Clinical course and prognosis in patients with Gaucher disease and parkinsonism

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ABSTRACT

Objective: The goal of this study was to characterize the parkinsonian phenotype in patients with Gaucher disease (GD) who developed parkinsonism in order to evaluate clinical course and prognosis.

Methods: This is a retrospective observational study conducted at the Clinical Center of the NIH, Bethesda, MD, over a period of 10 years. The study included 19 patients with GD and parkinsonism. The severity of Gaucher and parkinsonian symptoms was determined from clinical data including physical, neurologic, pathologic, and neurocognitive evaluations, family histories, imaging studies, olfactory testing, and validated questionnaires.

Results: We found an earlier age at onset of parkinsonism and evidence of mild cognitive dysfunction in our cohort. Although the clinical course in some patients was similar to that of idiopathic Parkinson disease with a favorable levodopa response, others exhibited features characteristic of dementia with Lewy bodies. When we examined the patients as a group, we did not observe a uniformly aggressive form of parkinsonism after the initial onset of symptoms, contrary to other published reports.

Conclusions: Appreciable clinical variation was seen in this cohort with GD and parkinsonism. Although some patients had early onset and prominent cognitive changes, others had a later, slower course, indicating that *GBA1* mutations may not be a reliable prognostic indicator in Parkinson disease in clinical settings. ***Neurol Genet* 2016;2:e57; doi: 10.1212/NXG.0000000000000057**

GLOSSARY

AAD = age at death; **AAO** = age at onset; **BVMT-R** = Brief Visuospatial Memory Test-Revised; **COD** = cause of death; **DLB** = dementia with Lewy bodies; **ERT** = enzyme replacement therapy; **GCase** = glucocerebrosidase; **GD** = Gaucher disease; **iPD** = idiopathic Parkinson disease; **PD** = Parkinson disease; **UPDRS** = Unified Parkinson's Disease Rating Scale; **UPSIT** = University of Pennsylvania Smell Identification Test.

The association between the lysosomal enzyme glucocerebrosidase (GCase) and parkinsonism has radically influenced research in this field. Hints of this relationship came from sporadic cases[1] and small cohorts of patients with Gaucher disease (GD) and Parkinson disease (PD).[2–6] Family histories revealed that even heterozygosity for glucocerebrosidase (*GBA1*) mutations was associated with PD.[7] A multicenter analysis including more than 5,000 patients with PD and controls unequivocally demonstrated that patients were over 5.43 times more likely to carry a *GBA1* mutation, rendering mutations in *GBA1* the most common genetic risk factor for parkinsonism.[8,9] Similar associations were also reported between *GBA1* mutations and both dementia with Lewy bodies (DLB)[10] and multiple system atrophy,[11] emphasizing the role of the lysosome in the pathogenesis of these neurodegenerative diseases.

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PD affects approximately 2% of the population by age 70.[12] It is characterized by bradykinesia in addition to tremor, rigidity, and/or postural instability.

GD is caused by mutations in *GBA1* resulting in deficient GCase in lysosomes and glycolipid storage in macrophages. The disorder often manifests with hepatosplenomegaly, skeletal involvement, anemia, and thrombocytopenia. Although only a minority of patients ultimately develop PD, characterization of these patients may help to elucidate the mechanisms underlying this association and potential prognostic indicators.

We describe 19 patients with homozygous or compound heterozygous mutations in *GBA1* with parkinsonism, aiming to characterize the disease phenotype and prognosis in this population.

