Title Page

Title: Comorbid alpha synucleinopathies in idiopathic normal pressure hydrocephalus

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Declarations

Funding: The authors have no relevant financial or non-financial interests to disclose.

Conflicts of interest/Competing interests: Anri Sakurai, Taiji Tsunemi, Yuta Ishiguro, Ayami Okuzumi, Taku Hatano and Nobutaka Hattori have no conflict of interest to declare.

Availability of data and material: We will inform you individually if you wish.

Code availability: Not applicable

Authors' contributions: Anri Sakurai collected data, conducted statistical analysis, and wrote the draft. Yuta Ishiguro collected samples. Ayami Okuzumi conducted RT-QuIC. Taku Hatano edited the draft. Taiji Tsunemi Initiated and organized the project and finalized the manuscript. Nobutaka Hattori organized the project.

Ethics approval: This study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of Juntendo University.

Consent to participate: Informed consent was obtained from all individual participants.

Consent for publication: The participants have consented to the submission to the journal.

Abstract

Objectives: To determine the prevalence and clinical features of Parkinson's disease/PD dementia (PD/PDD) or dementia with Lewy bodies (DLB) in idiopathic normal pressure hydrocephalus (iNPH).

Methods: We retrospectively analyzed patients with iNPH who were admitted to the Department of Neurology, Juntendo University School of Medicine over the past 10 years. The diagnosis of iNPH and concomitant PD/PDD or DLB was established using the diagnostic criteria. Motor symptoms were assessed by the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) PartⅢ. 123I-ioflupane single photon emission computed tomography (DaTscan), cerebrospinal fluid real-time quaking-induced conversion-based assay (RTQuIC) for alpha synuclein aggregation.

Results: Seventy-nine patients met the criteria for iNPH. Of these, 34 patients developed iNPH without accompanying disorders (iNPHa; 43.0%), 23 patients developed iNPH with comorbid PD/PDD (iNPHc +

PD/PDD; 29.1%), and eight developed iNPH with comorbid DLB (iNPHc + DLB; 10.1%). Significant differences in facial expansion and upper limb parkinsonism were observed with comorbid either PD/PDD or DLB. The specific binding ratio of DaTscan was reduced in iNPHa ($p = 0.02$), but it reduced further with comorbid PD/PDD ($p < 0.01$) or DLB ($p < 0.01$). RT-QuIC was positive for all 13 comorbid PD/PDD and negative for all 19 iNPHa.

Conclusions: These results highlight that synucleinopathies coexist with iNPH. We can be differentiated by DaTscan and RT-QuIC and affect its clinical features.

Keywords: normal pressure hydrocephalus, Parkinson's disease, dementia with Lewy bodies, DaTscan, lumboperitoneal shunt surgery

Introduction

Normal pressure hydrocephalus (NPH) is a condition in which cerebrospinal fluid (CSF) shunting can improve a triad of symptoms including cognitive decline, gait disturbance, and urinary incontinence. NPH occurs as idiopathic NPH (iNPH) or secondary NPH due to a specific cause[1]. Usually, iNPH is difficult to diagnose because its symptoms are common in healthy aged individuals as well as in patients with several neurodegenerative disorders[2], [3]. One such disorder is Alzheimer's disease (AD)[4]. Typical iNPH-associated cognitive dysfunction is similar to what is described as the front-subcortical dementia[5]; however, the former also includes short memory disturbance, common in AD[6, 7]. Clinical similarities have prompted numerous studies on CSF biomarkers that can distinguish AD from iNPH[8].

It is clinically important because comorbid AD results in a poor outcome of lumboperitoneal shunt (LPS) surgery[9].

It has been reported that iNPH also accompanies synucleinopathies, such as Parkinson's disease (PD)[10], PD dementia (PDD), and dementia with Lewy bodies (DLB)[11]. The diagnosis of comorbid PD/PDD or DLB has also been challenging because parkinsonism is frequently observed in iNPH, suggesting that the intrinsic impairment of dopaminergic pathways [12], which has been reported recent studies (ref 24, 25). However, the prevalence and the effect of comorbid synucleinopathies on iNPH has never been examined in detail. In this study, we retrospectively analyzed the prevalence and clinical features of comorbid PD/PDD and DLB among the patients with iNPH.

