Neurobiology of Aging 36 (2015) 3306–3313

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease

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ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form 2 August 2015
Accepted 29 August 2015
Available online 7 September 2015

Keywords:
Parkinson's disease
Glucocerebrosidase gene
Risk factor
Clinical course
SPECT
MIBG scintigraphy

ABSTRACT

Homozygous mutations of the glucocerebrosidase gene (*GBA*) cause Gaucher disease (GD), and heterozygous mutations of *GBA* are a major risk factor for Parkinson's disease (PD). This study examined the impact of *GBA* mutations on the longitudinal clinical course of PD patients by retrospective cohort design. *GBA*-coding regions were fully sequenced in 215 PD patients and GD-associated *GBA* mutations were identified in 19 (8.8%) PD patients. In a retrospective cohort study, time to develop dementia, psychosis, wearing-off, and dyskinesia were examined. Survival time analysis followed a maximum 12-year observation (median 6.0 years), revealing that PD patients with GD-associated mutations developed dementia and psychosis significantly earlier than those without mutations ($p < 0.001$ and $p = 0.017$, respectively). Adjusted hazard ratios of *GBA* mutations were 8.3 for dementia ($p < 0.001$) and 3.1 for psychosis ($p = 0.002$). No statistically significant differences were observed for wearing-off and dyskinesia between the groups. N-isopropyl-p[^{123}I] iodoamphetamine single-photon emission tomography pixel-by-pixel analysis revealed that regional cerebral blood flow was reduced in the bilateral parietal cortex, including the precuneus of GD-associated mutant PD patients, compared with matched PD controls without mutations.

1. Introduction

Homozygous and compound heterozygous mutations in *GBA* encoding glucocerebrosidase lead to Gaucher disease (GD). A link between heterozygous *GBA* mutations and Parkinson's disease (PD) has been suggested (Bembi et al., 2003; Goker-Alpan et al., 2004; Halperin et al., 2006; Machaczka et al., 1999; Neudorfer et al., 1996; Tayebi et al., 2001, 2003). In 2009, a 16-center worldwide analysis of *GBA* revealed that heterozygous *GBA* mutation carriers have a strong risk of PD (Sidransky et al., 2009).

In addition, heterozygote *GBA* mutations not only carry a risk for PD development but also the possibility of some risk burden on the progression of PD clinical course. In cross-sectional analyses of *GBA* mutations in PD patients, earlier disease onset, increased cognitive impairment, a greater family history of PD, and more frequent pain were reported in patients with mutations, compared with no mutations (Chahine et al., 2013; Clark et al., 2007; Gan-Or et al., 2008; Kresojevic et al., 2015; Lwin et al., 2004; Malec-Litwinowicz et al., 2014; Mitsui et al., 2009; Neumann et al., 2009; Nichols et al., 2009; Seto-Salvia et al., 2012; Sidransky et al., 2009; Swan and Saunders-Pullman, 2013; Wang et al., 2012). Recently, a few prospective studies have investigated clinical features of PD with *GBA* and showed a more rapid progression of motor impairment and cognitive decline in *GBA* mutation cases than in PD controls (Beavan et al., 2015; Brockmann et al., 2015; Winder-Rhodes et al., 2013). However, in terms of motor complications such as wearing-off and dyskinesia, no studies exist in the longitudinal course of PD with *GBA* mutations.

Here, we conducted a multicenter retrospective cohort analysis, and the data were investigated by survival time analysis to show the impact of *GBA* mutations on PD clinical course. We also investigated regional cerebral blood flow (rCBF) and cardiac sympathetic nerve degeneration of subjects with *GBA* mutations, compared with matched PD controls.

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http://dx.doi.org/10.1016/j.neurobiolaging.2015.08.027

2. Materials and methods

2.1. Study design

At first the prevalence of *GBA* mutations was compared between PD patients and healthy controls and the relative risk of PD development according to *GBA* mutations were estimated. Then, PD features were compared between patients with *GBA* mutations and those without mutations. Finally, a retrospective cohort analysis was adopted to investigate the clinical course of PD according to *GBA* mutations. In addition, the cardiac sympathetic denervation and rCBF reduction were analyzed by ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy and N-isopropyl-p[^{123}I] iodoamphetamine single-photon emission tomography images, respectively, and the data of subjects with *GBA* mutations were compared to sex-, age (±5 years)-, and duration (±5 years)-matched subjects without mutations.

