Published in final edited form as:

Mov Disord. 2010 July 30; 25(10): 1364–1372. doi:10.1002/mds.23046.

Gaucher Disease Ascertained through a Parkinson's Center: Imaging and Clinical Characterization

R Saunders-Pullman^{1,2}, J Hagenah⁴, V. Dhawan⁵, K Stanley¹, G Pastores⁶, S Sathe⁶, M Tagliati⁸, K Condefer¹, C Palmese¹, N Brüggemann⁴, C Klein⁴, AM Roe³, R Kornreich⁷, LJ Ozelius^{7,8}, and SB Bressman^{1,2}

¹ Departments of Neurology, Beth Israel Medical Center, New York, NY

² Department of Neurology, Albert Einstein College of Medicine, Bronx, NY

³ Department of Obstetrics and Gynecology, Albert Einstein College of Medicine, Bronx, NY

⁴ Department of Neurology, University of Luebeck, Luebeck, Germany

⁵ Feinstein Institute for Medical Research, Manhasset, NY

⁶ Department of Neurology, New York University School of Medicine, New York, NY

⁷ Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, New York

⁸ Department of Neurology, Mount Sinai School of Medicine, New York, New York

Abstract

Among the genes implicated for parkinsonism is glucocerebrosidase (*GBA*), which causes Gaucher disease (GD). Despite a growing literature that GD may present as parkinsonism, neuroimaging, olfaction and neuropsychological testing have not been extensively reported. We describe transcranial sonography (TCS), 18F-fluorodopa (F DOPA) and fluorodeoxyglucose (FDG) PET, olfaction testing, neuropsychological testing and clinical features in homozygous and compound heterozygous glucocerebrosidase mutation carriers identified through screening of 250 Ashkenazi Jewish parkinsonian individuals treated at a tertiary care center. We identified two individuals with N370S/R496H compound heterozygous mutations and two with N370S homozygous mutations; one individual died before completing detailed evaluation. TCS (n=3) demonstrated nigral hyperechogenicity that was greater than controls (median area maximal substantia nigra echogenicity (aSNmax) =0.28 cm² vs. 0.14 cm², p=0.005), but similar to IPD (aSNmax= 0.31 cm²). FDG PET (n=2) demonstrated hypermetabolism of the lentiform nuclei, and F-fluorodopa PET (n=2), bilateral reduction in striatal FDOPA uptake. Olfaction was markedly impaired in the two tested cases, including onset of smell disturbance in adolescence in one. Neuropsychological features (n=3) were consistent with Parkinson's disease (PD) or diffuse Lewy body disease (DLB). The imaging, neuropsychological and olfactory markers suggest the GD phenotype includes PD with and without features of DLB, marked olfactory loss, nigral hyperechogenicity on TCS, and FDOPA and FDG PET abnormalities.

Corresponding author: Rachel Saunders-Pullman MD MPH, Department of Neurology, Beth Israel Medical Center, 10 Union Square East, Suite 5J PACC, New York, NY 10003 tel: 212-844-8719 fax: 212-844-8710.

Documentation of Author Roles: Rachel Saunders-Pullman 1A, B, C, 2A, B, 3A, Johann Hagenah 1B, C, 2C, 3B, Vijay Dhawan 1B, C, 2C, 3C, Kaili Stanley 1B, C, 2B, C, 3B, Gregory Pastores 1B, C, 2C, 3B, Swati Sathe 1B, C, 2C, 3B, Michele Tagliati 1B, C, 2C, 3B, Kelly Condefer 1B, C, 2C, 3B, Christina Palmese 1B, C, 2C, 3B, Norbert Brüggemann 1B, C, 2C, 3B, Christine Klein 1B, C, 2C, 3B, Ann Marie Roe 1B, C, 2C, 3B, Ruth Kornreich 1B, C, 2C, 3B, Laurie Ozelius 1B, C, 2C, 3B and Susan Bressman 1B, C, 2C, 3B.

Keywords

Parkinson's disease; Gaucher Disease; Glucocerebrosidase Mutations; Transcranial sonography; Functional Imaging; Olfaction

Introduction

Parkinsonism comprises a spectrum of neurodegenerative disorders with diverse phenotypes and many genetic causes, although the etiology for most parkinsonism remains obscure. Among the genes implicated in parkinsonism is that coding for glucocerebrosidase (*GBA*) (1–3). Homozygous and compound heterozygous mutations in *GBA* cause Gaucher disease (GD), the most prevalent autosomal recessive lysosomal disorder. While hematologic, bone and pulmonary features are prominent, over the last decade it has become evident that parkinsonism may be a feature of GD, even in those categorized as having “non-neuronopathic” disease (4–6). In some cases, parkinsonism may be the presenting clinical feature (1–3,7).

Several findings support a causal association between *GBA* mutations and parkinsonism. Young-onset parkinsonism has been reported in patients both after and preceding their diagnosis of GD (5,8,9). The CNS pathology in GD individuals who develop parkinsonism resembles idiopathic Parkinson disease (PD) with loss of dopaminergic neurons in the substantia nigra, and synuclein-positive Lewy bodies (10–12). There is also an increased rate of parkinsonism in family members of GD patients (13). Finally, an increased frequency of PD is found among *GBA* gene mutation carriers compared to controls in Jewish (2,7,14,15), mixed ancestry North American (16,17), Venezuelan (18), Chinese (19,20), Portuguese (21), Norwegian (22) and Italian populations (23), and an excess of *GBA* mutation carriers have been identified in US and UK brain bank samples of confirmed PD and Diffuse Lewy Body disease (DLB) (12,24,25).

