News Release

Title

Subjects at risk of Parkinson's disease in health checkup examinees: cross-sectional analysis of baseline data of the NaT-PROBE study

Key Points

- **Lewy body disease (LBD) is a neurodegenerative disorder associated with intra-neuronal accumulation of alpha-synuclein. LBD includes 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.**
- **Here we found that approximately 6% of the population aged 50 years or older had ≥ 2 core prodromal symptoms: dysautonomia, hyposmia, and RBD.**
- **Such at-risk subjects also had worse scores of questionnaires about depression and daytime sleepiness, indicating that they had multiple prodromal symptoms similar to patients with PD and DLB.**
- **Male subjects in the at-risk group showed lower hemoglobin and cholesterol levels, which was consistent with the results of previous studies on epidemiology of PD.**
- **Questionnaire is a simple, non-invasive, and inexpensive method to screen the risk of LBD in a large community-based population.**
- **We are currently performing a detailed analysis of the at-risk subjects we identified, and preparing a preventive clinical research on LBD.**

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.) have revealed the prevalence of prodromal symptoms in the Japanese general population, and that approximately 6% of the population aged 50 years or older had ≥ 2 core prodromal symptoms: dysautonomia, hyposmia, and REM sleep behavior disorder (RBD). This work was published online in *Journal of Neurology* on February 7, 2020.

Lewy body disease (LBD) is a neurodegenerative disorder 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 the prevalence of prodromal symptoms in the Japanese general population.

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. They found that approximately 6% of the population aged 50 years or older had ≥ 2 core prodromal symptoms: dysautonomia, hyposmia, and RBD. In addition, male subjects in the at-risk group showed lower hemoglobin and cholesterol levels, which was consistent with the results of previous studies on epidemiology of PD.

In general, the main purpose of health checkup is to detect cancers and lifestyle-related diseases at an early stage, but little has been done to assess the risk of neurodegenerative disorders. It is difficult to identify at-risk subjects of LBD in the daily medical practice, but our study showed that a questionnaire is a simple, non-invasive, and appropriate method to identify such at-risk subjects in a large medical checkup cohort in Japan.

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 neurodegenerative disorder 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 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.

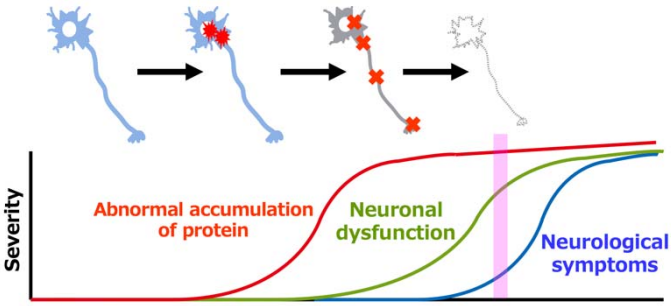

Fig.1 Preclinical progression of neurodegenerative diseases

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. 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.

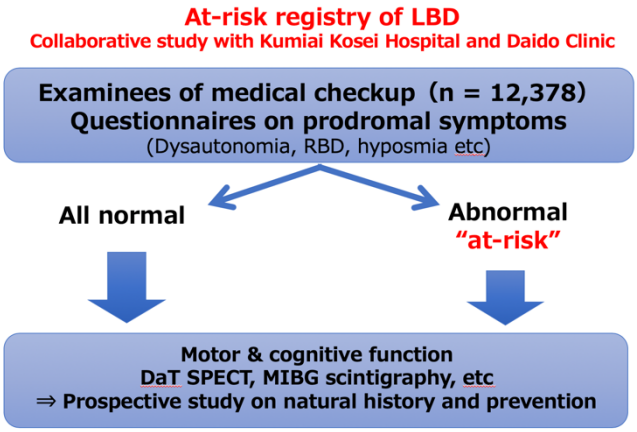

Fig.2 Study design

Here we 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 (Fig. 2).

Research Results

A total of 4,953 of 12,378 (40.0%) participants completed all the questionnaires. Among 2,726 subjects who were ≥ 50 years of age, 155 subjects (5.7%) had ≥ 2 core prodromal symptoms: dysautonomia, hyposmia, and RBD. We defined them as the at-risk group (Fig. 3). Such at-risk subjects also had worse scores of questionnaires about depression and daytime sleepiness, indicating that they had multiple prodromal symptoms similar to patients with PD and DLB (Table 1). Male subjects in the at-risk group showed lower hemoglobin and cholesterol levels, which was consistent with the serum biomarkers of prodromal-phase PD reported in previous studies (Table 2). It is difficult to identify at-risk subjects of LBD in the daily medical practice, but our study showed that a questionnaire is a simple, non-invasive, and appropriate method to identify such at-risk subjects in a large medical checkup cohort in Japan.

