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# The Spectrum of Parkinsonian Manifestations Associated With Glucocerebrosidase Mutations

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## Abstract

**Background—**Mutations in the glucocerebrosidase gene (*GBA*) result in Gaucher disease and can be associated with a phenotype characterized by adult-onset progressive neurologic deterioration and parkinsonism.

**Objective—**To define the clinical and neurologic spectrum of parkinsonian manifestations associated with *GBA* mutations.

**Design, Setting, and Patients—**A prospective case series of 10 patients (7 men and 3 women) with parkinsonism and *GBA* mutations evaluated at the National Institutes of Health Clinical Center.

**Main Outcome Measures—**The *GBA* genotypes were identified by means of DNA sequencing. Tests evaluating neurologic, motor, cognitive, ocular, and olfactory functions were performed and the results were analyzed by a single team.

**Results—**Genotyping identified *GBA* mutations *N370S*, *L444P*, and *c.84dupG* and recombinant alleles. The mean age at onset of parkinsonian manifestations was 49 years (range, 39–65 years), disease duration was 7.8 years (range, 1.2–16.0 years), and Unified Parkinson Disease Rating Scale part III score was 26.3 (range, 13–38). Half of the patients reported cognitive changes later in the disease course. Six patients were diagnosed as having Parkinson disease, 3 as having Lewy body dementia, and 1 as having a “Parkinson plus” syndrome. The most frequent nonmotor finding was olfactory dysfunction. Atypical manifestations included myoclonus, electroencephalographic abnormalities, and seizures.

**Conclusions—**In the homozygous and heterozygous states, *GBA* mutations are associated with a spectrum of parkinsonian phenotypes ranging from Parkinson disease, mostly of the akinetic type, to a less common phenotype characteristic of Lewy body dementia.

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In Parkinson disease (PD) and related syndromes, the degeneration of dopaminergic neurons and the formation of Lewy bodies (LBs) manifest clinically as motor dysfunction that includes bradykinesia, resting tremor, and rigidity. Early non-motor signs associated with PD may include olfactory dysfunction, mood and behavioral disturbances, and subtle neurocognitive changes.[1] Although genetic alterations have been identified in some with familial PD, in most sporadic cases the cause of neurodegeneration remains unknown. In recent years, multiple loci and mutations have been implicated in the etiology of rare Mendelian forms of PD, with a spectrum of phenotypes encountered.[2]

Mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (*GBA*) (OMIM 606463) result in the autosomal recessive disorder Gaucher disease (GD), which affects the skeletal, hematologic, and nervous systems with varying severity.[3] Different lines of evidence suggest that mutant glucocerebrosidase may be a risk factor for parkinsonism. Parkinsonian manifestations have been noted in a subset of patients with GD,[4,5] and *GBA* mutations have been observed with increased frequency in different series of patients with parkinsonism, first in 57 brain bank samples, where 14% had *GBA* mutations,[6] and then in 99 Israeli patients with PD, where 2 *GBA* mutations were present in 31.3%.[7] An increase in *GBA* mutations subsequently was demonstrated in patients of different ethnicities with PD.[8–10] The carrier frequency for *GBA* mutations is cited as being less than 1% in the general population and 6% to 7% in Ashkenazi Jews.[3] Furthermore, a family history of parkinsonism is often reported in probands with GD.[11]

Although initial studies noted that patients with GD and parkinsonism had early-onset, levodopa-unresponsive disease, recent studies demonstrated that the pathologic entities associated with *GBA* mutations include a variety of synucle-inopathies,[12] and, hence, the clinical phenotype might also be diverse. The present study details the clinical and neurologic spectrum of the parkinsonian phenotype in 10 patients carrying *GBA* mutations and is the first documentation, to our knowledge, of olfactory dysfunction in glucocerebrosidase-associated parkinsonism.