2.2. Sample size calculation

In a previous study on the incidence of dementia in PD patients during a 20-year follow-up, 48% of the patients developed dementia in 15 years and 83% of the survivors had dementia within 20 years (Hely et al., 2008). Based on these figures, we assumed that the cumulative incidence of dementia (according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM IV) was 30% in PD patients without *GBA* mutations within 12 years from disease onset; and that it would be twice that in PD patients with mutations, though there was no longitudinal report of the incidence of dementia in PD patients with *GBA* mutations. The prevalence of GD-associated *GBA* heterozygote mutations in Japanese patients with PD has been reported as 9.4% (Mitsui et al., 2009). Therefore, the sample size for a log-rank test was calculated as 215 participants on condition that α was 0.05 (bilateral) and that the power was 0.9.

2.3. Study participants

From April 2010 to May 2014, we enrolled 224 PD patients in 3 neurological centers in the Kansai region of Japan. A PD diagnosis was made according to steps 1 and 2 of the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria, except for the criterion of >1affected relative in step 2 (Gibb and Lees, 1988). Dementia with Lewy bodies (DLB) was diagnosed according to criteria for the clinical diagnosis of DLB with the 1-year rule (McKeith et al., 2005) and was excluded from subjects. In addition, 1.5-Tesla brain magnetic resonance imaging (MRI) was performed in all patients, excluding those with MRI findings compatible with multiple system atrophy or vascular parkinsonism. To calculate the risk ratios of PD by *GBA* mutations, healthy spouses who were not members of the extended family of the study patients, with no family history of PD or GD and who provided written informed consent, were enrolled as controls.

2.4. Ethics

The study was designed and performed according to the Ethical Guidelines for Clinical Studies from the Ministry of Health, Labor, and Welfare of Japan. The protocol was approved by the ethics committees of the participating institutions. All eligible individuals were informed of the purpose and methods of the study, and all provided written consent. All the individual genomic testing for *GBA* was done strictly according to research protocol, without return of results.

2.5. Sequencing of the GBA

Genomic DNA was extracted from peripheral blood leukocytes or buccal mucosal swabs using standard procedures. To amplify *GBA* by polymerase chain reaction, we used 3 primer pairs described in previous reports that were designed to selectively amplify *GBA* and not its pseudogene (Koprivica et al., 2000; Mitsui et al., 2009). The polymerase chain reaction products were subjected to direct nucleotide sequence analyses for the *GBA*-coding sequences and flanking splice sites using the primers selected according to a previous report (Mitsui et al., 2009) with a DNA analyzer (ABI3730xl; Life Technologies, Grand Island, NY, USA). The identified *GBA* mutations were used to search against reported GD mutations with HGMD professional (Biobase, Wolfenbuettel, Germany) to distinguish GD-associated mutations from other unreported mutations. The allele names refer to the processed protein (excluding the 39-residue signal peptide).

2.6. Data collection

Data were collected by the investigators (Tomoko Oeda, Atsushi Umemura, Satoshi Tomita, Masayuki Kohsaka, Kwiyoung Park, Kimiko Inoue, Harutoshi Fujimura, Hiroshi Hasegawa, Hiroshi Sugiyama, and Hideyuki Sawada) who all are neurologists qualified by the Japanese Society of Neurology. They filled in the forms of case cards designed for the study according to the protocol. The data of modified Hoehn and Yahr stage (on period), the Unified Parkinson's Disease Rating Scale part 3 (on period), and the Mini-Mental State Examination were recorded at study enrollment. Development of wearing-off, dyskinesias, orthostatic hypotension symptoms, and dementia were collected by reviewing medical records retrospectively. A diagnosis of dementia was made according to DSM IV, that is, when the patient had both memory disturbance and any other disturbances in language, calculation, execution, and praxis ability. Additional information (age, sex, age of PD onset, onset symptoms [tremor-dominant or not], family history of PD [first- or second-degree relatives], psychosis history [hallucination and delirium], current or previous impulse control disorder, mood disorders [defined as prescribing of antidepressants or antianxiety agents], history of stereotactic surgery for PD, and onset-year of dementia, psychosis [hallucination or delirium], wearing-off, dyskinesia) was collected from the clinical records. When information was insufficient, the investigators interviewed the patients or their caregivers. If not obtained, the subjects were excluded from the analyses and their numbers were shown. Dopaminergic medications (e.g., daily L-dopa dose, dopamine agonists, selegiline, amantadine, and entacapone) on the day of enrollment were recorded. The levodopa equivalent dose was calculated with the formula for levodopa equivalent doses for antiparkinsonian drugs described in a systematic review by Tomlinson et al. (2010). Early and late heart/mediastinum (H/M) ratios on ^{123}I- MIBG myocardial scintigraphy, and IMP-SPECT at Utano National Hospital were collected together with the examination date.