Material and Methods

Participants

We retrospectively analyzed patients who were admitted to the Department of Neurology, Juntendo University School of Medicine from 2010 to 2019. Written informed consent was obtained from all patients. The study included iNPH patients who met the criteria for both probable iNPH and definite iNPH, according to the established clinical guidelines[13], depending on whether patients underwent LPS surgery or not because improvement after surgery is mandatory for definite iNPH in the Japanese guidelines[14]. The patients whose CSF showed Aβ42 < 500 pg/ml, total tau > 600 pg/ml, or phosphorylated tau > 60 pg/ml were excluded because of the possibility of co-existing Alzheimer's disease[15]. The diagnosis of PD was made when patients met the criteria for clinically established PD or clinically probable PD from the MDS-PD criteria with a small modification, which omits one exclusion criteria— "an alternative condition that causes Parkinson's symptoms" in the case of considering the comorbidity[16]. L-dopa responsiveness was confirmed by L-dopa challenge test as described in the criteria. The DLB patients met the criteria for probable DLB in the DLB criteria from the DLB consortium of Lewy bodies[17]. PD patients presenting with dementia were diagnosed as PDD according to the criteria[18]. The "one year rule" was used to separate PDD from DLB where the onset of dementia no later than 12 months of parkinsonism led to the diagnosis of DLB[17]; whereas, parkinsonism occurring for more than 12 months before the development of dementia suggested the diagnosis of PDD.

Radiological analysis

Myocardial uptake of metaiodobenzylguanidine (MIBG) was measured[19]. The patients were confirmed to not have taken monoamine oxidase B inhibitors, selective serotonin reuptake inhibitors, or antidepressant drugs. At 30 min and 3 hours after intravenous injection of ^{123}I-MIBG (MyoMIBG-I 123 injection, 111 MBq; FUJIFILM RI Pharma Co. Ltd.), planar and single photon emission computed tomography (SPECT) images were obtained by E-CAM dual-head gamma camera (Siemens Healthcare, Erlangen, Germany). The uptake was quantified by calculating the heart-to-mediastinum (H/M) ratio by setting regions of interest over the heart and the mediastinum on the anterior planar view of the chest. We conducted ^{123}I-ioflupane SPECT (DaTscan)[20] (**Fig 1**). In brief, about 3 hours after injection of approximately 185 MBq of ^{123}I-FP-CIT, projection data were acquired using a 128 × 128 matrix on a Siemens Symbia T16 equipped with a low-to-medium-energy general-purpose collimator (Siemens Healthcare, Erlangen, Germany). The projection data were acquired for 28 min. The SPECT data were reconstructed using the three-dimensional ordered subset expectation maximization method (iteration 8, subset 6) and corrected for attenuation by computed tomography (CT). The specific binding ratio (SBR) was semi-quantitatively calculated using DAT VIEW software (Nihon Medi-Physics, Tokyo, Japan) based on Bolt's method, by which SBR was calculated by dividing Cs by Cr, where Cs is the count concentration in the whole striatum and Cr is the count concentration in the whole brain.

Collection of CSF

CSF was collected by performing high-volume tap by lumbar puncture. All CSF samples were centrifuged at 4^{o}C, 1,690 g for 10 min for removing cells and debris. The supernatant fractions were then aliquoted, and stored in polypropylene tubes at −80^{o}C until biochemical analysis.

Real-time quaking-induced conversion (RT-QuIC)-based assay

The RT-QuIC-based assay was performed[21]. The RT-QuIC reaction buffer (RB) was composed of 100 mmol/L phosphate buffer (pH 7.4), 10 mmol thioflavin T (ThT), 0.1 mg/mL human recombinant full-length alpha-synuclein, and complete mini (Roche, Switzerland). Each well of a black 96-well plate with a clear bottom (Nalgene Nunc International, Fisher Scientific Ltd, UK) contained 90 μl of RB and 37 ± 3 mg of 0.5 mm zirconium/silica beads (Thistle Scientific Ltd, UK). The reaction was seeded with 15 μl of

CSF in 85 μl of RB. The plates were incubated in a BMG OPTIMA FluoSTAR plate reader (BMG LABTECH, Germany) at 30°C for 7 days with intermittent shaking cycle: double orbital with 1 min shake (200 rpm) and 14 min rest. ThT fluorescence was measured every 15 min[21]. Thirty-four CSF samples including 19 iNPH without accompanying disorders (iNPH alone, i.e., iNPHa), 13 iNPH with comorbid PD/PDD (iNPHc + PD/PDD), two iNPHc + DLB were analyzed.

Statistical analysis

Data were assessed for normality of distribution using the Shapiro–Wilk test, then for equality of variance using Levene's test. One-way ANOVA *post hoc* Dunnett's test was used to analyze the clinical features of iNPHc + PD/PDD or iNPHc + DLB compared with iNPHa. The Mann–Whitney U-test was used to compare the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III scores between the iNPHc and iNPHa groups. One-way ANOVA *post hoc* Steel Dawss test was used to analyze SBR calculated from DaTscan between the groups. Receiver operating characteristic curve (ROC) analysis was performed to evaluate the specificity and sensitivity of SBR. The optimum cut-off points were calculated using the Youden's index. All error bars represent standard deviation (SD) in the Figs. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using a standard spreadsheet software (JMP 14 and Prism 8).

Data availability

Summary data will be shared by qualified researchers.

