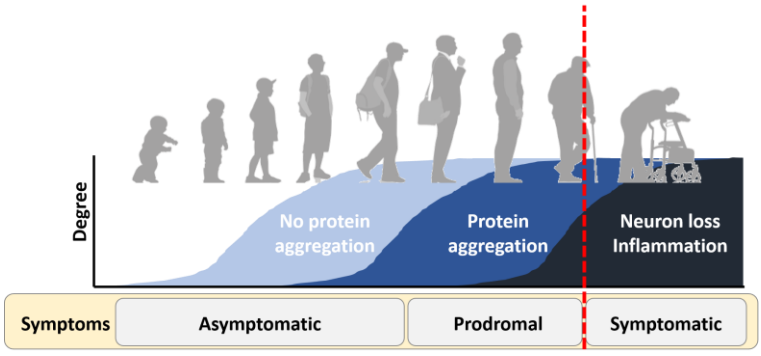

Figure 1. Time-course of neurodegeneration

of LBD, but there is no therapy which suppresses the disease progression during the pre-manifest stage of LBD. Initially levodopa controls motor symptoms well, but motor complications, such as dyskinesia and wearing off, occur frequently as the disease progresses. Because > 50% of neurons in the substantia nigra are already lost at the clinical diagnosis of PD, earlier detection and treatment of individuals at greater risk of developing PD is important.
Prodromal symptoms, such as dysautonomia, hyposmia, and REM sleep behavior disorder (RBD), antecede the onset of motor or cognitive dysfunction by 10–20 years. In addition, DaT SPECT and MIBG scintigraphy may help diagnosing patients with LBD at a very early stage. To date, many risk factors and prodromal markers of LBD have been reported, but little has been reported on the prevalence of prodromal symptoms in the Japanese general population and the appropriate method for identifying high-risk individuals before developing neurological symptoms was unknown.

In our previous study using questionnaires on prodromal symptoms, we found that approximately 8% of health checkup examinees with ≥ 50 years old had ≥ 2 prodromal symptoms (dysautonomia, hyposmia, and RBD), and defined them as high-risk subjects (Fig. 2, Hattori et al. ***J Neurol*** 267(5):1516-1526, 2020 modified). Here we analyzed neurological and imaging indices, including DaT-SPECT and MIBG scintigraphy, in the high-risk individuals with prodromal symptoms as well as low-risk individuals without prodromal symptoms, to clarify the manifest LBD-related changes at possible prodromal subjects and to verify the plausibility of our screening methods using questionnaires.

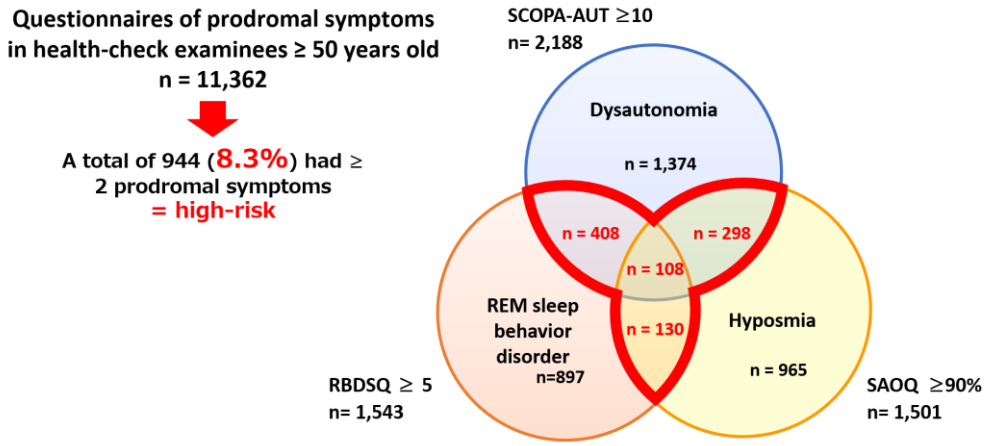

Figure 2. Questionnaire-based evaluation of risk for Lewy body disease

Research Results

The present study revealed that high-risk subjects with two or more prodromal symptoms had mild cognitive decline and hyposmia compared to low-risk subjects without prodromal symptoms. The prevalence of abnormalities on DaT-SPECT was higher in the high-risk group, indicating that dopamine

neurodegeneration occurs even at the prodromal stage (Fig. 3). A decreased uptake on DaT-SPECT was associated with motor impairment, and MIBG scintigraphy defects were associated with hyposmia (Fig. 4). In addition, high-risk subjects who showed abnormalities in both DaT-SPECT and MIBG scintigraphy were approximately 10 years older than other groups, and had more severe motor impairment, cognitive decline, and olfactory dysfunction, suggesting that LBD-related pathological changes developed more extensively in such subjects and possibly closer to the onset of LBD than in other groups.