2.7. Statistics

2.7.1. Relative risk of PD related to GBA mutations

The relative risk of PD related to GD-associated *GBA* mutations and other *GBA* mutations was estimated separately as odds ratios (ORs) in the analyses between PD patients and healthy controls, and statistical significance was examined by Fisher's exact tests. If no mutations were observed in a cell, OR was calculated after a 0 cell correction (0.5 was added to all cells), because of the inability to divide it by a 0 cell count.

2.7.2. Comparison of clinical features at enrollment by GBA-mutation groups

Collected clinical features at enrollment were compared between the PD patients with GD-associated *GBA* mutations, with mutations unreported in GD and without mutations. The categorical data were examined by Fisher's exact tests, and the scale data were examined by Student *t* tests (after Levene's test to determine equality of variances) or Mann–Whitney *U*-tests (non-Gaussian distributions).

2.7.3. Survival time analyses in motor and nonmotor features by GBA-mutation groups

Kaplan–Meier survival curves were obtained from retrospective cohort analyses to compare time-to-event between patients with and without mutations, and the statistical differences were examined by a log-rank test. The survival time was defined as the duration from PD onset to the development of wearing-off, dyskinesia, dementia, and psychosis, for up to 12 years. Hazard ratios (HRs) of *GBA* mutations for these symptoms were calculated in Cox proportional-hazard regression models adjusted for sex and age at PD onset.

p-Values of <0.05 were considered statistically significant. The statistical analyses were performed with the statistical software program IBM SPSS Statistics version 19.0 (IBM Corporation, Armonk, NY, USA).

2.8. N-isopropyl-p[^{123}I] iodoamphetamine single-photon emission tomography imaging and analysis

A dose of 111 MBq ^{123}I-IMP was injected (supine position, quiet surroundings, and eye closed), and scanning was done for 15–30 minutes after injection. Using a gamma camera (Symbia E Dual Head System, SIEMENS) and an analytical workstation (syngo MI Workplace V, SIEMENS), the projection data were obtained in a 128×128 format for 36 angles in 180° increments at a rate of 30 seconds per angle. To elucidate the relatively decreased IMP uptake, a semiquantitative analytic approach originally developed for positron-emission tomography images by Minoshima et al. (1995) was adapted to single-photon emission tomography (SPECT) imaging (Bartenstein et al., 1997; Hirsch et al., 1997). After global normalization to the mean cerebral blood flow (CBF) for the entire brain, pixel-by-pixel comparisons of rCBF were performed to elucidate the CBF reduction patterns of subjects with GD-associated mutations versus subjects without mutations (matched by sex, age ±5 years, and disease duration ±5 years). T-statistic values (converted Z) were calculated between both groups at each pixel and displayed by color-coding representation onto the imaged brain anatomy. Image analysis was performed using software NEUROSTAT iSSP version 3.5, 2tZ (developed by Minoshima et al., University of Washington, Seattle, USA).

3. Results

3.1. Subjects

Among the 224 eligible PD patients (the subjects were not related to each other), 9 subjects were excluded from the analysis (4 due to multiple system atrophy findings on subsequent brain MRI and 5 because of insufficient clinical information). Therefore, 215 PD patients [female, 52.1%; age, 66.7 ± 10.8 (mean ± standard deviation)] were analyzed. For non-PD healthy controls, 126 patients' spouses (female, 58.7%; age, 67.3 ± 10.3) without a family history of PD or GD were enrolled.

3.2. GBA mutations and risk ratios for PD

In the PD subjects, we identified 10 nonsynonymous and 2 synonymous *GBA* variants. Within the nonsynonymous variants, 7 mutations were previously reported in GD [R120W, L444P-A456P-V460 (Rec*Nci*I), L444P, D409H, A384D, D380N, and ^{444}L(1447-1466 del 20, insTG)] as GD-associated mutations. Three nonsynonymous mutations have never been reported in GD patients [I(-20)V, I489V, and there was one novel mutation (Y11H)].