Most reported cases of PD associated with GD are ascertained because of systemic features, such as anemia or bone changes; only a few cases of *GBA* homozygotes or compound heterozygotes, asymptomatic for other features of GD, have been identified in a PD clinic setting (2). Further, neuroimaging, and formal neuropsychological assessment have not been extensively reported in this cohort. Herein we describe neuroimaging, neuropsychological tests, and olfaction in parkinsonian patients with homozygous or compound heterozygous *GBA* mutations who were identified through a tertiary PD center, and present, to our knowledge, the first report of transcranial ultrasonography (TCS) in these patients.

Methods

Genetic

250 unrelated Ashkenazi Jewish parkinsonian patients were evaluated at the Movement Disorder Center at Beth Israel Medical Center (26). Blood and or saliva samples were obtained after informed consent under IRB approval, and DNA extracted as previously reported (27). Ancestry was by self-report, and all but one patient, who had one Sephardic parent, noted that both parents were Ashkenazic. Patients were screened for the eight most common AJ *GBA* mutations (N370S, L444P, 84GG, IVS2+1G->A, V394L, del55bp, D409H and R496H). Genotyping was performed using the Tag-It™ Mutation Detection Kit (Luminex Molecular Diagnostics, Toronto, ON, Canada) according to the manufacturer's instructions. In brief, the regions surrounding the mutations were multiplex PCR-amplified, subjected to allele-specific primer extension, hybridized to specific Luminex® beads via Universal Tags, and sorted on a Luminex® 100 IS platform (Luminex Corporation, Austin,

TX, USA). Genotypes for each sample were determined using Tag-It™ Data Analysis Software (Luminex Molecular Diagnostics).

Four homozygous or compound heterozygous and 28 heterozygous mutation carriers were identified. Analysis of the heterozygous mutation carriers and the overall comparison to the larger cohort will be described separately, as they do not yet have detailed imaging, and olfactory data.

Complete Unified Parkinson's Disease Rating Scales (UPDRS) were performed on all subjects. Motor features and dyskinesias were rated by the treating physician with UPDRS Parts III and IV, and clinical response was categorized using established rating criteria (28,29).

Neuropsychological Examination

Three patients underwent comprehensive neuropsychological examination as part of the standard medical work-up for treatment of parkinsonism. Assessment measures included the Wechsler Test of Adult Reading (WTAR (30)), Barona Index (31), Wechsler Adult Intelligence Scale- 3rd Edition (WAIS-III (32)), Wechsler Memory Scale-3rd Edition (WMS-III; Story Memory) (33), Boston Naming Test-2nd Edition (BNT) (34,35), Controlled Oral Word Association (FAS) (35), Animal Fluency (Animals) (35), Judgment of Line Orientation (JLO; Short Form) (36), and Trailmaking Test (35,37). For each patient, test scores were compared against demographically adjusted normative data (30–37) (Table 4). Test scores falling one standard deviation below expectation were “mild” difficulties; scores falling between one and two standard deviations below expectation were “moderate” deficits; scores two or more standard deviations below expectation were “severe” deficits.

Positron Emission Tomography (PET)

Clinical FDG PET was performed on Subjects 1 and 3 as previously described (38): the subjects were injected with 5mCi of FDG and waited in a dimly-lit room for 20 minutes. A 10 minute 3D emission scan was performed starting 35 min post injection. A 10-min transmission was performed and measured attenuation correction as well as corrections for scatter and randoms were applied. Subjects 3 and 4 were scanned with ¹⁸F-fluorodopa (FDOPA) PET (39). Subjects were orally administered 150 mg of carbidopa one hour before the 5-mCi injection of FDOPA. A single scan of 10-min duration was acquired at 90 minutes post-injection in addition to a 10-min transmission scan. The striato-occipital ratio (SOR) was assessed by placing the regions of interest for the caudate, putamen, and the occipital cortex (0.6, 1.6 and 3.9 cm² respectively) on composite FDOPA PET brain slices. SOR values were obtained by subtracting occipital from striatal activity and dividing by occipital activity and averaging for the left and right putamen. A dopaminergic deficit was defined when the putamen SOR value was reduced beyond two standard deviations (SD) below the mean for nine healthy control subjects (mean age: 53.3 years ± 15.9 [SD; range: 34–70 years]). Putaminal FDOPA uptake ratios were compared to 20 early PD patients (mean age: 50.3 years ± 11.7 [SD], disease duration: 2.92 years 2.6 [SD]).

Olfaction

The 40 item UPSIT (University of Pennsylvania Smell Identification Test, Inc. Haddonfield, NJ) was assessed using odor identification cards (40). Scores were compared to age and gender normative data.