METHODS This is primarily a retrospective observational study of 19 patients with GD and parkinsonian manifestations. The clinical diagnosis of GD was confirmed by low GCase activity in leukocytes or fibroblasts[13] and/or molecular analysis by full *GBA1* sequencing.[14] Seventeen patients were evaluated at the NIH, and patients had follow-up evaluations between 0 and 10 years after the initial visit. The remaining 2 patients were autopsied at the Clinical Center at the NIH and clinical records were provided. Several of the patients included were previously reported in the literature without longitudinal follow-up.[15] All patients had a diagnosis of PD or DLB that was made based on the UK Parkinson Disease Society Brain Bank clinical diagnostic criteria[16] or DLB criteria,[17] respectively. Clinical data describing GD clinical manifestations and PD clinical course and outcome were determined by review of medical records and longitudinal evaluations when possible. These data included family history, physical and neurologic evaluations, neurocognitive testing, imaging studies, and laboratory parameters. Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was used to assess the severity of motor symptoms (n = 11 in the "on" state and n = 5 in both the "on" and "off" states).[18] Patients were examined by a single neuropsychologist who performed a consistent battery of tests during each visit for the majority of patients (n = 12). The intellectual domains evaluated include memory, verbal and nonverbal reasoning, processing speed, focus/attention, and visuospatial skills. However, not all subtests could be administered in every patient. The University of Pennsylvania Smell Identification Test (UPSIT) was used to test olfactory function (n = 10); scores were adjusted for age and sex.[19] Autopsy reports, when available, were also reviewed (n = 5). Unfortunately, not all of these evaluations were available for each patient, but because of the rarity of patients sharing the 2 diagnoses, we included as much clinical data as possible.

Standard protocol approvals, registrations, and patient consents. The National Human Genome Research Institute Institutional Review Board at the NIH approved the study (clinical trial identifier number NCT00001215). All participants or their legal representatives provided written informed consent. The protocol consent explicitly stated that participation was entirely voluntary and that if enrolled, a study participant could withdraw from the study at any time.

RESULTS The genotypes and Gaucher clinical features of the 19 patients (10 male and 9 female) are summarized in table 1. Consistent with the clinical history of GD, a vast spectrum of systemic manifestations was observed. Although the cohort was genotypically heterogeneous, most patients carried at least 1 N370S allele. Nine of 19 patients (47.4%) were homozygous for N370S. Only 1 patient (genotype L444P/D409H) had a diagnosis of GD type 3 based on slowed horizontal saccades.[6] The mean age at onset (AAO) of Gaucher symptoms was 27.6 years with a median of 24 years and a range of 4 to 61 years. The mean duration between symptom onset and most recent evaluation was 26.6 years with a median of 26 years and a range of 5 to 60 years (table 2). In most patients, the presenting manifestations were an enlarged spleen and/or liver or hematologic abnormalities. Eight of the 19 patients (42.1%) had undergone splenectomy. The majority of patients (14 of 19 [73.7%]) received enzyme replacement therapy (ERT) with recombinant GCase, and most started the therapy many years before the onset of parkinsonian manifestations (table 3). Skeletal involvement, especially osteoporosis, was common in this cohort. In addition, 9 of 19 patients (47.4%) experienced either avascular necrosis of one or both hips or spontaneous fractures.

The parkinsonian phenotype (table 3) was also diverse. The mean AAO of symptoms was 49.7 years with a median of 50 years and a range of 33 to 64 years (table 2). In the majority of patients, a unilateral rest tremor was the initial presenting sign. The classical parkinsonian motor features—tremor, bradykinesia, rigidity, and gait problems—became prevalent as the disease progressed. The 15 patients who received dopaminergic therapy reported at least some positive response. Olfactory function was assessed using the UPSIT in 10 patients at the time of evaluation (table 3). The average UPSIT score was 19.3 (a normal score is >35 of 40 items) and the median was 19, indicating severe microsmia in this cohort (table 2).

In a subgroup of patients, the severity of motor dysfunction was assessed with the UPDRS-III, which has a maximum score of 108; higher numbers indicate more motor impairment (table 3). For the 11 patients tested, the average "on" score was 26.9 with a median of 29. Of these 11 patients, 5 were also evaluated in the "off" state and showed an average motor improvement of ~19.1% with levodopa therapy.

Neuropsychiatric symptoms were commonly reported in this cohort (table 3). The most prevalent