GD-associated *GBA* mutations were found in 19 of the 215 (8.8%) PD patients but none in the healthy controls. The risk of PD development relative to these GD-associated mutations was estimated as an OR of 25.1 [95% confidence interval (CI), 1.50–420, $p = 0.0001$] with 0-cell correction. The nonsynonymous mutations that were not reported in GD patients had no association with PD development ($p = 0.506$; OR, 1.3; 95% CI, 0.7–2.6) (Table 1). Four subjects had double mutations. For subsequent analyses, 2 subjects with double mutations of I (-20)V and K466K were adopted to the group of mutations unreported in GD, and 2 subjects with double mutations of R120W and I(-20)V, and of R120W and L336L were adopted to the group of GD-associated mutations.

3.3. Clinical features of PD patients by GBA mutation groups

The clinical features of PD patients with GD-associated mutations, those with mutations unreported in GD, and those without mutations are shown in Table 2. In the GD-associated mutation group, females, those with a family history and those with dementia (DSM IV) were significantly more frequent than those in the no-mutation group ($p = 0.047$, 0.012, and 0.020, respectively). The age of PD onset was lower in patients with GD-associated mutations (55.2 ± 9.9 years ± standard deviation), compared with those without mutations (59.3 ± 11.5), although the statistical difference was not significant. There were no differences in clinical manifestations between subjects with mutations unreported in GD and

Table 1
Frequency of glucocerebrosidase gene allele in Parkinson's disease patients and controls

Allele name	PD (n = 215)	Controls (n = 126)	*p*	Odds ratio (95% CI)
GD-associated mutations				
R120W	7[a]	0	0.050	9.1 (0.5–160.8)
Rec*Nci*I (L444P-A456P-V460)	4	0		
L444P	4	0		
D409H	1	0		
A384D	1	0		
D380N	1	0		
^{444}L(1447-1466 del 20, insTG)	1	0		
Subtotal, n (%)	19 (8.8%)	0 (0%)	<0.001	25.1 (1.5–419.8)[b]
Nonsynonymous mutations not reported in GD				
I(-20)V	27[a]	13	0.603	1.3 (0.6–2.5)
I489V	3	0		
Y11H[c]	0	1		
Subtotal, n (%)	30 (14.0%)	14 (11.1%)	0.506	1.3 (0.7–2.6)
Synonymous, n				
K466K	2[a]	1		
L336L	1[a]	0		

Allele names refer to the processed protein (excluding the 39-residue signal peptide).
Key: CI, confidence interval; GD, Gaucher disease; PD, Parkinson's disease.
[a] Four subjects had double mutations; 2 of I(-20)V and K466K, 1 of I(-20)V and R120W, and 1 of R120W and L336L.
[b] Odds ratio was calculated by adding 0.5 to each value.
[c] Novel mutation.

Table 2
Epidemiological and clinical features of PD patients with Gaucher disease–associated *GBA* mutations, those with mutations previously unreported in GD and those without mutations

Variables	Total n = 215	Mutation (-)	GD-associated mutations		Mutations unreported in GD	
		167	19[a]	p[b]	29[c]	p[d]
Sex	Female, n (%)	83 (49.7)	14 (73.7)	0.047	15 (51.7)	ns
Age	Mean (SD)	67.0 (10.8)	62.2 (10.7)	0.063[e]	67.5 (11.2)	ns[f]
Disease duration (y)	Mean (SD)	7.7 (5.5)	6.9 (4.6)	ns[f]	7.2 (4.9)	ns[f]
Onset age	Mean (SD)	59.3 (11.5)	55.2 (9.9)	ns	60.3 (11.8)	ns
Family history	Yes, n (%)	17 (11.0)[g]	6 (31.6)	0.012	0 (0.0)	ns
Dementia (DSM-IV)	Yes, n (%)	29 (17.4)	9 (47.4)	0.020	5 (17.2)	ns
MMSE	Mean (SD)	25.8 (5.4)[h]	23.3 (7.7)	ns[f]	27.0 (3.4)[i]	ns[f]
Onset symptom (tremor vs. others)	Tremor, n (%)	78 (46.8)	9 (47.4)	ns	15 (51.7)	ns
Modified H-Y on (<3 vs. ≥3)	≥3, n (%)	82 (49.1)	14 (73.7)	0.042	16 (55.2)	ns
UPDRS part 3	Mean (SD)	23.6 (12.2)[j]	28.5 (13.8)	ns[f]	21.9 (8.7)	ns[f]
Wearing off	Yes, n (%)	70 (41.9)	9 (47.4)	ns	13 (44.8)	ns
Dyskinesia	Yes, n (%)	49 (29.3)	8 (42.1)	ns	8 (27.6)	ns
Mood disorder	Yes, n (%)	43 (25.7)	8 (42.1)	ns	7 (24.1)	ns
Orthostatic hypotension symptom	Yes, n (%)	21 (12.6)	5 (26.3)	ns	7 (24.1)	ns
Psychosis history	Yes, n (%)	59 (35.3)	10 (52.6)	ns	7 (24.1)	ns
ICD history	Yes, n (%)	8 (4.8)	1 (5.3)	ns	1 (3.4)	ns
Stereotactic brain surgery for PD	Yes, n (%)	4 (2.4)	0 (0.0)	ns	0 (0.0)	ns
Agonist LED mg/d	Mean (SD)	92.8 (114.2)	72.1 (137.7)	ns[e]	163.7 (155.6)	0.026[e]
Levodopa LED mg/d	Mean (SD)	400.7 (184.2)	456.7 (206.9)	ns[f]	369.2 (230.3)	ns[e]
Total LED mg/d	Mean (SD)	496.4 (233.7)	537.9 (258.9)	ns[f]	525.7 (287.4)	ns[f]