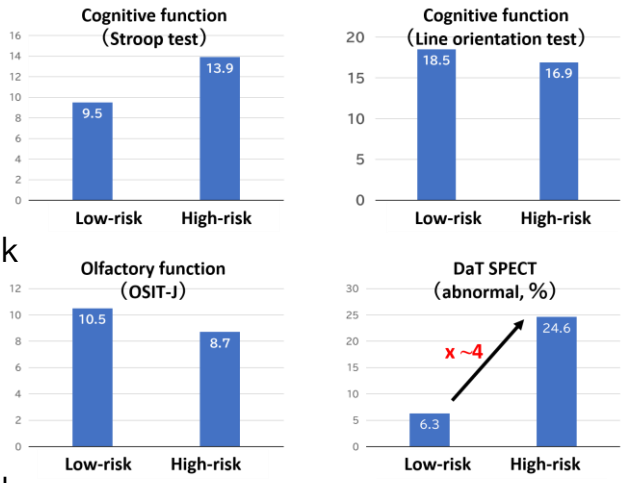

Figure 3. Neurological and imaging indices of the participants

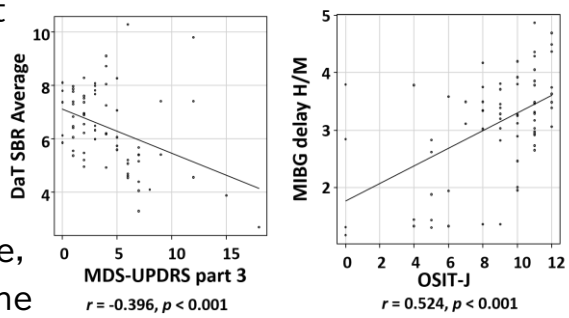

Figure 4. Correlation between imaging and neurological function

The clinical course of PD is diverse, especially in the early stages of the disease, with some patients having predominantly motor deficits and less prominent non-motor symptoms, and others having predominantly non-motor symptoms and less prominent motor deficits. Since neurodegeneration is mild at the prodromal stage compared with patients with LBD, there are many cases in which only one of DaT-SPECT and MIBG scintigraphy show abnormalities. We found that the simultaneous evaluation of DaT-SPECT and MIBG scintigraphy may capture a wide range of individuals with prodromal LBD. Although it has been difficult to identify high-risk subjects without neurological symptoms in daily medical practice, our study showed that a registry linked to a health checkup system and detailed imaging tests such as DaT-SPECT and MIBG scintigraphy can be used to assess the risk of developing neurodegenerative diseases and dementia.

Research Summary and Future Perspective

Our study revealed that high-risk subjects with two or more prodromal symptoms had mild cognitive decline and hyposmia compared to low-risk subjects, and the prevalence of abnormalities on DaT-SPECT was higher in the high-risk group. We are currently conducting a clinical study titled “Study on efficacy and safety of zonisamide in at-risk subjects of Lewy body disease” in patients with prodromal LBD detected in this study (Fig. 5). Zonisamide, which was selected as the study drug, is widely used in daily medical practice as a previously approved drug for PD and DLB, and has been reported to show

neuroprotective effects in basic studies using rats, mice, and cells. We expect that zonisamide would delay the onset of LBD by administering it very early to patients with prodromal LBD.

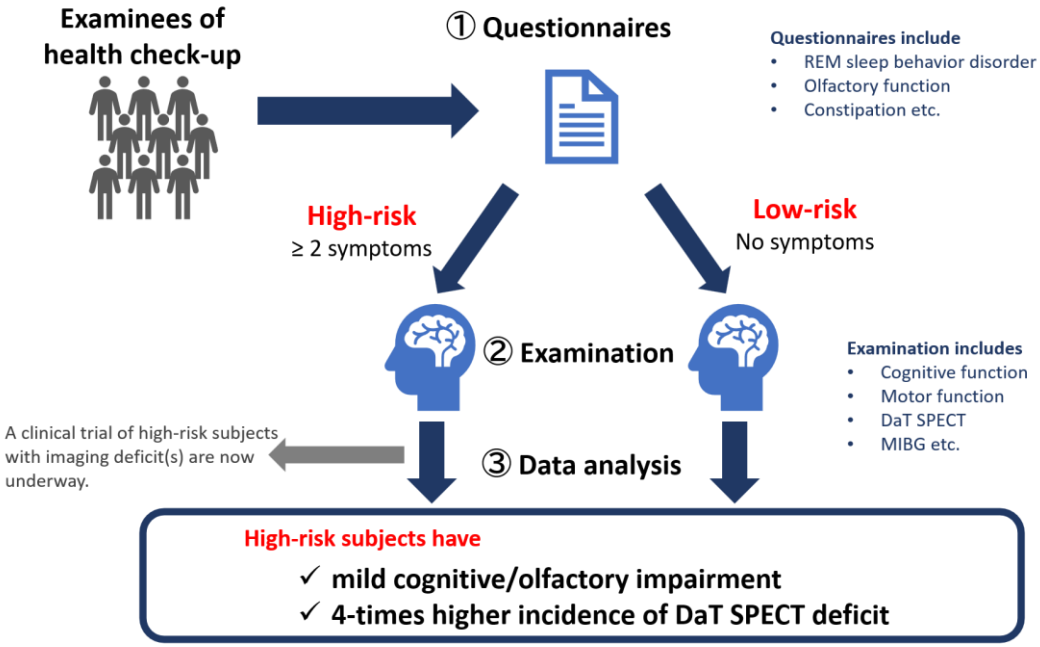

Figure 5. Summary of current study

Publication

Makoto Hattori, Keita Hiraga, Yuki Satake, Takashi Tsuboi, Daigo Tamakoshi, Maki Sato, Katsunori Yokoi, Keisuke Suzuki, Yutaka Arahata, Akihiro Hori, Motoshi Kawashima, Hideaki Shimizu, Hiroshi Matsuda, Katsuhiko Kato, Yukihiko Washimi, and Masahisa Katsuno.
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