## METHODS

### PATIENTS

Ten consecutive patients with parkinsonism who carried *GBA* mutations were evaluated at the National Institutes of Health Clinical Center between January 1, 2003, and October 31, 2007 (Table 1 and Table 2). All the patients provided consent and were enrolled under National Institute of Mental Health or National Human Genome Research Institute institutional review board–approved protocols.

### CLINICAL STUDIES

Each patient underwent complete physical and neurologic examinations. Motor deficits were quantified using the motor section of the Unified Parkinson Disease Rating Scale (UPDRS III),[13] and disease staging was performed according to Hoehn and Yahr criteria.[14] Autonomic nervous system function was evaluated using a structured interview to assess postural hypotension, gastrointestinal function, sweating, heat regulation, and bladder and erectile dysfunction, and blood pressure and heart rate were recorded while in the supine position and 5 minutes after standing upright to evaluate orthostatic changes. The Mini-Mental State Examination[15] was used to screen for cognitive deficits. Patients 1 through 7 underwent neuropsychometric evaluations using standard methods.[16] Mood and behavior were assessed using a semistructured interview, and psychiatric evaluations were completed independently. All neurocognitive and neuropsychiatric assessments were performed while the patient was taking levodopa. Olfaction was evaluated using the University of Pennsylvania Smell

Identification Test (UPSIT).[17] Normal olfaction corresponded to a raw UPSIT score of 35 or higher, and UPSIT scores were corrected for age and sex. Patients 1 to 6 and 10 had a neuro-ophthalmologic evaluation, with recording of saccadic eye movements. All the patients except patients 8 and 9 had a 21-channel electroencephalogram, and 1 patient with myoclonus was evaluated using multichannel surface electromyography. Patients with GD underwent laboratory and radiologic studies, including echocardiography, pulmonary function testing, and abdominal magnetic resonance imaging to assess disease severity.

### GENETIC ANALYSIS

Genomic DNA was sequenced to identify *GBA* mutations by selectively amplifying all exonic sequences and most intronic portions in 3 fragments ranging from 1.7 to 3.0 kilobases (kb) long.[18] Southern blot analyses were performed to detect recombinant alleles in each patient with an *L444P* mutation.[19] Screening for 3 mutations in the *LRRK2* gene (OMIM 609007) was performed as previously described.[20]

## RESULTS

The demographics, genotypes, and clinical features of the 7 patients with GD and the 3 carriers (7 men and 3 women) are summarized in Table 1. *N370S* was the most common allele identified; 4 patients were homozygotes and 3 were compound heterozygotes for mutation *N370S* and either *L444P*, *c.84dupG*, or a recombinant allele. Mutation *c.84dupG* was detected in 2 of the carriers, and a recombinant allele was found in the third. The *LRRK2* gene was evaluated in all but patient 8, and no mutations were detected.

The mean age at diagnosis of GD was 32.1 years (range, 12–61 years). The diagnosis of GD was incidental in patients 2 and 6. Five patients had skeletal involvement of moderate severity, with episodes of recurrent bone pain, avascular necrosis, or fractures. Patients 1, 3, and 7 underwent splenectomy and subsequently received enzyme replacement therapy (ERT) for a mean of 14 years; each developed parkinsonism during ERT.

The primary parkinsonian features in the 10 patients, including clinical history, motor and olfactory functions, and Hoehn and Yahr staging, are reported in Table 2. Age at onset ranged from 39 to 65 years (mean, 49 years). Half of the patients presented before age 50 years, and the mean disease duration at the time of evaluation was 7.8 years (range, 1.2–16.0 years). Hoehn and Yahr stage and UPDRS III scores also varied considerably. The mean UPDRS III score was 26.3 (range, 13–38), and motor fluctuations were frequent. Tremor and bradykinesia were the most common symptoms at onset, and presentation was asymmetrical in 9 patients. All the patients received either levodopa or dopamine agonists during the study, with a favorable response in 9. Only patient 3 developed “on-state” dyskinesias.