Results

After excluding 10 patients due to the lack of improvement after tap test or LPS surgery, 79 patients remained. Then, we excluded 14 patients from iNPHa because five of them were suggested to have possible AD (6.3%) from the CSF analysis and nine iNPH patients presented with progressive supranuclear palsy (PSP)-like clinical features that met the MDS-PSP criteria (11.3%). Thirty-four patients (43.0 %) developed iNPHa. Twenty-three patients concomitantly had PD/PDD (28.6 %), and eight patients concomitantly had DLB (10.1%). There were no statistically significant differences in the

ages at onset, ages at diagnosis, and duration of illness between the groups (**Table 1**). Although the Mini-Mental State Examination (MMSE) scores, number and time of steps taken in Timed up and go test, and Evans' index were not different, comorbid PD/PDD or DLB decreased MIBG uptakes and increased positivity rate of RT-QuIC (**Table 2**). While myocardial MIBG uptakes in all 34 patients with iNPHa were normal (normal value for H/M ratio, ≥2.0), 20 out of 23 iNPHc + PD/PDD, all eight iNPHc + DLB patients showed reduced myocardial MIBG uptake. No patient had a history of diabetes mellitus or heart disease. The results of the CSF RT-QuIC analysis revealed that 19 out of 19 iNPHa were negative, whereas 13 out of 13 iNPHc + PD/PDD, and two out of two iNPHc + DLB were positive. In terms of parkinsonism assessed by MDS UPDRS PartⅢ, the total scores were decreased with synucleinopathies (p < 0.01 for both) (**Table 3**). Especially scores in facial expression (p = 0.03 for iNPHc + PD/PDD, p = 0.02 for iNPHc + DLB) and scores in upper-limb rigidity or akinesia were reduced. SBR on DaTscan reduced in iNPHa compared to healthy controls (p = 0.02) (**Fig 1a, b**). Comorbid PD/PDD or DLB further decreased striatal uptake compared to patients with iNPHa (p < 0.01 for both) (**Fig 1a, b**). The area under the curve from the ROC curves of SBRs for the detection of iNPHa vs. control was 0.75 (**Fig 1c**), that of iNPHc + PD/PDD vs. iNPHa was 0.90 (**Fig 1d**), and that of iNPHc + DLB vs. iNPHa was 0.96 (**Fig 1e**). The optimum cut-off point of SBRs for the detection of iNPHa vs. control was 4.25 (specificity 83.3%, sensitivity 64.7%) (**Fig 1c**), that of iNPHc + PD/PDD vs. iNPHa was 3.39 (specificity 87.5%, sensitivity 85.7%) (**Fig 1d**), and that of iNPHc + DLB vs. iNPHa was 2.16 (specificity 100%, sensitivity 85.7%) (**Fig 1e**).

Discussion

Among 79 patients with iNPH, we found that 23 patients met the criteria for PD/PDD (29.1 %), and eight patients met the criteria for DLB (10.1 %). The rates of the comorbid synucleinopathies in patients with iNPH are more than previously reported[11]. A previous study demonstrated some patients with iNPH that presented parkinsonism, suggesting the comorbidity of PD[11], but pathological examination revealed co-existing neurodegeneration (like PD or PSP) only in the patients who were finally diagnosed with comorbid diseases[22], and most iNPH cases accompanied with pathological changes only for those associated with hydrocephalus, suggesting that simple mechanical pressure against the nigra-striatum

pathway may cause extrapyramidal symptoms[23]. Recent studies also confirmed the high prevalence of parkinsonism[24] and the impairment of the nigra-striatum pathway in iNPH[25]; however, both of them did not take comorbid synucleinopathies into account. Our further investigation using functional imaging and biochemical analysis revealed the high prevalence of comorbid synucleinopathies, and it modified clinical symptoms in iNPH by adding "upper" parkinsonism in already existing iNPH-associated lower parkinsonism (**Table 3**). To further investigate the dopaminergic nigrostriatal pathway in iNPH, we conducted a DaTscan. Given that striatum DaT binding decreases with age, we analyzed the relationship between age and SBR and found a small but statistically significant reduction in SBR in iNPHa with respect to healthy controls ($p = 0.02$) (**Fig 1a, b**), indicating an impaired dopaminergic pathway, which is consistent with previous reports[25, 26]. Our analysis further revealed that comorbid PD/PDD or DLB further decreased SBR compared to patients with iNPHa due to the degeneration of dopaminergic neurons, and establishing DaTscan as a diagnostic marker not only for detecting iNPHa but also for identifying comorbid PD/PDD or DLB in iNPH (**Fig 1a, b**).

Recently, two diagnostic techniques—cardiac ^{123}I-MIBG scintigraphy[16, 27] and RT-QuIC based assay[21, 28]—have been demonstrated to be useful for confirming synucleinopathies. Indeed, we found that 20 out of 23 patients, who were clinically diagnosed as having PD based on our criteria, revealed decreased myocardial MIBG uptake, showing similar positive rates in sporadic PD[29]. Furthermore, all 19 out of 19 iNPHa were negative for RT-QuIC; whereas, 13 out of 13 iNPHc + PD/PDD, and two out of two iNPHc + DLB were positive (**Table 2**), highlighting the high correlation between the clinical symptoms and these diagnostic techniques, and strongly indicating the existing Lewy pathology in these patients.