Table 1 Gaucher disease: Clinical characteristics

Patient, sex	Ethnicity	Genotype	Age at onset of symptoms, y	Initial presentation	Findings	Splenectomy	ERT	Age at death, y
Patient 1, F	AJ	N370S/L444P	29	Thrombocytopenia	Mild osteopenia, minimal Erlenmeyer flask deformity, HSM	No	No	—
Patient 2, F	French/English	N370S/L444P	17	Splenomegaly	Kidney tumor in 2000, history of absence seizures, spontaneous fracture of ribs, Erlenmeyer flask deformity, osteopenia	Yes, at age 18	Yes	70
Patient 3, F	AJ	N370S/IVS 2 + 1	5	HSM, bone crisis	AVN of the right hip	Yes, at age 14	Yes	—
Patient 4, M	Irish	N370S/N370S	47	Brother diagnosed	Osteoporosis, spontaneous vertebral fracture, abnormal EEG	No	No	—
Patient 5, F	AJ	N370S/rec	24	Splenomegaly, thrombocytopenia	Osteoporosis, liver enzyme abnormalities	Yes, at age 30	Yes	—
Patient 6, M	AJ	N370S/c.84insG	12	Bone crisis	6–7 blackout episodes daily of unknown etiology, osteoporosis	Yes, at age 12	Yes	59
Patient 7, M	Italian	N370S/N370S	24	AVN of the right femur	AVN of the right hip, mild HSM	No	Yes	—
Patient 8, F	AJ	N370S/N370S	4	HSM	AVN of the right hip, Erlenmeyer flask deformity	No	Yes	—
Patient 9, M	AJ	N370S/N370S	48	Thrombocytopenia, fatigue	Osteoporosis	No	Yes	62
Patient 10, M	AJ	N370S/N370S	33	HSM, CMV infection	HSM, mild osteopenia, thrombocytopenia	No	No	59
Patient 11, M	NA	N370S/R257Q	31	Thrombocytopenia but bone crisis since age 4	AVN of the right hip (replaced), splenomegaly	No	Yes	—
Patient 12, F	Scottish	N370S/55bpdel	16	Splenomegaly, nosebleeds, bone crisis	Osteopenia, spinal surgery, restless legs syndrome	Yes	Yes	—
Patient 13, M	AJ	N370S/N370S	26	Splenomegaly	Marrow involvement, AVN of the left femoral head, cortical renal cysts	Yes, at age 26	Yes	—
Patient 14, F	Irish/English	L444P/D409H	19	HSM	11-lb spleen, osteopenia, abnormal EEG	Yes, at age 34	Yes	53
Patient 15, M	AJ	N370S/N370S	61	Thrombocytopenia	Osteopenia, splenomegaly	No	No	76
Patient 16, M	AJ	N370S/N370S	47	HSM, thrombocytopenia	Osteoporosis, splenomegaly, abnormal EEG	No	Yes	73
Patient 17, F	AJ	N370S/c.84insG	14	Bone crisis since age 10	Bilateral hip replacement, severe bone pain, liver involvement	Yes, at age 18	Yes	61
Patient 18, M	AJ	N370S/V394L	20	Low platelets, anemia	Pain crises, osteopenia	No	No	—
Patient 19, F	AJ	N370S/N370S	47	Anemia, vasculitis of legs, polyclonal gammopathy	Osteopenia, thrombocytopenia, mild hepatosplenomegaly, AVN of the right hip (replaced), severe disc disease, lymphocytic interstitial pneumonitis, renal failure	No	Yes	73

Abbreviations: AJ = Ashkenazi Jewish; AVN = avascular necrosis; CMV = cytomegalovirus; ERT = enzyme replacement therapy; HSM = hepatosplenomegaly; NA = not available.

Table 2 Quantitative measures related to Gaucher disease and/or parkinsonism

	Average	Median
Age at onset of GD symptoms, y (n = 19)	27.6	24
Length of time followed since GD diagnosis, y (n = 19)	26.6	26
Age at PD onset, y (n = 19)	49.7	50
UPSIT score (of 40) (n = 10)[a]	19.3	19
Age at death, y (n = 9)	65.1	62

Abbreviations: GD = Gaucher disease; PD = Parkinson disease; UPSIT = University of Pennsylvania Smell Identification Test.
[a] Abnormal score is <35.

symptoms were depression and anxiety, reported by 13 of 19 patients. Ten patients described hallucinations, including 1 patient who was naive to dopaminergic therapy. Other neuropsychiatric symptoms observed included panic attacks, fugue episodes, "blackout" episodes, and paranoia.