Although cognition was normal at presentation, progressive decline was reported in 6 patients, with a mean duration of 6.3 years(range,2–10years). Of these patients,2 had overt dementia. Patient 1 presented with early cognitive changes, hallucinations, and delirium that partly remitted after adjusting therapy. Neurocognitive testing demonstrated impaired executive functions, including abstract reasoning, initiation and maintenance of goal-directed behavior, and sustained attention. Although word knowledge, recognition, and reading were spared, there were also deficiencies invisual perceptual areas with impaired verbal memory. Patient 4, who complained of memory problems early in his course, had moderate memory loss with disorientation and difficulty handling complex problems. Eight patients described mood and behavioral disorders, including depression and anxiety requiring therapy, and in 5, these symptoms began at or just before disease onset.

Seizures with electroencephalographic abnormalities, seen in 2 patients, were among the atypical features. Patient 1 was diagnosed as having myoclonus, and a multichannel surface electromyogram demonstrated frequent but asynchronous jerks of the proximal and distal muscles, suggestive of a subcortical origin. Patient 8 reported tonic seizures associated with falls. During the interview, 5 patients reported symptoms of dysautonomia, including constipation and bladder or erectile dysfunction. Patient 4 demonstrated orthostatic changes. Each of the 6 patients who had olfactory testing failed the UPSIT, and 3 had complete loss of smell. The mean UPSIT score was 17.6 (range, 10–33).

## COMMENT

An earlier description of 17 patients with GD and parkinsonism demonstrated different genotypes,[5] and screening patients with PD for *GBA* mutations has also identified multiple alleles, including the common *N370S*, *L444P*, and *c.84dupG* and other rare or novel mutations.[6–10] In this cohort, 6 different genotypes were encountered in 10 patients, and *N370S* was the most common allele. Although patients carrying *N370S* had slightly lower UPDRS III scores, the *GBA* genotype did not correlate with cognitive function or disease progression. Although the presence of an *N370S* allele is assumed to preclude central nervous system involvement in GD, the number of patients with parkinsonism carrying the mutation *N370S* in this study and others further complicates genotype-phenotype generalizations.

In contrast to earlier publications[4,5] in which patients with GD had early-onset, treatment-refractory PD, this study demonstrates that there is a range of age at onset, disease progression, levodopa responsiveness, and cognitive changes in *GBA*-associated parkinsonism. Herein, the mean age at onset was 49 years, and only 1 patient was considered to have early-onset PD. This differs from other genetic forms of PD, which often have an earlier age at onset. The clinical diagnoses also ranged from PD to a phenotype characteristic of LB dementia (LBD). Although previous publications[5] suggested that patients with *GBA* mutations have a limited response to levodopa or dopamine agonists, herein, the response was mostly favorable.

The profile of the motor symptoms at onset may be a determinant of clinical and cognitive outcome in PD. Patients presenting with tremor tend to show less functional impairments and fewer mental status changes, whereas pronounced bradykinesia or rigidity may correlate with progressive cognitive impairment. The finding of motor symptoms consistent with the akinetic-rigid PD in this patient series suggests that early use of rehabilitative services and rigorous treatment of GD skeletal manifestations should be emphasized, as these patients may become significantly disabled because of the comorbidity of both diseases.

Patients with PD exhibit cognitive deficits that may correlate with the neuropathologic stage or the “spread” of the LB abnormalities from brainstem neurons to cortical areas, and, thus, may occur later in the disease course.[21] However, in a series of patients with PD and cognitive impairment, postmortem analysis showed limbic and neocortical LB involvement compatible with LBD. Although the present patients reported cognitive changes with a later onset, their progression resembled that of patients with LBD, correlating with the increased frequency of *GBA* mutations in LBD.[12]

Although differing olfactory deficits occur in parkinsonian syndromes, a markedly decreased sense of smell remains highly characteristic of PD.[22,23] Olfactory dysfunction is a less prominent finding in other genetic conditions, and patients with α-synuclein and *LRRK2* mutations mostly have normal olfaction.[24,25] Further studies are indicated to determine the predictive value of olfactory testing as a bio-marker in patients carrying *GBA* mutations.