However, this study has several limitations. First, it is a retrospective study, and many clinical data were extracted from electronic health records; therefore, some of the data are incomplete. RT-QuIC, for example, could be applied only for a small number of participated patients due to insufficient sample availability; however, its results perfectly match our clinical diagnosis, demonstrating our diagnostic reliability. In addition, Frontal Assessment Battery and Wechsler's Adult Intelligence Scale-Ⅲ test may be needed for further evaluation of frontal lobe function and psychomotor speed. Therefore, we applied cardiac MIBG scintigraphy and CSF RT-QuIC for synuclein aggregates, both of which have recently

proved to detect the existence of PD[16, 21] and DLB[27, 28] with a relatively high sensitivity and specificity, and the results from both tests were in line with the clinical diagnosis, suggesting that the diagnostic criteria could still be applied (with a small modification) in patients having iNPH. Third, in terms of the study population, patients were mainly recruited from our outpatient department, potential recruitment bias may exist. The actual prevalence of alpha synucleinopathies in iNPH would require further investigation.

In conclusion, our studies revealed that some patients with iNPH accompany alpha synucleinopathies. Comorbid synucleinopathies added facial and upper-limb parkinsonism in existing lower-parkinsonism in NPH. DaTscan, cardiac MIBG scintigraphy, and RT-QuIC were useful for detecting synucleinopathies in iNPH.

Conflict of interest

Anri Sakurai, Taiji Tsunemi, Yuta Ishiguro, Ayami Okuzumi, Taku Hatano, and Nobutaka Hattori have no conflict of interest to declare.

Table 1. Baseline characteristics of the study participants

	iNPHa (n = 34)	iNPHc + PD/PDD (n = 23)	*p*	iNPHc + DLB (n = 8)	*p*
sex (female/male)	10/24	16/7		4/4	
age at onset (means ± SD)	71 ± 9.4	68.5 ± 6.6	*0.58*	71.6 ± 6.8	*0.99*
age at diagnosis (means ± SD)	75.6 ± 6.2	76.6 ± 5.0	*0.87*	75.8 ± 5.4	*0.10*
duration of illness (means ± SD)	4.5 ± 7.4	8.0 ± 4.9	*0.10*	4.1 ± 3.1	*0.10*

Table 1. **Baseline characteristics of the study participants**

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; PDD, Parkinson' disease with dementia; DLB, dementia with Lewy bodies; n, number; SD, standard deviation

One-way ANOVA *post hoc* Dunnett's test was used to analyze clinical features of iNPHc + PD/PDD or iNPHc + DLB compared with iNPHa. Significant *p* values are indicated in red.

Table 2. Clinical features of the study participants

	iNPHa	iNPHc + PD/PDD		iNPHc + DLB	
	(n = 34)	(n = 23)	*p*	(n = 8)	*p*
MMSE (means ± SD)	22.7 ± 4.9	22.0 ± 5.9	0.97	16.7 ± 7.4	0.19
Timed up & go steps (means ± SD)	23.1 ± 17.3	32.1 ± 15.8	0.42	18.0 ± 9.4	0.92
Timed up & go time (means ± SD)	32.4 ± 33.6	38.3 ± 42.9	0.95	15.4 ± 5.1	0.79
Evans' index (means ± SD)	0.36 ± 0.03	0.37 ± 0.04	0.37	0.37 ± 0.02	0.45
^{123}I-MIBG (normal/reduced)	34/0	3/20	< 0.01	0/8	< 0.01
^{123}I-MIBG early H/M ratio (means ± SD)	3.21 ± 0.54	1.86 ± 0.58	< 0.01	1.49 ± 0.18	< 0.01

^{123}I-MIBG delayed H/M ratio (means ± SD)	3.31 ± 0.70	1.71 ± 0.90	< 0.01	1.27 ± 0.14	< 0.01
RT-QuIC (positive/negative)	0/19	13/0	< 0.01	2/0	< 0.01

Table 2. Clinical features of the study participants

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies; n, number; SD, standard deviation; MMSE, Mini-Mental State Examination; LPS, lumboperitoneal shunt; MIBG, 123I-meta-iodo-benzyl-guanidine; H/M, heart-to-mediastinum; RT-QuIC, real-time quaking-induced conversion

One-way ANOVA *post hoc* Dunnett's test was used to analyze clinical features of iNPHc + PD/PDD or iNPHc + DLB compared with iNPHa. Significant *p* values are indicated in red.