Transcranial Ultrasound

TCS was performed on patients 1, 3 and 4, as well as 23 patients with IPD without *GBA* mutations from Beth Israel Medical Center and the University of Luebeck (9 women, 14

men, range 33–79 years, median age of 52 years) and 40 control individuals (15 women, 25 men, range 40–70 years, median age of 47.5 years) ascertained at the University of Luebeck. Using a SONOS 5500 ultrasound system (Philips Medical Systems) in connection with a 2.0–2.5MHz sector transducer (S4 probe; Philips), examinations were carried out from both sides and only the ipsilateral side of the SN was evaluated in a standard axial mesencephalic plane (landmark: butterfly-shaped brainstem) with a maximum depth of 14–16 cm from the temporal bone window. After focusing and zooming (2x magnification) between 10–30 images were digitally stored. The area of substantia nigra hyperechogenicity (aSN) was calculated after choosing the image representing best the hyperechogenic area in the SN by manually encircling using standardized previously established methods (41,42) by a rater blinded to phenotype and genotype. Additionally, thalamus, lenticulate nucleus and heads of the caudate were evaluated for echogenicity, and labelled hyperechogenic if they contained areas that were of greater intensity than surrounding white matter (45). For statistical analysis, the larger aSN of each individual was selected (aSNmax) or, in cases of an insufficient bone window on one side, the ipsilateral aSN of the analyzable side.

Comparisons of aSNmax between GD subjects and PD patients, and controls were performed using K-sample equality of medians test, using Stata8 software (Stata, TX).

Results

We identified four individuals with *GBA* homozygous or compound heterozygous mutations. Two were homozygous for N370S (Patients 1 and 2) and two were compound heterozygotes for N370S and R496H (Patients 3 and 4). Clinical features are summarized in Table 1 for all patients. Olfaction and Imaging results are reported in Table 2, neuropsychological testing is detailed in Table 1 and 4, and GD features are summarized in Table 3 for patients 1, 3 and 4. Patient 2 died of pancreatic cancer prior to additional testing.

Clinical Features

summarized in Table 1

Patient 1: had loss of smell as a teenager, and developed right hand rest tremor at age 48. While his course began as typical PD, within four years of symptoms, non-motor features, including cognitive complaints, depression, anxiety, orthostasis, urinary urgency and frequency and medication sensitivity became predominant clinical concerns. Serial neuropsychological examinations over the disease course revealed progressive deterioration with cognitive fluctuations and prominent deficits in spatial processing, semantic language, and attention. Eight years after onset, his disease remains asymmetric, but is characterized by rest tremor as well as action tremor, moderate rigidity and bradykinesia with good stride and negative pull test, and prominent neuropsychiatric features and dementia.

Patient 2: developed bilateral slowness of gait at the age of 60. He responded well to pramipexole monotherapy for 3 years, but developed pedal edema. Despite switching to levodopa (up to 800 mg/day), with improvement of his motor scores, dopamine agonists were most effective on his gait. He later developed fluctuations of response to levodopa with freezing of gait, occasional early morning dystonia, sialorrhea and urinary frequency. His cognitive status was overall well preserved, with only mild memory problems and occasional visual hallucinations with retained insight on dopamine agonist therapy when he died at age 67.

Patient 3: developed right arm action tremor and right leg dragging at age 58. She had a dramatic response to levodopa with mild dyskinesias on 200mg of l-dopa and pramipexole. Her course was complicated by a vertebral fracture after a fall, and subsequent

camptocormia that improved partially over time. Four years after onset, fluctuations in attention and memory were noted and she was started on donepezil with some improvement. Subsequent neuropsychological examination showed moderate letter fluency difficulties and mild bradyphrenia, executive dysfunction, and spatial processing deficits.

Patient 4: developed slowed and shuffling gait and cognitive changes characterized by periods of confusion at age 64 years. There was minimal response to levodopa (600mg per day), (reappearance of hallucinations 5 years following disease onset) with side effects. The prominent remaining motor features include difficulty rising from a chair, balance, including falls, tremor and mild dyskinesias. His cognition, as measured by serial neuropsychological assessments, was characterized by progressive cognitive decline with prominent attentional fluctuations, spatial processing deficits, dysnomia, executive dysfunction, and daily confusional episodes.

Functional Imaging

Patient 1: FDG PET at five years after onset demonstrated bilaterally increased FDG uptake in the lentiform nuclei, more pronounced on the left and in the thalamus consistent with idiopathic PD, with bilateral decrease in parieto-occipital and to a lesser degree anteromedial frontal cortex. While the scan was interpreted as consistent with moderately advanced idiopathic PD, the metabolic reductions in the prefrontal and parietal regions raised the possibility of a superimposed cognitive disturbance. Patient 3: FDOPA PET two years after symptom onset showed bilateral reduction in striatal FDOPA uptake consistent with moderately advanced idiopathic PD. FDG PET eight years after onset demonstrated bilateral lentiform-thalamic hypermetabolism, with reduction in cortical FDG uptake bilaterally in the parieto-occipital and temporal regions. Patient 4: FDOPA PET within one year of symptom onset showed reduced bilateral FDOPA uptake, most pronounced in the right posterior putamen with relative preservation of the caudate, consistent with idiopathic PD. Quantitative analysis is reported in Table 2. Statistical parametric mapping for FDG PETs for patients 1 and 3 showed hypermetabolism of the lentiform nuclei and thalamus that was different from controls, and in agreement with the visual interpretation. The values of putaminal SOR values for subjects 3 and 4 were similar to those in the early PD group ($p>0.1$).