Although the association between parkinsonism and GD has been described for almost a decade, there has not been a descriptive study of such patients evaluated in a uniform manner.

Although the cohort assembled was evaluated prospectively, a significant amount of data, especially related to cognition and disease progression, had to be collected retrospectively, which could have introduced a bias related to patient recall. Owing to the small cohort size, raters were not blinded, which is another limitation. However, the study is ongoing, and future assessments will better establish the natural history and symptom progression in these patients.

Genes implicated in mendelian forms of PD have provided new insights into the disease pathogenesis, and the molecular pathways identified in monogenic cases may also play a role in sporadic forms of PD. Different molecular mechanisms that contribute to PD and related disorders lead to a common pathologic condition characterized by the death of dopaminergic neurons in vulnerable brain regions. The clinical heterogeneity seen in parkinsonism is likely to be the cumulative result of different gene-environment and gene-gene interactions. Although not all genetic causes of parkinsonism were explored in this cohort, no mutations in *LRRK2*, a gene also associated with varied neuropathologic features, were identified. In monogenic forms of parkinsonism, the mutated gene or the gene product likely contributes to the observed phenotypic spectrum. Several inherited parkinsonian syndromes are postulated to result from loss-of-function mutations,[2,26] yet, in some dominant forms, a gain-of-function mechanism has been suggested.[2] Although the association with mutant *GBA* could be due to a loss of enzymatic activity, the identification of Gaucher carriers with parkinsonism renders a gain-of-function disease mechanism related to the aberrant protein more likely. We postulate that *GBA* mutations may be directly involved in the parkinsonian pathologic abnormality, playing a pivotal role in pathways involved in neurodegeneration.

Sporadic PD is a multifactorial condition, and contributory risk factors are likely to operate early in the causative chain of events. Mutations identified in Parkinson genes may also behave as susceptibility factors for idiopathic PD. Heterozygous mutations in *PARKIN* are believed to confer an increased risk of late-onset PD.[27] Similarly, *LRRK2* mutations can be considered a cause of and a susceptibility factor for PD.[28] The parkinsonian spectrum associated with *GBA* mutations likewise suggests that they may be causative in some and a risk factor in others. However, the range of parkinsonian phenotypes observed in Gaucher carriers and the diversity of genotypes encountered renders widespread screening for a single or a small number of *GBA* mutations inappropriate. Furthermore, the penetrance of *GBA* mutations leading to a parkinsonian phenotype is currently unknown. Before considering diagnostic or pre-symptomatic screening of “at-risk” individuals, detailed natural history studies and a meta-analysis of association data are necessary to determine the statistical significance and implications of *GBA* mutations as a risk factor for parkinsonism.

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**Table 1**

Demographic and Clinical Characteristics of Patients With Parkinsonism Carrying Glucocerebrosidase Mutations

| Patient No./Sex | Ethnicity | Genotype | Age at Onset of GD, y | Clinical Manifestations | Splenectomy | ERT, y |
|---|---|---|---|---|---|---|
| 1/M | Ashkenazi Jewish | *N370S/c.84dupG* | 12 | Hepatomegaly, moderate bone disease[a] | Yes | 15 |
| 2/M | Ashkenazi Jewish | *N370S/N370S* | 61 | Thrombocytopenia | No | No |
| 3/F | Ashkenazi Jewish | *N370S/Rec*[b] | 24 | Hepatomegaly, thrombocytopenia, moderate bone disease[a] | Yes | 14 |
| 4/M | Ashkenazi Jewish | *N370S/N370S* | 38 | Thrombocytopenia | No | No |
| 5/F | North European/American Indian | *N370S/L444P* | 17 | Hepatomegaly, thrombocytopenia, moderate bone disease[a] | Yes | 12 |
| 6/M | North European | *N370S/N370S* | 47 | Hepatosplenomegaly, mild bone disease[a] | No | No |
| 7/M | Ashkenazi Jewish | *N370S/N370S* | 26 | Hepatomegaly, moderate bone disease (AVN)[a] | Yes | 15 |
| 8/F | Ashkenazi Jewish | *WT/c.84dupG* | NA | NA | NA | NA |
| 9/M | North European | *WT/Rec*[b] | NA | NA | NA | NA |
| 10/M | Ashkenazi Jewish | *WT/c.84dupG* | NA | NA | NA | NA |

Abbreviations: AVN, avascular necrosis; ERT, enzyme replacement therapy; GD, Gaucher disease; NA, not applicable; WT, wild type.