Categorical data were examined by Fisher's exact test.
Key: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; *GBA*, glucocerebrosidase gene; GD, Gaucher disease; H-Y, Hoehn and Yahr; ICD, impulse control disorder; LED, levodopa equivalent dose; ns, not significant; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.
[a] Including a double-mutation subject (with a mutation unreported in GD).
[b] GD-associated mutations versus mutation (-).
[c] Two subjects with double mutation, including GD-associated mutations, were assigned to GD-associated mutation group.
[d] Other mutations versus mutation (-).
[e] Examined by Student *t* test after Levene's test for equality of variances.
[f] Examined by Mann-Whitney *U*-test because of non-Gaussian distribution.
[g] n = 155 due to 10 missing data.
[h] n = 164 due to 3 missing data.
[i] n = 28 due to 1 missing datum.
[j] n = 165 due to 2 missing data.

those without mutations, except for dopamine agonist dosage ($p = 0.026$) (Table 2).

3.4. Survival time analyses to develop dementia, psychosis, dyskinesia, and wearing-off

Time to develop clinical outcomes (dementia, psychosis, dyskinesia, and wearing-off) was compared in 19 subjects with GD-associated mutations, 29 with mutations unreported in GD, and 167 without mutation. The median observation time was 6.0 years. The subjects with GD-associated mutations showed a significantly earlier development of dementia and psychosis, compared with subjects without mutation ($p < 0.001$ and $p = 0.017$) (Supplementary Table e-1, Fig. 1A and B). We rereviewed the clinical record of the subject who showed early dementia (defined by DSM IV) (Fig. 1A) and made sure it did not satisfy the criteria of DLB (McKeith et al., 2005).

The associations of *GBA* mutations and these symptoms were estimated as HRs, adjusting for sex and age at PD onset. HRs were 8.3 for dementia (95% CI, 3.3–20.9; $p < 0.001$) and 3.1 for psychosis (95% CI, 1.5–6.4; $p = 0.002$). The time until development of wearing-off and dyskinesia complications was not statistically significant, with HRs of 1.5 (95% CI, 0.8–3.1; $p = 0.219$) and 1.9 (95% CI, 0.9–4.1; $p = 0.086$) (Table 3).

Subjects with mutations unreported in GD did not show significant differences in time to develop all 4 outcomes, compared with no mutation subjects. Therefore, subjects with GD-unreported mutations were regarded as subjects without *GBA* mutations in further analyses.

3.5. rCBF on SPECT in patients with GD-associated GBA mutations

We conducted pixel-by-pixel comparisons of rCBF on SPECT between PD subjects with mutations (cases) and sex-, age-, and disease duration-matched PD subjects without any mutations in *GBA* (controls). Four controls were adopted for each case (except for a 34-year-old female case who was matched to a control), and in total 12 cases (female 50%, age at SPECT mean ± standard error (SE); 58.9 ± 3.3 years, disease duration at SPECT 7.3 ± 1.5 years) and 45 controls (female 64.4%, age at SPECT mean ± SE; 61.0 ± 1.3 years, disease duration at SPECT 7.1 ± 0.7 years) were analyzed. As a result, a significantly lower rCBF was seen in the cases compared to the controls in the bilateral parietal cortex, including the precuneus (Fig. 2).