The neurocognitive assessments indicated impairments in memory and processing speed, with performance in the mildly impaired or low average ranges (table 4). Verbal and nonverbal reasoning were evaluated by the Similarities and Block Design tests, respectively. These domains were not impaired, as evident from the average score of 10.4 (n = 11, range 4–17) on Similarities and the average score of 8.7 (n = 12, range 2–15) on Block Design. The normal scores on Block Design indicate intact visuospatial function. The Digit Span test was administered to evaluate attention and effort, revealing performance in the normal range with an average score of 9.2 (n = 8, range 7–12). Analysis of the memory test results demonstrated mildly impaired performance on both the Hopkins Immediate and Delayed Memory Test, a list-learning test (n = 7, average T-score = 30.6; range = 20–54), and the Brief Visuospatial Memory Test-Revised (BVMT-R) Immediate and Delayed Memory Test, a test of visual learning and memory (n = 8, average T-score = 33.4; range = 20–50). On the BVMT-R Immediate Memory subtest, the average T-score was 31.6 (range 20–53), whereas on the BVMT-R Delayed Memory subtest, the average T-score was 31 (range 20–50). Lastly, the Digit Symbol Coding and Symbol Search tests, used to evaluate processing speed, revealed average scaled scores of 7.8 (n = 12, range 4–14) and 8 (n = 10, range 4–13), respectively, indicating a relative deficit in processing speed when compared with the other test scores. Overall, the cohort had lower-than-predicted performance on memory and processing speed tasks, ultimately demonstrating mild cognitive dysfunction as a group.

Nine of 19 patients (5 male and 4 female) died during our study follow-up period. Table 3 summarizes age at death (AAD), PD duration, and cause of death (COD), when known, for all 9 patients. For these patients, the average PD duration was 11.1 years with a median of 11 years. The average AAD was 65.1 years with a median of 62 years. The COD was unknown for patients 10 and 16. Three patients died of aspiration pneumonia. Other CODs included acute pyelonephritis, intractable infected decubitus ulcers, complications from cardiac surgery, and multiorgan failure with terminal pneumonia. Five autopsy studies were performed. Three patients were pathologically confirmed as having DLB and 2 others met pathologic criteria for PD.

Although our numbers are extremely limited, we attempted to explore whether the parkinsonian features correlated with the *GBA1* genotype by comparing patients with genotype N370S/N370S with those with N370S/other. The 9 N370S homozygotes had a mean AAO of GD of 37.4 years vs 18.6 years in those with N370S/other, indicating that, as expected, the non-N370S allele correlated with more severe systemic disease. Among the deceased patients, the 5 N370S homozygotes had a mean duration of PD of 11.8 years, whereas the 3 N370S compound heterozygotes had a mean duration of 9.6 years. These preliminary observations require substantiation with a larger group of patients in each cohort.

DISCUSSION Our phenotypic characterization of these 19 patients with GD and parkinsonism provides insight into the parkinsonian spectrum associated with *GBA1* mutations. Consistent with smaller published studies, we generally observed an earlier AAO of PD symptoms in these patients (mean 49.7 years) compared with the mean AAO of 62.4 years seen in patients with idiopathic Parkinson disease (iPD)[20] and the mean AAO of 54.9 years seen in *GBA1* heterozygotes with PD.[8] In this study, the mean PD duration in the deceased individuals was 11.1 years, which is 2 years shorter than the mean PD duration of 13.1 years reported with iPD.[20] However, many factors may contribute to this finding. The clinical course of the 10 surviving patients in the cohort and their current length of disease duration demonstrate that the PD duration can be longer in some individuals. Also, 4 of the deceased patients had parkinsonism for 12 to 15 years. In addition, this cohort, like others reported in the literature, includes patients who met the diagnostic criteria for synucleinopathies other than PD. This heterogeneity complicates interpretation of the findings because the different synucleinopathies are characterized by different AAO and disease duration, so an average may not be a clinically useful measure. For example, disease duration and survival of patients with DLB tends to be shorter than in patients with PD (range 5–7 years[21]), and this could be a confounding factor in data analysis.