Table 3. The scores of MDS UPDRS part III

Items (means ± SD)	iNPHa (n = 34)	iNPHc + PD/PDD (n = 23)	*p*	iNPHc + DLB (n = 8)	*p*
speech	0.6 ± 0.72	1.3 ± 1.13	*0.01*	0.9 ± 1.05	*0.44*
facial expression	0.8 ± 0.73	1.3 ± 1.08	*0.03*	1.6 ± 1.22	*0.02*
rigidity	1.9 ± 2.28	6.1 ± 3.94	*< 0.01*	6.5 ± 4.21	*< 0.01*
finger tapping	1.8 ± 1.78	3.2 ± 2.04	*0.01*	3.0 ± 2.40	*0.15*
hand movements	1.2 ± 1.21	2.7 ± 2.31	*< 0.01*	3.3 ± 2.27	*< 0.01*
pronation-supination	1.6 ± 1.54	3.8 ± 1.92	*< 0.01*	3.9 ± 2.14	*< 0.01*

movements of hands					
toe tapping	2.5 ± 2.09	3.9 ± 2.16	*0.02*	4.9 ± 2.62	*0.01*
leg agility	1.6 ± 1.93	2.7 ± 2.35	*0.08*	3.9 ± 3.37	*0.02*
arising from chair	1.1 ± 1.34	1.8 ± 1.51	*0.12*	2.0 ± 1.66	*0.13*
gait	1.6 ± 1.12	2.0 ± 1.21	*0.21*	2.1 ± 1.54	*0.32*
freezing of gait	1.3 ± 1.32	1.7 ± 1.58	*0.45*	1.9 ± 1.45	*0.35*
postural stability	1.9 ± 1.20	2.4 ± 1.09	*0.15*	2.0 ± 1.41	*0.89*
posture	1.2 ± 1.05	2.0 ± 1.11	*0.02*	2.0 ± 1.32	*0.07*
body bradykinesia	1.3 ± 1.11	2.2 ± 0.99	*0.01*	2.1 ± 1.36	*0.08*
postural tremor of the hands	0.7 ± 1.23	0.9 ± 0.94	*0.61*	0.9 ± 1.36	*0.72*
kinetic tremor of the hands	0.4 ± 1.03	0.3 ± 0.64	*0.76*	0.9 ± 1.53	*0.34*
rest tremor amplitude	0.3 ± 1.14	0.5 ± 0.91	*0.49*	1.0 ± 1.41	*0.17*
constancy of rest tremor	0.1 ± 0.32	0.4 ± 0.90	*0.20*	0.6 ± 1.32	*0.09*
total	19.3 ± 14.9	39.3 ± 20.5	*< 0.01*	43.4 ± 27.9	*< 0.01*

Table 3. The scores of MDS-UPDRS part III

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies; n, number; SD, standard deviation; MDS, Movement Disorders Society; UPDRS, Unified Parkinson's Disease Rating Scale

The Mann–Whitney U-test was used to compare the MDS-UPDRS III scores between the iNPHc groups and iNPHa. Significant *p* values are indicated in red.

Figure legends

Fig 1. Functional analysis of striatum

(a) Scatter plot and linear regression illustrates the relationship between signal binding ratios (SBRs) of 123I-ioflupane single photon emission computed tomography (DaTscan) and age from normal controls (n = 39) and patients with idiopathic normal pressure hydrocephalus alone (iNPHa) (n = 23), iNPH comorbid (iNPHc) + PD/PDD (n = 13), and iNPHc+DLB (n = 7). The linear regression equations are shown below.

Control, SBR = -0.0489*age + 8.7707

iNPHa, SBR = -0.0187*age + 2.7207

iNPHc + PD/PDD, SBR = -0.0299*age + 4.2572

iNPHc+DLB, SBR = 0.0563*age – 2.4185

(b) SBRs of DaTscan from normal controls (n = 24) and patients with iNPHa (n = 17), iNPHc + PD/PDD (n = 13), iNPHc+DLB (n = 7) who were 62 or older were analyzed. One-way ANOVA *post hoc* Steel Dawss test was used to analyze SBR calculated from DaTscan between the groups.

(c) Receiver operating characteristic (ROC) curve for SBRs of DaTscan from normal controls (n = 24) vs. patients with iNPHa (n = 17) who were 62 or older.

(d) ROC curve for SBRs of DaTscan from patients with iNPHa (n = 17) vs. iNPHc + PD/PDD (n = 13) who were 62 or older.

(e) ROC curve for SBRs of DaTscan from patients with iNPHa (n = 17) vs. iNPHc + DLB (n = 7) who were 62 or older.

(f) Representative images of DaTscan

The representative images of DaTscan of a normal control and of a patient with iNPHa, iNPHc + PD/PDD, and iNPHc + DLB.