3.6. H/M ratios on MIBG scintigraphy in patients with GD-associated GBA mutations

Cardiac MIBG scintigraphy visualizes catecholaminergic terminals in vivo that are reduced as well as brain dopaminergic neurons in PD patients. We also investigated MIBG scintigraphy between 16 cases (female 68.8%, age at examination mean ± SE; 60.2 ± 2.6 years, disease duration at examination 6.2 ± 1.2 years) and sex-, age- and disease duration-matched 61 controls [(63.8 %, age 62.0 ± 1.1 years, disease duration 5.5 ± 0.6 years) (1:4 except for 1 young 34-year-old female case who was matched to a control)]. In the results, both early and late H/M ratios declined in both groups and did not show any significant differences ($p = 0.309$ and 0.244) (Supplementary Table e-2).

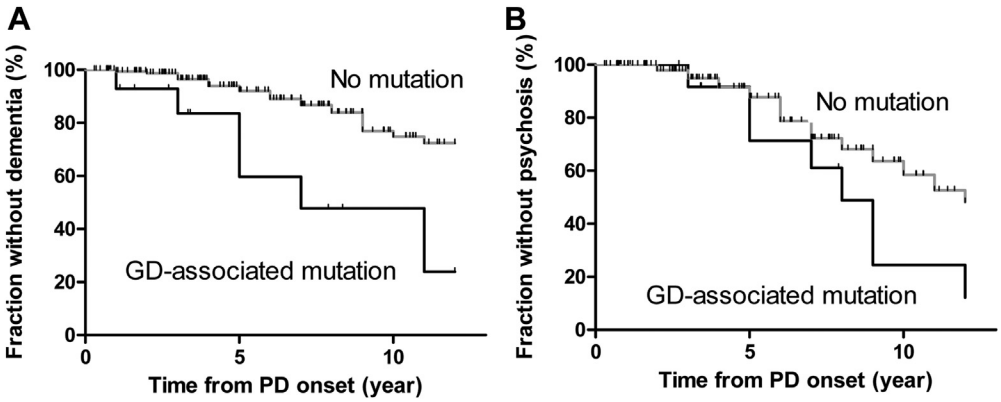

Fig. 1. Kaplan–Meier curves of dementia and psychosis in Parkinson's disease (PD) patients with Gaucher disease (GD)-associated glucocerebrosidase gene (*GBA*) mutations and those without mutations. PD patients with GD-associated *GBA* mutations and those without *GBA* mutations were compared to investigate the time taken to develop dementia (A) and psychosis (B). Because of insufficient information in several patients, the numbers in each analysis were different. The patients with and without mutations were 17 and 165 (A), 18 and 165 (B) against a total of 19 and 167. DSM IV, Diagnostic and Statistical Manual of Mental Disorders, revised fourth edition. *p*-Values were calculated by log-rank tests.

4. Discussion

4.1. Contributions of GD-associated GBA mutations to the development of PD

In the analysis of 215 PD patients and 126 non-PD controls, we identified 10 nonsynonymous heterozygous *GBA* mutations, including 1 novel mutation. Among these mutations, 7 were GD-associated, and the patients carrying these mutations represented 8.8% of the PD cohort. No significant association was found between the GD-unreported mutations and PD development, which suggests that only the GD-associated mutations are a genetic risk for PD. According to a worldwide multicenter analysis of 1883 fully sequenced PD patients, 7% of the GD-associated mutations are found in non-Ashkenazi Jewish PD patients (Sidransky et al., 2009). Although the mutation frequency in the present study was similar to previous results, the OR of GD-associated heterozygous mutations (25.1) was significantly greater than the OR (5.43) of other ethnic cohorts (Sidransky et al., 2009) and was consistent with an OR of 28.0 from a previous Japanese report (Mitsui et al., 2009). These results, taken together, suggest the possibility that *GBA* mutations are at a distinct risk for PD in the Japanese population. However, a larger Japanese cohort study is required to confirm this.

4.2. Cross-sectional clinical figures of PD with GBA mutations

Before the survival time analyses, we investigated clinical features at enrollment between mutation groups. The lower onset age, more frequent family history and dementia, and worse disease severity of PD in patients with *GBA* mutations, compared with those without mutations, were consistent with previous cross-sectional case-control reports (Anheim et al., 2012; Brockmann et al., 2011; Chahine et al., 2013; Lesage et al., 2011; Li et al., 2013; Mitsui et al., 2009; Neumann et al., 2009; Seto-Salvia et al., 2012; Sidransky et al., 2009). In contrast, female-predominance (73.7%, $p = 0.047$) in patients with mutations observed in the present study is inconsistent (Neumann et al., 2009; Seto-Salvia et al., 2012).