Table 3 Parkinsonian features

Patient, sex	Age at onset, y	Clinical diagnosis	Presenting features	Other motor symptoms	Mood disturbances	Dopaminergic therapy	UPSIT score (of 40)	ERT duration before PD onset, y	UPDRS-III score (of 108)		Age at death, y/disease duration, y	Cause of death
									On	Off		
Patient 1, F	48	PD	Stiffness on left	Rest tremors, bradykinesia, balance problems	Depression, anxiety, panic episodes	NT	24	NT	—	29	—	—
Patient 2, F	60	PD	Rest tremor of right hand, wrist, and foot	Rigidity, bradykinesia, shuffling gait, balance problems, falls	Anxiety, fugue episodes	Yes	26	9	33	41	70/10	Acute pyelonephritis
Patient 3, F	44	Functional tremor	Rest tremor of left leg, bradykinesia	Uses crutches, antalgic gait, slouched posture	Anxiety	NT	19	23, interrupted	—	40	—	—
Patient 4, M	52	PD	Rest tremor of left hand, bradykinesia	Rigidity, shuffling gait, freezing gait, falls	Hallucinations, depression, anxiety	Yes	11	NT	36	NA	—	—
Patient 5, F	52	PD	Gait problems	Dystonic dyskinesia, rigidity, shuffling gait, start hesitation	Hallucinations	Yes	NA	6	23	NA	—	—
Patient 6, M	45	DLB	Rest tremor of right hand, soft speech	Bradykinesia, rigidity, myoclonus, freezing, shuffling gait, balance problems	Psychosis, hallucinations, blackout episodes, anxiety	Yes	NA	2	NA	36	59/14	Aspiration pneumonia
Patient 7, M	37	PD	Rest tremor of right hand and leg	Rigidity, cramps, pain	Depression, anxiety	NT	34	9	NA	8	—	—
Patient 8, F	33	PD	Left leg, neck, and shoulder pain	Rest tremors, dystonia, rigidity, movement arrest	None	Yes	NA	17	9	NA	—	—
Patient 9, M	53	DLB	Rest tremor of right hand	Rigidity, dyskinesia, shuffling gait, propulsion, balance problems	Hallucinations, panic attacks, depression, anxiety, anhedonia	Yes	25	1	36	36	62/10	Intractable infected decubitus ulcers
Patient 10, M	50	PD vs DLB	Rest tremor of left hand, fatigue	Rigidity, dyskinesia, bradykinesia, shuffling gait, balance problems	Depression, anxiety	Yes	19	NT	27	30	59/10	Unknown
Patient 11, M	46	PD	Rest tremor of right leg	Rigidity, numbness, dyskinesia, dystonia	Anxiety, hallucinations	Yes	NA	13	NA	29	—	—
Patient 12, F	59	PD	Rest tremor of left leg	Rigidity, bradykinesia, stooped posture, falls	Hallucinations, anger, tearfulness	NT	NA	18	NA	18	—	—
Patient 13, M	40	PD	Rest tremor of right hand and wrist, stiffness	Bradykinesia, stiffness, masked facies, balance problems	Depression, anxiety, irritability	Yes	11	>8	17	32	—	—
Patient 14, F	42	PD with dementia	Rest tremor of left hand	Stiffness, masked facies, balance problems, falls	Depression, confusion	Yes	NA	0	NA	NA	53/12	Aspiration pneumonia
Patient 15, M	64	PD	Rest tremor of right hand	Rigidity, bradykinesia, stiffness, shuffling, falls	Irritability	Yes	14	NT	34	42	76/13	Complications from cardiac surgery

Continued

Table 3 Continued

Patient, sex	Age at onset, y	Clinical diagnosis	Presenting features	Other motor symptoms	Mood disturbances	Dopaminergic therapy	UPSIT score (of 40)	ERT duration before PD onset, y	UPDRS-III score (of 108)		Age at death, y/disease duration, y	Cause of death
									On	Off		
Patient 16, M	63	PD	Shuffling gait, dragging left leg	Rest tremor, rigidity, bradykinesia, dystonia, masked facies	Hallucinations	Yes	NA	16	NA	NA	73/11	Unknown
Patient 17, F	56	DLB	Memory problems	Cogwheel rigidity, abnormal gait, masked facies	Hallucinations, paranoia, depression	Yes	NA	>14	NA	NA	61/5	Aspiration pneumonia
Patient 18, M	42	PD	Rest tremor of right hand	Stiffness, weakness, masked facies, falls, had DBS	Hallucinations, anxiety, depression	Yes	10	NT	12	NA	—	—
Patient 19, F	58	DLB	Rest tremor of right hand	Balance problems, dyskinesias	Cognitive decline, psychosis	Yes	NA	0	NA	NA	73/15	Multiorgan failure with terminal pneumonia, chronic renal failure, respiratory failure

Abbreviations: DBS = deep brain stimulation; DLB = dementia with Lewy bodies; ERT = enzyme replacement therapy; GD = Gaucher disease; NA = not available/applicable; NT = not tried; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test.