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Table 1. Baseline characteristics of the study participants

	iNPHa	iNPHc + PD/PDD		iNPHc + DLB	
	(n = 34)	(n = 23)	*p*	(n = 8)	*p*
sex (female/male)	10/24	16/7		4/4	
age at onset (means ± SD)	71 ± 9.4	68.5 ± 6.6	0.58	71.6 ± 6.8	0.99
age at diagnosis (means ± SD)	75.6 ± 6.2	76.6 ± 5.0	0.87	75.8 ± 5.4	0.10
duration of illness (means ± SD)	4.5 ± 7.4	8.0 ± 4.9	0.10	4.1 ± 3.1	0.10

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid;
PD, Parkinson's disease; PDD, Parkisnon' disease with dementia ; DLB, dementia with Lewy bodies ; n, number; SD, standard deviation

Table 1. Baseline characteristics of the study participants

	iNPHa (n = 34)	iNPHc + PD/PDD (n = 23)	iNPHc + DLB (n = 8)
sex (female/male)	10/24	16/7	4/4
age at onset (means ± SD)	71 ± 9.4	68.5 ± 6.6*	71.6 ± 6.8*
age at diagnosis (means ± SD)	75.6 ± 6.2	76.6 ± 5.0*	75.8 ± 5.4*
duration of illness (means ± SD)	4.5 ± 7.4	8.0 ± 4.9*	4.1 ± 3.1*

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid;
PD, Parkinson's disease; PDD, Parkisnon' disease with dementia ; DLB, dementia with Lewy bodies ; n, number; SD, standard deviation

Table 2. Clinical features of the study participants

	iNPHa (n = 34)	iNPHc + PD/PDD (n = 23)	*p*	iNPHc + DLB (n = 8)	*p*
MMSE (means ± SD)	22.7 ± 4.9	22.0 ± 5.9	0.97	16.7 ± 7.4	0.19
Timed up & go steps (means ± SD)	23.1 ± 17.3	32.1 ± 15.8	0.42	18.0 ± 9.4	0.92
Timed up & go time (means ± SD)	32.4 ± 33.6	38.3 ± 42.9	0.95	15.4 ± 5.1	0.79
Evans' index (means ± SD)	0.36 ± 0.03	0.37 ± 0.04	0.37	0.37 ± 0.02	0.45
^{123}I-MIBG (normal/reduced)	34/0	3/20	< 0.01	0/8	< 0.01
^{123}I-MIBG early H/M ratio (means ± SD)	3.21 ± 0.54	1.86 ± 0.58	< 0.01	1.49 ± 0.18	< 0.01
^{123}I-MIBG delayed H/M ratio (means ± SD)	3.31 ± 0.70	1.71 ± 0.90	< 0.01	1.27 ± 0.14	< 0.01
RT-QuIC (positive/negative)	0/19	13/0	< 0.01	2/0	< 0.01

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; PDD, Parkisnon' disease with dementia ; DLB, dementia with Lewy bodies; n, number; SD, standard deviation; MMSE, Mini-Mental State Examination; LPS, lumboperitoneal shunt; MIBG, 123I-meta-iodo-benzyl-guanidine; H/M, heart-to-mediastinum; RT-QuIC, real-time quaking-induced conversion

*** $p < 0.01$, ** $p < 0.05$, * not significant

Table 2. Clinical features of the study participants

	iNPHa (n = 34)	iNPHc + PD/PDD (n = 23)	iNPHc + DLB (n = 8)
MMSE (means ± SD)	22.7 ± 4.9	22.0 ± 5.9*	16.7 ± 7.4*
Timed up & go steps (means ± SD)	23.1 ± 17.3	32.1 ± 15.8*	18.0 ± 9.4*
Timed up & go time (means ± SD)	32.4 ± 33.6	38.3 ± 42.9*	15.4 ± 5.1*
Evans' index (means ± SD)	0.36 ± 0.03	0.37 ± 0.04*	0.37 ± 0.02*
^{123}I-MIBG (normal/reduced)	34/0	3/20***	0/8***
^{123}I-MIBG early H/M ratio (means ± SD)	3.21 ± 0.54	1.86 ± 0.58***	1.49 ± 0.18***
^{123}I-MIBG delayed H/M ratio (means ± SD)	3.31 ± 0.70	1.71 ± 0.90***	1.27 ± 0.14***
RT-QuIC (positive / negative)	0 / 19	13 / 0***	2 / 0***

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; PDD, Parkisnon' disease with dementia ; DLB, dementia with Lewy bodies; n, number; SD, standard deviation; MMSE, Mini-Mental State Examination; LPS, lumboperitoneal shunt; MIBG, 123I-meta-iodo-benzyl-guanidine; H/M, heart-to-mediastinum; RT-QuIC, real-time quaking-induced conversion