[a]Bone disease classifications: mild, radiologic abnormalities or occasional mild pain; moderate, fractures (including AVN) or chronic pain; and severe, surgery or long-term disability due to pain.

[b]Recombinant allele carrying glucocerebrosidase pseudogene–derived mutations: 55–base pair deletion, *D409H*, *L444P*, *A456P*, and *V460V*.

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**Table 2**

Parkinsonian Manifestations in Patients With Glucocerebrosidase Mutations

| Patient No. | Presentation | Age at Onset, y | Disease Duration, y | Premorbid Risks | Cognitive Changes and Psychiatric Features | Levodopa Response | Clinical Diagnosis | Autonomic Dysfunction | Olfactory (UPSIT Score) | UPDRS III Score | H&Y Stage | Other Features |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Asymmetrical resting tremor, gait disturbance | 44 | 10 | Unknown | Dementia (9 y), psychosis on levodopa | Yes | Parkinson plus | Yes | Severe microsmia (20) | 36 | 3 | Camptocormia, myoclonus, abnormal EEG findings, slowed horizontal saccades |
| 2 | Asymmetrical resting tremor | 65 | 3 | Pesticide exposure | None | Yes | PD | No | Complete anosmia (10) | 13 | 1 | Unknown |
| 3 | Bradykinesia gait, disturbance | 51 | 10 | Unknown | Depression | Yes | PD | No | Unknown | 23 | 3 | Periodic leg movements |
| 4 | Bilateral tremor, fatigue, gait disturbance | 50 | 2.5 | Smoker (40 y), welding material exposure | Mild cognitive decline (2 y), depression | Yes | PD vs LBD | Yes | Severe microsmia (23) | 23 | 2.5 | Unknown |
| 5 | Asymmetrical resting tremor, gait disturbance | 56 | 6 | Unknown | Fuguelike memory loss episodes | Yes | PD | No | Moderate microsmia (26) | 36 | 3 | RBD, complex seizures |
| 6 | Bradykinesia, gait disturbance | 50 | 1.2 | Unknown | Depression and anxiety | Yes | PD | Yes | Complete anosmia (16) | 26 | 2 | Unknown |
| 7 | Bradykinesia, asymmetrical resting tremor, gait disturbance | 39 | 2 | Unknown | Depression, anxiety | Yes | PD | No | Complete anosmia (11) | 32 | 3 | Unknown |
| 8 | Bradykinesia, apraxia | 40 | 16 | Unknown | Dementia (10 y), depression | No | LBD | Unknown | Unknown | 35 | 4 | Hallucinations, camptocormia, tonic seizures, abnormal EEG findings |
| 9 | Bradykinesia | 45 | 9 | Unknown | Cognitive decline (4 y), depression | Yes | PD vs LBD | Yes | Unknown | 38 | 3 | Hallucinations |
| 10 | Bradykinesia, gait and balance disturbance | 48 | 9 | Unknown | Cognitive decline (5 y), depression | Yes | PD | Yes | Unknown | 37 | 4 | Difficulty in saccade initiation, hypometric saccades |

Abbreviations: EEG, electroencephalogram; H&Y, Hoehn and Yahr staging; LBD, Lewy body dementia; PD, Parkinson disease; RBD, rapid eye movement behavioral disorder; UPDRS III, Unified Parkinson Disease Rating Scale part III; UPSIT, University of Pennsylvania Smell Identification Test.