Although PD and DLB have overlapping pathologic findings, the 2 disorders have important clinical differences and present distinct clinical challenges. For example, because patients with DLB have psychotic features and hallucinations, the use of dopaminergic medications is of great concern in this population.[21] The inclusion of patients with different synucleinopathies will also skew generalizations regarding levodopa response, as patients with DLB have a more limited response to dopaminergic therapy.[22] Thus, a poorer prognosis does not necessarily apply to all patients with *GBA1*-associated parkinsonism but will greatly depend on the specific underlying pathologic mechanism. However, given the small sample size, we could not perform subgroup analyses to establish the contribution of the inclusion of patients ultimately found to have DLB to the overall findings.

The UPDRS-III score is the most widely used measure to assess motor function in patients with parkinsonism, and the average "on" score of 26.9 for the 11 patients assessed does identify impairment. Although there is variation in therapeutic response to L-dopa, patients with iPD usually have an improvement of 20% to 70% in their motor symptoms,[23] especially early in the disease course. The small subgroup of patients who were tested in both "on" and "off" states had an average response of 19.1% to L-dopa therapy, which is relatively low, and the interpretation of this finding can be complicated by several factors. First, many of these patients had a diagnosis of parkinsonism several years before their evaluation at the NIH and may have developed motor fluctuations and a more limited response to levodopa associated with disease progression. Second, the fact that some patients had a DLB phenotype likely contributes to the limited response seen in the group as a whole. Third, the orthopedic and mobility problems sometimes encountered in patients with GD could contribute to higher motor scores on specific items on the UPDRS-III.

In addition to motor symptoms, it is now understood that patients with iPD have a wide range of nonmotor features, often many years before motor manifestations.[24] These nonmotor manifestations, including cognitive impairment, olfactory dysfunction, and sleep and neuropsychiatric disturbances, are experienced by a majority of patients with iPD at some point during their disease course and contribute to decreased independence in activities of daily living and increased emotional burden.[25]

Many of the patients in our cohort demonstrated some form of cognitive impairment, especially in memory and processing speed (table 4), although not all patients performed poorly. Decision-making, visuospatial abilities, and attention were preserved in

Table 4 Neurocognitive testing

Test	Mean score	Median score	Z-score	Percentile
Similarities (n = 11)[a]	10.4	10	0.07	50th
Block Design (n = 12)[a]	8.7	8.5	−0.67	25th
Digit Span (n = 8)[a]	9.2	9.5	−0.33	37th
Hopkins Immediate Memory (n = 7)[b]	30.6	24	−2	2nd
Hopkins Delayed Memory (n = 7)[b]	33.4	33	−1.7	4th
Brief Visuospatial Memory Test-Revised Immediate Memory (n = 8)[b]	31.6	27	−1.8	3rd
Brief Visuospatial Memory Test-Revised Delayed Memory (n = 8)[b]	31	28	−1.9	3rd
Digit Symbol Coding (n = 12)[a]	7.8	6.5	−0.84	20th
Symbol Search (n = 10)[a]	8	7.5	−0.67	25th

[a] Mean ± SD is 10 ± 3.
[b] Mean ± SD is 50 ± 10.

many patients even though these cognitive domains are frequently affected in patients with Parkinson-associated dementia,[26] hinting that a different mechanism might be responsible for cognitive dysfunction in our cohort. Moreover, it suggests that not all patients with *GBA1*-associated parkinsonism are destined to develop dementia, which highlights the need to proceed with caution when counseling patients and their families about the probability of severe cognitive dysfunction early in the disease process. Some patients may have a very similar disease progression to that seen in iPD. More generally, evaluations of cognitive function in patients with *GBA1*-associated parkinsonism showed stronger verbal than nonverbal abilities, similar to what has been reported in patients with iPD.