*** $p < 0.01$, ** $p < 0.05$, * not significant

Table 3. The scores of MDS UPDRS part III

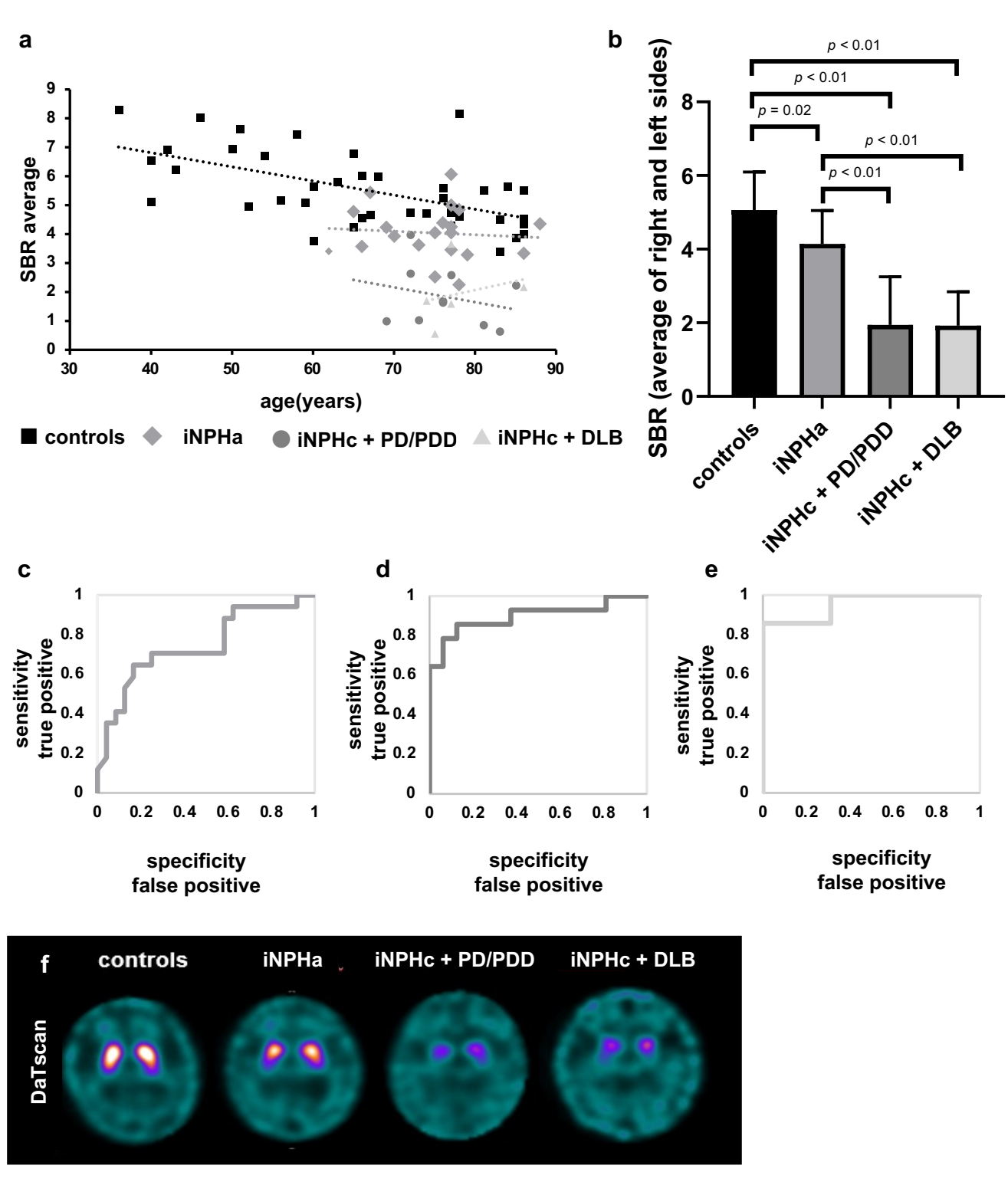
items	iNPHa	iNPHc + PD/PDD		iNPHc + DLB	
	(n = 34)	(n = 23)	*p*	(n = 8)	*p*
speech (means ± SD)	0.6 ± 0.72	1.3 ± 1.13	0.01	0.9 ± 1.05	0.44
facial expression (means ± SD)	0.8 ± 0.73	1.3 ± 1.08	0.03	1.6 ± 1.22	0.02
rigidity (means ± SD)	1.9 ± 2.28	6.1 ± 3.94	< 0.01	6.5 ± 4.21	< 0.01
finger tapping (means ± SD)	1.8 ± 1.78	3.2 ± 2.04	0.01	3.0 ± 2.40	0.15
hand movements (means ± SD)	1.2 ± 1.21	2.7 ± 2.31	< 0.01	3.3 ± 2.27	< 0.01
pronation-supination movements of hands (means ± SD)	1.6 ± 1.54	3.8 ± 1.92	< 0.01	3.9 ± 2.14	< 0.01
toe tapping (means ± SD)	2.5 ± 2.09	3.9 ± 2.16	0.02	4.9 ± 2.62	0.01
leg agility (means ± SD)	1.6 ± 1.93	2.7 ± 2.35	0.08	3.9 ± 3.37	0.02
arising from chair (means ± SD)	1.1 ± 1.34	1.8 ± 1.51	0.12	2.0 ± 1.66	0.13
gait (means ± SD)	1.6 ± 1.12	2.0 ± 1.21	0.21	2.1 ± 1.54	0.32
freezing of gait (means ± SD)	1.3 ± 1.32	1.7 ± 1.58	0.45	1.9 ± 1.45	0.35
postural stability (means ± SD)	1.9 ± 1.20	2.4 ± 1.09	0.15	2.0 ± 1.41	0.89
posture (means ± SD)	1.2 ± 1.05	2.0 ± 1.11	0.02	2.0 ± 1.32	0.07
body bradykinesia (means ± SD)	1.3 ± 1.11	2.2 ± 0.99	0.01	2.1 ± 1.36	0.08
postural tremor of the hands (means ± SD)	0.7 ± 1.23	0.9 ± 0.94	0.61	0.9 ± 1.36	0.72
kinetic tremor of the hands (means ± SD)	0.4 ± 1.03	0.3 ± 0.64	0.76	0.9 ± 1.53	0.34
rest tremor amplitude (means ± SD)	0.3 ± 1.14	0.5 ± 0.91	0.49	1.0 ± 1.41	0.17
constancy of rest tremor (means ± SD)	0.1 ± 0.32	0.4 ± 0.90	0.20	0.6 ± 1.32	0.09
total (means ± SD)	19.3 ± 14.9	39.3 ± 20.5	< 0.01	43.4 ± 27.9	< 0.01