Table 3
Hazard ratios of GBA pathogenic mutations for clinical symptoms

Model	Clinical feature	Hazard ratio	95% CI	*p*
1	Dementia (DSM-IV)	8.3	3.3–20.9	<0.001
2	Psychosis	3.1	1.5–6.4	0.002
3	Wearing-off	1.5	0.8–3.1	0.219
4	Dyskinesia	1.9	0.9–4.1	0.086

Each model was adjusted for sex and age at onset.
Key: CI, confidence interval; DSM-IV; The Diagnostic and Statistical Manual of Mental Disorders part 1IV; GBA, glucocerebrosidase.

4.3. Impact of GBA mutations on the clinical course of PD

To investigate the impact of *GBA* mutations on the clinical course of PD, a prospective-designed study over a long period is preferred. Although there has been a few longitudinally designed study to date, follow-up clinical data for a median of 6 years of 121 PD cases from a community-based incident cohort was recently reanalyzed; results demonstrate that progression to dementia defined by DSM IV (HR 5.7) and Hoehn and Yahr stage 3 (HR 3.2) are significantly earlier in 4 *GBA* mutation-carrier patients compared with 117 patients with wild-type *GBA* (Winder-Rhodes et al., 2013). A 2-year follow-up clinical report of 28 heterozygous *GBA* carriers who were recruited from relatives of GD-patients shows slight but significant deterioration of cognition and smelling, compared to healthy controls (Beavan et al., 2015). Brockmann et al. (2015) assessed motor and nonmotor symptoms including cognitive and mood disturbances for 3 years in 20 PD patients with *GBA* mutations and showed a more rapid disease progression of motor impairment and cognitive decline in *GBA* mutation cases comparing to sporadic PD controls. The current long-term retrospective cohort study up to 12 years reinforced these results. It revealed that dementia and psychosis developed significantly earlier in subjects with GD-associated mutations compared with those without mutation, and the HRs of *GBA* mutations were estimated at 8.3 for dementia and 23.1 for psychosis, with adjustments for sex and PD onset age. In contrast, the results showed no significant difference in developing wearing-off and dyskinesia.

In this study, we also investigated whether GD-unreported mutations affected the clinical course of PD. In both cross-sectional and survival time analyses, the mutations unreported in GD carried no increased burden on clinical symptoms such as dementia, psychosis, wearing-off, and dyskinesia.

4.4. Reduced rCBF in PD with GBA mutations compared with matched PD controls

We found a significantly decreased rCBF, reflecting decreased synaptic activity, in the bilateral parietal cortex including the precuneus, in subjects with GD-associated mutations compared with

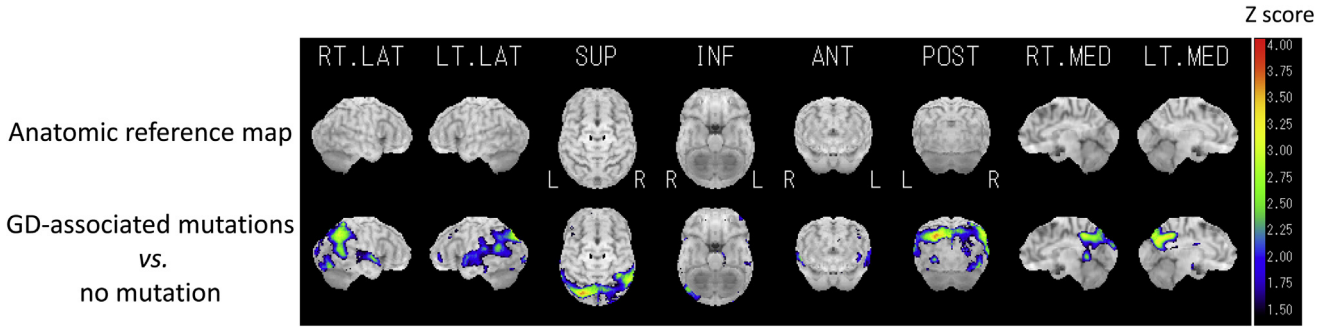

Fig. 2. Regional cerebral blood flow in the group with GD-associated mutations compared with the matched Parkinson's disease group without mutations. Regions with lower regional cerebral blood flow in the group with GD-associated mutations displayed on an anatomic reference map. Abbreviation: GD, Gaucher disease.