Transcranial sonography (TCS)

TCS was performed on patients 1, 3, and 4 (Table 2), and all demonstrated increased nigral echogenicity. For all subjects, there was no increased echogenicity in the other basal ganglia, including lenticular and caudate nuclei. The *GBA*, IPD and control groups differed ($p<0.003$), with the median aSNmax greatest in the IPD (0.31 cm^2) vs. *GBA* (0.28 cm^2) vs. control (0.14 cm^2). The *GBA* and PD groups were not different ($p=.52$), but the *GBA* group alone showed greater echogenicity than controls ($p=.005$).

Further GD evaluation

Patients 1, 3, and 4 had extensive evaluations after the mutations were identified which are summarized in Table 3.

Discussion

Our identification of four out of 250 individuals with GD from a Parkinson's Center who were screened based on their Ashkenazi Jewish ethnicity and their parkinsonian features strongly supports the idea that parkinsonism may be the presenting feature of GD. Further, detailed testing suggests that while the motor phenotype of GD associated parkinsonism is broad, neuropsychiatric features are prominent, ferritin may be elevated, olfactory loss is an

early feature, and imaging with PET and transcranial ultrasound are consistent with parkinsonism. While none of the cases met the temporal criteria for DLB of cognitive decline developing within one year of motor symptoms (43), most developed cognitive decline, fluctuation, and sensitivity (with hallucinations) to dopaminergic agents suggestive of DLB. Therefore some patients encountered in the Parkinson clinic may have GD, and this etiology should also be considered in patients with a clinical picture consistent with the diagnosis of DLB, particularly in those people with Ashkenazi Jewish ancestry.

Early markers of PD were abnormal in all patients tested. We demonstrate hyperechogenicity of the substantia nigra in GD associated parkinsonism. Furthermore no alterations of other basal ganglia structures were found, as are suggested in other parkinsonian neurodegenerative diseases such as multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) (44,45). The presence of hyperechogenicity is notable as pathologic studies of Gaucher do not report nigral iron deposition, which has been inferred as the pathophysiologic explanation for the hyperechogenicity in PD (46). Although presumed secondary to a synucleinopathy, the mechanism by which Gaucher mutations cause parkinsonism remains unclear, and other mechanisms have been posited, including disruption of neuronal function through decreased enzymatic activity leading to an accumulation of glucosylceramide (47), although the relation between such dysfunction and development of hyperechogenicity is unknown.

While TCS was clearly different from controls, we were unable to distinguish GD from idiopathic PD (IPD) cases. TCS also does not definitively support a Lewy body pattern. Greater hyperechogenicity has been reported in DLB than IPD and PD with dementia (48), and we did not observe this in our patients. We did observe a clear lack of asymmetry in 2 of 3 of our patients, which has been reported as a prominent feature in DLB but not IPD (48). We were only able to perform TCS on three of the subjects, it is therefore possible that the *GBA* group might be discriminated from IPD in a larger group of *GBA* patients, and may also be different from DLB.

Both patients tested had markedly reduced olfaction. In IPD, olfactory loss may be the first neuropathologic process and could be due to early involvement of the long unmyelinated olfactory axons (49). Of particular note is that the olfactory disturbances in Patient 1 began when he was a teenager, suggesting that neurologic pathology may have preceded other clinical symptoms by more than thirty years. Olfactory loss has been reported in GD patients with parkinsonism (3), and it is of interest to determine whether non-parkinsonian GD patients or heterozygote carriers might also have olfactory loss. Because olfactory loss is non-specific and can be due to a multitude of causes, we cannot be certain that it is due to Gaucher. While both subjects had remote smoking history, this postceded the olfactory loss in Patient 1, and Patient 3 stopped smoking 21 years prior to olfactory testing. Neither subject had trauma or known viral infection preceding the smell loss. Further testing of GD patients and family members are needed to assess both the strength and temporality of the associations between nigral hyperechogenicity or olfactory decline and parkinsonism.

The PET findings reinforce a pre-synaptic dopaminergic cell loss as a major feature of GD associated PD. Decreased [11C] CFT uptake on PET in a patient with GD and dopa-responsive parkinsonism (50), and his father, a heterozygote *GBA* carrier with dopa-responsive parkinsonism has been demonstrated. The pre-synaptic dopaminergic deficit is also consistent with pathologic studies of GD and parkinsonism patients, which demonstrate substantia nigra loss and gliosis, as well as “brain-stem type” Lewy bodies in the substantia nigra (11,12). Unusual features in our patients include the relatively significant decrease in F-dopa uptake in Patient 3 despite clinically mild disease at this time, and the decreased uptake in bilateral parietal-occipital regions as well as in anteromediofrontal cortex in

patient 1 which raises the possibility of a more diffuse and cortical process. For patient 3, the metabolic pattern, including the asymmetry was consistent with IPD.