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; DLB, dementia with Lewy bodies; n, number; SD, standard deviation; MDS, Movement Disorders Society; UPDRS, Unified Parkinson's Disease Rating Scale

Table 3. The scores of MDS-UPDRS part III

items	iNPHa (n = 34)	iNPHc + PD/PDD (n = 23)	iNPHc + DLB (n = 8)
speech (means ± SD)	0.6 ± 0.72	1.3 ± 1.13***	0.9 ± 1.05*
facial expression (means ± SD)	0.8 ± 0.73	1.3 ± 1.08***	1.6 ± 1.22**
rigidity (means ± SD)	1.9 ± 2.28	6.1 ± 3.94***	6.5 ± 4.21***
finger tapping (means ± SD)	1.8 ± 1.78	3.2 ± 2.04***	3.0 ± 2.40*
hand movements (means ± SD)	1.2 ± 1.21	2.7 ± 2.31***	3.3 ± 2.27***
pronation-supination movements of hands (means ± SD)	1.6 ± 1.54	3.8 ± 1.92***	3.9 ± 2.14***
toe tapping (means ± SD)	2.5 ± 2.09	3.9 ± 2.16**	4.9 ± 2.62**
leg agility (means ± SD)	1.6 ± 1.93	2.7 ± 2.35*	3.9 ± 3.37**
arising from chair (means ± SD)	1.1 ± 1.34	1.8 ± 1.51*	2.0 ± 1.66*
gait (means ± SD)	1.6 ± 1.12	2.0 ± 1.21*	2.1 ± 1.54*
freezing of gait (means ± SD)	1.3 ± 1.32	1.7 ± 1.58*	1.9 ± 1.45*
postural stability (means ± SD)	1.9 ± 1.20	2.4 ± 1.09*	2.0 ± 1.41*
posture (means ± SD)	1.2 ± 1.05	2.0 ± 1.11**	2.0 ± 1.32*
body bradykinesia (means ± SD)	1.3 ± 1.11	2.2 ± 0.99**	2.1 ± 1.36*
postural tremor of the hands (means ± SD)	0.7 ± 1.23	0.9 ± 0.94*	0.9 ± 1.36*
kinetic tremor of the hands (means ± SD)	0.4 ± 1.03	0.3 ± 0.64*	0.9 ± 1.53*
rest tremor amplitude (means ± SD)	0.3 ± 1.14	0.5 ± 0.91*	1.0 ± 1.41*
constancy of rest tremor (means ± SD)	0.1 ± 0.32	0.4 ± 0.90*	0.6 ± 1.32*
total (means ± SD)	19.3 ± 14.9	39.3 ± 20.5***	43.4 ± 27.9***

iNPHa, idiopathic normal pressure hydrocephalus alone; iNPHc, idiopathic normal pressure hydrocephalus comorbid; PD, Parkinson's disease; DLB, dementia with Lewy bodies; n, number; SD, standard deviation; MDS, Movement Disorders Society; UPDRS, Unified Parkinson's Disease Rating Scale


a
SBR average
age(years)
controls
iNPHa
iNPHc + PD/PDD
iNPHc + DLB
b
SBR (average of right and left sides)
p < 0.01
p < 0.01
p = 0.02
p < 0.01
p < 0.01
controls
iNPHa
iNPHc + PD/PDD
iNPHc + DLB
c
d
e
sensitivity
true positive
specificity
false positive
f
controls
iNPHa
iNPHc + PD/PDD
iNPHc + DLB
DaTscan