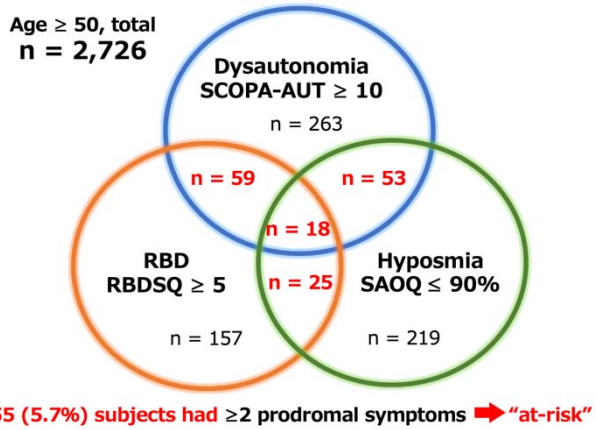

Fig. 3 Venn diagram of questionnaires on prodromal symptoms

	Age ≥50, total	At-risk group	Normal group	PD/DLB patients
Number (n, M:F)	2726 (1531 : 1195)	155 (113:42)	1653 (900:753)	34 (18:16) (PD 30: DLB 4)
Age (years)	58.8 ± 6.2	61.4 ± 7.1	58.6 ± 6.0	68.9 ± 7.7
PASE (Physical activity)	132.7 ± 82.9	123.1 ± 79.5	133.5 ± 83.0	118.4 ± 80.3
SCOPA-AUT (Dysautonomia)	5.3 ± 4.2	12.5 ± 5.2*	3.6 ± 2.5	8.9 ± 6.4
SAOQ (Hyposmia, %)	96.1 ± 11.9	82.4 ± 19.8*	99.5 ± 1.6	72.9 ± 34.3
RBDSQ (REM sleep behavior disorder)	1.9 ± 2.0	5.0 ± 2.7*	1.3 ± 1.2	3.8 ± 2.3
BDI-Ⅱ (depression)	6.6 ± 6.2	12.0 ± 8.3*	4.5 ± 3.8	9.3 ± 5.4
ESS (daytime sleepiness)	7.6 ± 4.3	9.6 ± 5.0*	6.3 ± 3.2	7.8 ± 3.8
Prodromal PD score	1.35 ± 3.00 (0.13-67.54)	6.39 ± 9.64* (0.35-67.54)	0.64 ± 0.69 (0.13-13.37)	

Table1. Scores of questionnaires on prodromal symptoms in the at-risk group

	At-risk group	Normal group	*p*-value
Number	113	667	
Age (years)	62.5 ± 7.0	61.5 ± 5.2	0.067
WBC (10^3/μL)	5005 ± 1303	5323 ± 1397	**0.023**
Hb (g/dL)	14.8 ± 1.3	15.0 ± 1.1	**0.032**
RBC (10^4/μL)	466.9 ± 45.7	481.0 ± 37.3	**<0.001**
Hct (%)	43.3 ± 3.5	44.0 ± 2.9	**0.010**
Plt (10^4/μL)	21.2 ± 5.6	22.2 ± 5.0	0.121
UA (mg/dL)	6.14 ± 1.28	6.11 ± 1.21	0.789
Cre (mg/dL)	0.92 ± 0.32	0.89 ± 0.15	0.217
Glu (mg/dL)	102.7 ± 18.3	101.4 ± 22.4	0.548
HbA1c (%)	5.91 ± 0.68	5.93 ± 0.70	0.868
TG (mg/dL)	125.4 ± 84.8	125.6 ± 79.8	0.983
T-Cho (mg/dL)	198.2 ± 36.1	207.4 ± 32.9	**0.007**
HDL-Cho (mg/dL)	57.4 ± 15.2	58.9 ± 14.9	0.341
LDL-Cho (mg/dL)	114.5 ± 30.3	123.0 ± 28.9	**0.004**

Table2. Results of serological examinations in males

Research Summary and Future Perspective

We performed a questionnaire-based survey of prodromal symptoms of PD in a large medical checkup cohort in Japan, and identified subjects ≥ 50 years of age with ≥ 2 core prodromal symptoms: dysautonomia, hyposmia, and RBD. We are currently performing a detailed analysis of the motor function, cognitive function, and imaging (DaT SPECT and MIBG scintigraphy) on those at-risk subjects. Our preliminary results suggest that some of them have a deficit in either MIBG scintigraphy or DaT SPECT, even though they have no motor or cognitive decline. Thus, they may be appropriate targets for prediagnostic clinical research on LBD in the future.

Publication

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