Clinical and neuropsychological features of the three well-studied patients were varied, as has been reported in GD individuals with parkinsonism. While none of our patients exhibited asymmetric tremor predominant parkinsonism with excellent response to levodopa, their motor features ranged from PD (but with minimal rest tremor) that responded well to levodopa, to tremor predominant parkinsonism with moderate levodopa response, but preservation of postural reflexes, to gait instability with falls. It is notable that neuropsychological features were prominent. While no patient met the temporal requirements (43) of cognitive and motor presentation necessary to meet criteria for DLB, motor and cognitive deficits presented simultaneously in Patient 4, and neuropsychological testing showed features of DLB in two of three tested patients. This suggests that *GBA* mutations may be responsible for a share of DLB-associated parkinsonism or PD with dementia. Pathologic investigation of 75 subjects with synucleinopathies showed the highest *GBA* carrier rate in DLB subjects (23%) (51). A similarity between GD and DLB is also noted in the predominance of CA4-CA2 hippocampal region Lewy bodies (10,51). Therefore while most studies have included strict IPD criteria, it is possible that there may be an even greater number of cases attributable to *GBA* mutations if a DLB cohort is examined (25). Mata et al reported an increased frequency of *GBA* mutations in DLB patients compared to controls, although this was only approximately 3% and was a mixed European group without an apparent founder (52).

Our study highlights the need to consider GD among the genetic etiologies of PD. This is exemplified by the fact that our patients were ascertained through a movement disorder clinic independent of family history of GD. It is of interest that two of the four patients had a family history of parkinsonism in a parent; however, family history has been shown not to be a factor that discriminates GD associated PD (2). Further, our patients all had “milder” GD mutations, which include N370S and R496H. The frequency of *GBA* mutations in our group is lower than some but not all (53) groups and this may be attributable to broad confidence intervals as the number of individuals screened is small at most sites, and to our screening for only the eight most common AJ mutations, whereas others sequenced the entire gene.

In presenting a composite study with detailed imaging, neuropsychological, and olfactory markers of GD cases ascertained from a Parkinson's Center, we suggest that the phenotype of GD associated parkinsonism may include not only PD, PD with dementia, DLB, and marked olfactory loss, but also nigral hyperechogenicity on TCS and pre-synaptic dopaminergic deficits on PET. None of our patients were treated with glucosylceramide synthase inhibitors, and the role of such therapy in GD associated parkinsonism is debated. An 81-year-old man with adult onset GD who developed parkinsonism and dementia and had been treated with enzyme replacement therapy for fatigue tolerated the switch to miglustat well (54). However, it is unclear whether the miglustat had any effect on the parkinsonism, and it has been argued that miglustat is unlikely to treat the parkinsonian features of GD (55). Therefore at this time, the only clear recommendations regarding unique treatment of these patients is the need to undergo comprehensive evaluation of GD associated systemic disorders; this evaluation is of particular import with regard to bone metabolism and fractures as Parkinsonian patients are already at increased risk for fractures.

Acknowledgments

We are grateful to the study participants, and thank Yaritza Rodriguez for expert technical assistance, and Luminex Molecular Diagnostics for reagents. This study was supported by The Thomas Hartman Foundation for Parkinson's Research, NIH/K23-NS047256, Edwin and Carolyn Levy, and the Reich Family Foundation.

References

1. Rogaeva E, Hardy J. Gaucher and Parkinson diseases: Unexpectedly related. *Neurology*. 2008 Jun 10; 70(24):2272–3. [PubMed: 18541881]
2. Gan-Or Z, Giladi N, Rozovski U, Shifrin C, Rosner S, Gurevich T, et al. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. *Neurology*. 2008 Jun 10; 70(24):2277–83. [PubMed: 18434642]
3. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E. The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations. *Arch Neurol*. 2008 Oct; 65(10):1353–7. [PubMed: 18852351]
4. McKernan RO, Bradbury P, Taylor D, Stern G. Neurological involvement in type 1 (adult) Gaucher's disease. *J Neurol Neurosurg Psychiatry*. 1985 Feb; 48(2):172–5. [PubMed: 3981177]
5. Neudorfer O, Giladi N, Elstein D, Abrahamov A, Turezkite T, Aghai E, et al. Occurrence of Parkinson's syndrome in type I Gaucher disease. *QJM*. 1996 Sep; 89(9):691–4. [PubMed: 8917744]
6. Cherin P, Sedel F, Mignot C, Schupbach M, Gourfinkel-An I, Verny M, et al. Neurological manifestations of type 1 Gaucher's disease: Is a revision of disease classification needed? *Rev Neurol (Paris)*. 2006 Nov; 162(11):1076–83. [PubMed: 17086144]
7. Clark LN, Ross BM, Wang Y, Mejia-Santana H, Harris J, Louis ED, et al. Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. *Neurology*. 2007 Sep 18; 69(12):1270–7. [PubMed: 17875915]
8. Machaczka M, Rucinska M, Skotnicki AB, Jurczak W. Parkinson's syndrome preceding clinical manifestation of Gaucher's disease. *Am J Hematol*. 1999 Jul; 61(3):216–7. [PubMed: 10398575]
9. Tayebi N, Callahan M, Madike V, Stubblefield BK, Orvisky E, Krasnewich D, et al. Gaucher disease and parkinsonism: A phenotypic and genotypic characterization. *Mol Genet Metab*. 2001 Aug; 73(4):313–21. [PubMed: 11509013]
10. Tayebi N, Walker J, Stubblefield B, Orvisky E, LaMarca ME, Wong K, et al. Gaucher disease with parkinsonian manifestations: Does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? *Mol Genet Metab*. 2003 Jun; 79(2):104–9. [PubMed: 12809640]
11. Wong K, Sidransky E, Verma A, Mixon T, Sandberg GD, Wakefield LK, et al. Neuropathology provides clues to the pathophysiology of Gaucher disease. *Mol Genet Metab*. 2004 Jul; 82(3):192–207. [PubMed: 15234332]
12. Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME, Sidransky E. Glucocerebrosidase mutations in subjects with parkinsonism. *Mol Genet Metab*. 2004 Jan; 81(1):70–3. [PubMed: 14728994]
13. Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E. parkinsonism among Gaucher disease carriers. *J Med Genet*. 2004 Dec; 41(12):937–40. [PubMed: 15591280]
14. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N Engl J Med*. 2004 Nov 4; 351(19):1972–7. [PubMed: 15525722]
15. Clark LN, Nicolai A, Afridi S, Harris J, Mejia-Santana H, Strug L, et al. Pilot association study of the beta-glucocerebrosidase N370S allele and Parkinson's disease in subjects of Jewish ethnicity. *Mov Disord*. 2005 Jan; 20(1):100–3. [PubMed: 15517591]
16. Sato C, Morgan A, Lang AE, Salehi-Rad S, Kawarai T, Meng Y, et al. Analysis of the glucocerebrosidase gene in Parkinson's disease. *Mov Disord*. 2005 Mar; 20(3):367–70. [PubMed: 15517592]
17. Nichols WC, Pankratz N, Marek DK, Pauciulo MW, Elsaesser VE, Halter CA, et al. Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. *Neurology*. 2009 Jan 27; 72(4):310–6. [PubMed: 18987351]
18. Eblan MJ, Scholz S, Stubblefield B, Gutti U, Goker-Alpan O, Hruska KS, et al. Glucocerebrosidase mutations are not found in association with LRRK2 G2019S in subjects with Parkinsonism. *Neurosci Lett*. 2006 Aug 14; 404(1–2):163–5. [PubMed: 16781064]
19. Ziegler SG, Eblan MJ, Gutti U, Hruska KS, Stubblefield BK, Goker-Alpan O, et al. Glucocerebrosidase mutations in Chinese subjects from Taiwan with sporadic Parkinson disease. *Mol Genet Metab*. 2007 Jun; 91(2):195–200. [PubMed: 17462935]