Studies of iPD indicate that many of these patients experience varying levels of depression and anxiety at some point during their PD course. Psychotic symptoms and hallucinations are also often seen in iPD, most frequently among patients who are on antiparkinsonian medications,[27] necessitating close monitoring and careful management of these patients. Almost half of our patients experienced depression. Anxiety and/or panic attacks were seen in 58% of patients. In addition, 53% of patients reported psychotic features, most often presenting as hallucinations. Although such mood and psychotic features may be more frequent in this cohort, it is unclear whether they are related to parkinsonism, mutant GCase, or our mixed population of patients with different synucleinopathies. Further exploration of these nonmotor features is necessary.

Pneumonia is a frequent COD among patients with PD.[28] In this cohort, 3 of the 9 deceased patients died of aspiration pneumonia as an immediate cause. Other CODs included acute pyelonephritis and sepsis, also common in the elderly population and in patients with mobility issues.

Other smaller studies have examined specific disease manifestations in patients with GD who developed parkinsonism. In a study from Israel of 11 patients with both disorders, an earlier AAO of parkinsonism, more frequent cognitive problems, and more frequent and earlier complications from levodopa therapy, including motor fluctuations and dyskinesias, were noted. In a study of 10 patients with GD and PD from the French national Gaucher disease registry pooled with 49 cases of GD and PD taken from the literature, it was noted that these patients exhibited a poorer response to L-dopa therapy when compared with patients with iPD.[29] However, at this time, no specific phenotypic presentation is unique to patients with parkinsonism who carry *GBA1* mutations. A study of 4 patients with both GD and PD identified from a tertiary Parkinson center described prominent neuropsychiatric problems, anosmia, as well as hyperechogenicity of the substantia nigra on ultrasound and presynaptic dopaminergic cell loss on PET, all of which are seen in patients with iPD.[30] Of note, all 4 patients were diagnosed with GD only after the development of PD.

In contrast to reports that *GBA1*-associated parkinsonism is uniformly associated with a more aggressive course, our 19 patients exhibited an array of Gaucher manifestations, PD symptoms, and nonmotor manifestations. This heterogeneity in patients with a rare disorder and an even rarer comorbidity needs to be taken into consideration, especially because the majority of patients with GD and *GBA1* mutation carriers never develop parkinsonism. The published literature is confusing: in 1 study of American patients with GD type 1, those who developed parkinsonism had higher scores on the GD Severity Score Index and Hermann score,[31] whereas in a study from the global International Collaborative Gaucher Group Gaucher Registry, patients who developed parkinsonism had a milder

Gaucher phenotype than those without PD.[32] Thus, even within this very specific subset of patients, there are complexities and nuances in the disease presentation and course, rendering it difficult to make generalizations about all patients with GD and PD. It is also unknown whether chronic therapy with ERT will alter (increase or decrease) the risk of developing PD in the future.

In addition to the small sample size, one limitation of this study is that it was conducted at a tertiary referral center. It is possible that patients with GD and PD with more severe manifestations might have been unable or unwilling to travel to the NIH, and this may be a source of bias in recruitment.

Further characterization of patients with both GD and parkinsonism will continue to provide insight into our understanding of the relationship between the 2 disorders. Clarification of the prognostic indicators for each is of value to patients and caregivers as they consider lifestyle changes as both diseases progress. Although this study is limited by the small cohort size, we identify issues to consider when deliberating prognosis and treatment for patients with *GBA1*-associated parkinsonism. Standardized clinical outcome measures, longitudinal follow-up of at-risk individuals, and pathologic confirmation of clinical diagnosis will greatly enhance our ability to identify pathophysiologic mechanisms underlying disease onset and progression, discover useful clinical biomarkers, and develop preventive treatments for PD.

AUTHOR CONTRIBUTIONS

Ellen Sidransky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Grisel Lopez, Jenny Kim, and Ellen Sidransky designed the study, analyzed data, and wrote the manuscript. Edythe Wiggs performed the neurocognitive testing and interpreted the data, Dahima Cintron analyzed clinical data, Nahid Tayebi performed the patient genotyping and interpreted the results, and Ozlem Goker-Alpan, Pramod K. Mistry, Gregory M. Pastores, Ari Zimran, and Catherine Groden were involved in conceptualization of the study, patient care, and the interpretation of clinical data.

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DISCLOSURE

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