matched subjects without mutations. The pattern of reduced rCBF was very similar to the pattern of $H_2^{15}O$ positron-emission tomography that Goker-Alpan et.al. (2012) reported, showing decreased resting rCBF in the lateral parietal association cortex and the precuneus bilaterally in GD subjects with parkinsonism (7 subjects with homozygous or compound heterozygous *GBA* mutations), compared with 11 PD without *GBA* mutations. Results suggest that PD with heterozygous *GBA* mutations and GD patients presenting parkinsonism had a common reduced pattern of rCBF. Interestingly, in their study, rCBF in the precuneus—but not in the lateral parietal cortex—correlated with IQ, suggesting that the involvement of the precuneus is critical for defining *GBA*-associated patterns.

4.5. Reduced cardiac MIBG H/M ratios as well as matched PD controls

We also showed that cardiac MIBG H/M ratios in subjects with GD-associated mutations were lower than the cutoff point for PD discrimination (Sawada et al., 2009), suggesting that postganglionic sympathetic nerve terminals to the epicardium were denervated, as well as in PD without mutations.

4.6. Mechanisms of impact on PD clinical course by GD-associated GBA mutations

Experimental studies suggesting a bidirectional pathogenic loop between α-synuclein and glucocerebrosidase have been accumulated (Fishbein et al., 2014; Gegg et al., 2012; Mazzulli et al., 2011; Noelker et al., 2015; Schondorf et al., 2014; Uemura et al., 2015). Loss of glucocerebrosidase function compromises α-synuclein degradation in lysosome, whereas aggregated α-synuclein inhibits normal lysosomal function of glucocerebrosidase. The pathogenic loop may facilitate neurodegeneration in GD-associated PD brain, resulting in early development of dementia or psychosis as shown in the present study. Several recent researches propose the possibility that the similar mechanism as in PD with *GBA* mutations exists even in idiopathic PD brain (Alcalay et al., 2015; Chiasserini et al., 2015; Gegg et al., 2012; Murphy et al., 2014). On the other hand, the impacts of GD-associated *GBA* mutations for the development of motor complications such as wearing-off and dyskinesia were not statistically significant, suggesting other pathophysiological mechanisms in the striatal circuit brought out after long-term therapy especially by L-dopa.

4.7. Limitations

Our study has several limitations. In the design of the study, we assumed that the sample size was 215 (PD patients) for survival time analyses and investigated 224 PD patients. We assumed that the mutation prevalence would be 9.4%, and in fact, we found 19 patients with mutations (8.5%) of the 224 patients. Based on these figures, we estimated the risk ratios of heterozygous *GBA* mutations for the risk of PD development and PD clinical symptoms as ORs in the cross-sectional multivariate analyses, although the 95% CIs were broad. More of subject numbers will be needed to determine robust risk ratios. For cross-sectional analyses, as for comparisons of the CBF imaging studies the number was insufficient. For that reason, we compared the images of the positive patients to those of age-, sex- and disease duration-matched PD controls. Another limitation of the study concerns its nature as a retrospective cohort study; Although we determined the onset time of dementia, psychosis, wearing-off, and dyskinesia from clinical records or interview from both patients and their caregivers, we had to exclude several subjects from analysis because of insufficient information about onset-year (the missing numbers are shown in Supplementary Table e-1).

5. Conclusions

In conclusion, we showed that GD-associated mutations were not only associated with the development of PD but also had a great impact on developing dementia and psychosis in the clinical course of PD. The rCBF analysis in this study suggests that the dysfunction of the bilateral parietal cortex, including the precuneus, may play a role, although we have to wait for other investigations to determine the molecular mechanism. In terms of the development of motor complications, the GD-associated mutations did not show a significant influence.

Disclosure statement

The authors have no conflicts of interest to disclose.

Acknowledgements

This study was supported by a grant in aid (No.H22-NHO-03) from the Japan National Hospital Organization. Hideyuki Sawada and Tomoko Oeda conceived and designed the experiments. Tomoko Oeda, Yuko Mori, Atsushi Umemura, Yuko Mori, Satoshi Tomita, Masayuki Kohsaka, Kwiyoung Park, Kimiko Inoue, Harutoshi Fujimura, Hiroshi Hasegawa, Hiroshi Sugiyama, and Hideyuki Sawada performed the experiments. Tomoko Oeda and Hideyuki Sawada analyzed the data and wrote the article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2015.08.027.

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