20. Tan EK, Tong J, Fook-Chong S, Yih Y, Wong MC, Pavanni R, et al. Glucocerebrosidase mutations and risk of Parkinson disease in Chinese patients. *Arch Neurol*. 2007 Jul; 64(7):1056–8. [PubMed: 17620502]
21. Bras J, Paisan-Ruiz C, Guerreiro R, Ribeiro MH, Morgadinho A, Januario C, et al. Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Portugal. *Neurobiol Aging*. 2007 Dec 19.
22. Toft M, Pielsticker L, Ross OA, Aasly JO, Farrer MJ. Glucocerebrosidase gene mutations and Parkinson disease in the Norwegian population. *Neurology*. 2006 Feb 14; 66(3):415–7. [PubMed: 16476943]
23. De Marco EV, Annesi G, Tarantino P, Rocca FE, Provenzano G, Civitelli D, et al. Glucocerebrosidase gene mutations are associated with Parkinson's disease in southern Italy. *Mov Disord*. 2008 Feb 15; 23(3):460–3. [PubMed: 18074383]
24. Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain*. 2009 Mar 13.
25. Clark LN, Katsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, et al. Association of glucocerebrosidase mutations with dementia with Lewy bodies. *Arch Neurol*. 2009 May; 66(5): 578–83. [PubMed: 19433657]
26. Pankratz N, Nichols WC, Uniacke SK, Halter C, Rudolph A, Shults C, et al. Genome screen to identify susceptibility genes for Parkinson disease in a sample without Parkin mutations. *Am J Hum Genet*. 2002 Jul; 71(1):124–35. [PubMed: 12058349]
27. Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med*. 2006 Jan 26; 354(4): 424–5. [PubMed: 16436782]
28. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. *Neurology*. 1967 May; 17(5):427–42. [PubMed: 6067254]
29. Fahn, S.; Elton, RL. Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn, S.; Marsden, CD.; Goldstein, M.; Caine, DB., editors. *Recent developments in Parkinson's disease*. Florham Park, N.J. 25 Hanover Rd., Florham Park, 07932: Macmillan Healthcare Information; 1987. p. 153–63.
30. Wechsler, D. Wechsler test of adult reading. San Antonio, TX: The Psychological Corporation; 1997.
31. Barona A, Reynolds C, Chastain R. A demographically based index of premorbid intelligence for the WAIS-R. *Journal of Consulting and Clinical Psychology*. 1984; 52(5):885–7.
32. Wechsler, D. Wechsler adult intelligence scale. 3. San Antonio, TX: The Psychological Corporation; 1997.
33. Wechsler, D. Wechsler memory scale. 3. San Antonio, TX: The Psychological Corporation; 1997.
34. Kaplan, E.; Goodglass, H.; Weintraub, S. Boston naming test. 2. Austin, TX: Pro- Ed Inc; 2001.
35. Heaton, RK.; Miller, SW.; Taylor, MJ.; Grant, I. professional manual. Lutz, FL: Psychological Assessment Resources; 2004. Revised comprehensive norms for an expanded halstead-reitan battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults.
36. Woodard JL, Benedict RH, Salthouse TA, Toth JP, Zgaljardic DJ, Hancock HE. Normative data for equivalent, parallel forms of the judgment of line orientation test. *J Clin Exp Neuropsychol*. 1998 Aug; 20(4):457–62. [PubMed: 9892049]
37. Reitan, RM.; Wolfson, D. The Halsted- Reitan neuropsychological test battery. Tucson, AZ: Neuropsychology Press; 1985.
38. Eidelberg D, Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Chaly T, et al. Early differential diagnosis of Parkinson's disease with 18F-fluorodeoxyglucose and positron emission tomography. *Neurology*. 1995 Nov; 45(11):1995–2004. [PubMed: 7501148]
39. Dhawan V, Ma Y, Pillai V, Spetsieris P, Chaly T, Belakhlef A, et al. Comparative analysis of striatal FDOPA uptake in Parkinson's disease: Ratio method versus graphical approach. *J Nucl Med*. 2002 Oct; 43(10):1324–30. [PubMed: 12368370]

40. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiol Behav.* 1984 Mar; 32(3):489–502. [PubMed: 6463130]
41. Hagenah JM, Konig IR, Becker B, Hilker R, Kasten M, Hedrich K, et al. Substantia nigra hyperechogenicity correlates with clinical status and number of Parkin mutated alleles. *J Neurol.* 2007 Oct; 254(10):1407–13. [PubMed: 17934880]
42. Hagenah JM, Becker B, Bruggemann N, Djarmati A, Lohmann K, Sprenger A, et al. Transcranial sonography findings in a large family with homozygous and heterozygous PINK1 mutations. *J Neurol Neurosurg Psychiatry.* 2008 Sep; 79(9):1071–4. [PubMed: 18469032]
43. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: Diagnosis, treatment, molecular pathology, and biomarkers. *Neurology.* 2007 Mar 13; 68(11):812–9. [PubMed: 17353469]
44. Walter U, Dressler D, Wolters A, Probst T, Grossmann A, Benecke R. Sonographic discrimination of corticobasal degeneration vs progressive supranuclear palsy. *Neurology.* 2004 Aug 10; 63(3):504–9. [PubMed: 15304582]
45. Behnke S, Berg D, Naumann M, Becker G. Differentiation of Parkinson's disease and atypical parkinsonian syndromes by transcranial ultrasound. *J Neurol Neurosurg Psychiatry.* 2005 Mar; 76(3):423–5. [PubMed: 15716540]
46. Zecca L, Berg D, Arzberger T, Ruprecht P, Rausch WD, Musicco M, et al. In vivo detection of iron and neuromelanin by transcranial sonography: A new approach for early detection of substantia nigra damage. *Mov Disord.* 2005 Oct; 20(10):1278–85. [PubMed: 15986424]
47. Korkotian E, Schwarz A, Pelled D, Schwarzmann G, Segal M, Futerman AH. Elevation of intracellular glucosylceramide levels results in an increase in endoplasmic reticulum density and in functional calcium stores in cultured neurons. *J Biol Chem.* 1999 Jul 30; 274(31):21673–8. [PubMed: 10419477]
48. Walter U, Dressler D, Wolters A, Wittstock M, Greim B, Benecke R. Sonographic discrimination of dementia with Lewy bodies and Parkinson's disease with dementia. *J Neurol.* 2006 Apr; 253(4):448–54. [PubMed: 16267638]
49. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003 Mar-Apr; 24(2):197–211. [PubMed: 12498954]
50. Kono S, Shirakawa K, Ouchi Y, Sakamoto M, Ida H, Sugiura T, et al. Dopaminergic neuronal dysfunction associated with parkinsonism in both a Gaucher disease patient and a carrier. *J Neurol Sci.* 2007 Jan 31; 252(2):181–4. [PubMed: 17182061]
51. Goker-Alpan O, Giasson BI, Eblan MJ, Nguyen J, Hurtig HI, Lee VM, et al. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. *Neurology.* 2006 Sep 12; 67(5):908–10. [PubMed: 16790605]
52. Mata IF, Cosentino C, Marca V, Torres L, Mazzetti P, Ortega O, et al. LRRK2 mutations in patients with Parkinson's disease from Peru and Uruguay. *Parkinsonism Relat Disord.* 2008 Nov 1.
53. Zimran A, Neudorfer O, Elstein D. The glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N Engl J Med.* 2005 Feb; 352(7):728–31. author reply 728–31. [PubMed: 15719452]
54. Hughes DA, Ginsberg L, Baker R, Goodwin S, Milligan A, Richfield L, et al. Effective treatment of an elderly patient with Gaucher's disease and Parkinsonism: A case report of 24 months' oral substrate reduction therapy with miglustat. *Parkinsonism Relat Disord.* 2007 Aug; 13(6):365–8. [PubMed: 17049454]
55. Goker-Alpan O, Sidransky E. Treating patients with Gaucher disease and parkinsonism: Misrepresentation in a title. *Parkinsonism Relat Disord.* 2008; 14(1):81–2. author reply 83. [PubMed: 17350320]

Figure 1.

Table 1

Clinical Features

	Patient #1	Patient #2	Patient #3	Patient #4
Mutation	N370S/N370S	N370S/N370S	N370S/R496H	N370S/R496H
Family history	–	unknown	+ (mother with dopa responsive PD, onset in 70's)	+ (mother with dopa responsive PD and dementia)
Age PD Diagnosis	48	60	54	64
<i>Initial Exam Features</i>				
Age Exam	54	65	58	65
Rest Tremor	+	–	–	+
Total Rest Tremor Score *	4.5	0	0	1
Bradykinesia	+	+	+	+
Total Bradykinesia Score *	6.5	12	1.5	3
Rigidity	+	+	+	+
Total Rigidity Score *	7	5	1.5	2.5
Dyskinesias	–	–	–	–
Asymmetry	+	+	+	+
Cognitive Impairment	–	–	–	+
<i>Last Exam Features</i>				
Age Exam	57	67	64	70
Rest Tremor	+	–	–	–
Total Rest Tremor Score	6	0	0	0
Bradykinesia	+	+	+	+
Total Bradykinesia Score	16	10	5	12
Rigidity	+	–	+	+
Total Rigidity Score	9	0	1	4
Dyskinesias	–	–	+	–
Total Dyskinesia Score *	0	0	1	0
Asymmetry	+	+	+	+
Cognitive Impairment**	+	–	+	+
<i>Ever</i>				
Depression	+	+	–	+
Anxiety	+	–	+	+
Quetiapine treatment	+	–	–	+
Medication induced hallucinations	+ (severe with selegiline)	+ (mild on dopamine agonist)	+ (on dopamine agonist and l-dopa)	+ (on l-dopa)
Other features	Restless legs ***	–	–	Hearing loss in 60's

* Total scores for UPDRS components calculated as follows: rest tremor= UPDRS #20; bradykinesia= UPDRS #23–26, 31, rigidity= UPDRS #22; dyskinesias= UPDRS #32–34 total

** See Table 4 for neuropsychological test results

** Evaluation for restless legs demonstrated elevated ferritin levels prior to Gaucher evaluation

Table 2

Imaging and olfactory features

	Patient 1	Patient 3	Patient 4
UPSIT	13/40	10/40	N/A *
FDOPA PET Posterior putamen	N/A	48% below control	38% below control
USG (aSNmax) **	.29	.25	.33
aSNmin ***	.25	.22	.26

* Patient 4 administered UPSIT, but unable to complete due to cognitive limitations

** area of Substantia nigra maximal hyperechogenicity

*** area if Substantia nigra hyperechogenicity on the less affected side (substantia nigra minimal hyperechogenicity)

Table 3Gaucher Features^{*}

	Patient 1	Patient 3	Patient 4
Mutation	N370S/N370S	N370S/R496H	N370S/R496H
Acid B-glucosidase	6.4 nmol/mg protein/hr	5.3 nmol/mg protein/hr	Not assessed
Ferritin	Increased (1217 ng/ml)	Normal Range	Normal Range
Hb, Platelets	Normal Range	Normal Range	Normal Range
Liver	Mildly enlarged (1.38 × normal)	Not palpable	Not palpable
Spleen	Moderately enlarged (3.81 × normal)	Not palpable	Not palpable
Fractures	Spine fracture ^{**}	None	None

No patients were treated with enzyme replacement therapy

^{*} Patient 2 died prior to formal evaluation for Gaucher.

^{**} No signs of active disease, started on biphosphonates

Table 4

Neuropsychological test results at most recent examination*

With the exception of years of education and IQ (shown as a standard score), data are represented as raw and z scores for each patient.

Neuropsychological Measure	Patient 1 Raw Score (z score)	Patient 3 Raw Score (z score)	Patient 4 Raw Score (z score)
Years of Education	19	16	16
IQ	119	116	109
Attention			
Digit Span Forward	4 (-1.62)	9 (+1.82)	5 (-0.73)
Digit Span Backward	3 (-0.99)	6 (+0.92)	5 (+0.47)
Trail Making Test A	Unable**	58" (-1.87)	Unable
Executive			
Trail Making Test B	Unable	226" (<-2.60)	Unable
Matrix Reasoning	0 (<-2.60)	7 (-1.00)	5 (-1.00)
Similarities	20 (0.00)	---	12 (-1.33)
Language			
FAS	28 (-1.60)	28 (-1.53)	27 (-1.20)
Animals	7 (<-2.60)	23 (+0.53)	4 (-2.60)
BNT	39 (-1.80)	57 (0.00)	37 (-2.13)
Visual Spatial			
JLO	Unable	8 (-1.20)	---
Block Design	Unable	---	2 (-2.00)
Memory			
Story Memory			
Immediate Recall	10 (-2.00)	40 (+0.33)	29 (-0.67)
Delayed Recall	6 (-1.73)	22 (+0.33)	15 (-0.33)
Recognition	17 (-1.80)	---	25 (+0.47)

* Test scores based on Wechsler Test of Adult Reading (WTAR(30)), Barona Index(31), Wechsler Adult Intelligence Scale- 3rd Edition (WAIS-III(32)), Wechsler Memory Scale-3rd Edition (WMS-III; Story Memory)(33), Boston naming test-2nd Edition (BNT)(34,35), Controlled Oral Word Association (FAS)(35), Animal Fluency (Animals)(35), Judgment of Line Orientation (JLO; Short Form)(36), and Trailmaking Test(35,37)

** Patient unable to perform the test