Original Investigation

Evolution of Prodromal Clinical Markers of Parkinson Disease in a *GBA* Mutation–Positive Cohort

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IMPORTANCE Numerically, the most important genetic risk factor for the development of Parkinson disease (PD) is the presence of a glucocerebrosidase gene (*GBA*) mutation.

OBJECTIVE To evaluate longitudinally and clinically a *GBA* mutation–positive cohort and the evolution of the prodromal features of PD.

DESIGN, SETTING, AND PARTICIPANTS Participants in a study of the etiology and prodrome of PD were reevaluated in this clinic-based 2-year follow-up report. Patients with type 1 Gaucher disease (GD) and heterozygous *GBA* mutation carriers were recruited in 2010 from the Lysosomal Storage Disorder Unit at the Royal Free Hospital, London, England. Thirty patients who previously received a diagnosis of type 1 GD, 28 heterozygous *GBA* mutation carriers, and 26 genetically unrelated controls were included. Exclusion criteria included a diagnosis of PD or dementia for both the patients with GD and the *GBA* mutation carriers and any existing neurological disease for the controls.

MAIN OUTCOMES AND MEASURES Assessment was performed for clinical markers using standardized scales for hyposmia, rapid eye movement sleep behavior disorder, depression, autonomic dysfunction, cognitive function, and parkinsonian motor signs (using the Unified Parkinson's Disease Rating Scale motor subscale [UPDRS part III]).

RESULTS Over 2 years, depression scores were significantly worse for heterozygous carriers (mean baseline, 0.65; mean follow-up, 2.88; $P = .01$), rapid eye movement sleep behavior disorder scores were significantly worse for patients with GD (mean baseline, 0.93; mean follow-up, 2.93; $P < .001$) and heterozygotes (mean baseline, 0.10; mean follow-up, 2.30; $P < .001$), and UPDRS part III scores were significantly worse for patients with GD (mean baseline, 4.29; mean follow-up, 7.82; $P < .001$) and heterozygotes (mean baseline, 1.97; mean follow-up, 4.50; $P < .001$). For controls, there was a small but significant deterioration in the UPDRS part II (activities of daily living) score (mean baseline, 0.00; mean follow-up, 0.58; $P = .006$). At 2 years, olfactory and cognitive assessment scores were lower in patients with GD and heterozygotes compared with controls, but they did not differ significantly from baseline. When the results from the patients with GD and the heterozygotes were combined, a significant deterioration from baseline was observed, as reflected in the Rapid Eye Movement Sleep Behaviour Disorder Questionnaire (mean baseline, 0.51; mean follow-up, 2.63; $P < .001$), Beck Depression Inventory (mean baseline, 1.72; mean follow-up, 4.44; $P = .002$), and UPDRS part II (mean baseline, 0.88; mean follow-up, 2.01; $P < .001$) and part III scores (mean baseline, 3.09; mean follow-up, 6.10; $P < .001$) (all $P < .01$), and at 2 years, significant differences in University of Pennsylvania Smell Identification Test, Unified Multiple System Atrophy Rating Scale, Mini-Mental State Examination, Montreal Cognitive Assessment, and UPDRS part II and part III scores were observed between patients with GD/heterozygotes and controls (all $P < .05$).

CONCLUSIONS AND RELEVANCE This study indicates that, as a group, *GBA* mutation–positive individuals show a deterioration in clinical markers consistent with the prodrome of PD. Within this group of individual, 10% appear to be evolving at a more rapid rate.

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Homozygous *GBA* mutations cause Gaucher disease (GD), a lysosomal storage disease. It is presently estimated that homozygous or heterozygous *GBA* mutations confer a 20- to 30-fold increased risk for Parkinson disease (PD),[1,2] and at least 7% of patients with PD have *GBA* mutations.[2,3] The percentage is higher among the Ashkenazi Jewish population.[4] The percentage of *GBA* mutation carriers who develop PD has been estimated to be 13.7% at 60 years of age and 29.7% at 80 years of age,[5] and so a method to determine individual risk for PD expression in this population would be very valuable. In addition, those with dementia with Lewy bodies are 8 times more likely to carry a mutation in *GBA* than healthy controls, which suggests a role for *GBA* mutations in other Lewy body disorders.[6]

For any neuroprotective treatment or disease-modifying therapy to be most effective, PD should be detected at as early a stage as possible. The deposition of α-synuclein is not restricted to the brain; for example, deposits have been found in the olfactory bulb, the peripheral nervous system, the enteric nervous system, the heart, and the pelvic plexuses.[7] This pathology probably underlies the early nonmotor manifestations of PD, which may precede the onset of more typical PD motor symptoms by several years.[8]

Candidate biomarkers have been proposed and may be useful objective measures for the early detection of PD.[9,10] In our study, we have used early clinical markers to quantify nonmotor symptoms such as hyposmia, rapid eye movement sleep behavior disorder, depression, cognition, and autonomic dysfunction.

The aim of our study was to provide longitudinal data on a *GBA*-positive cohort at high risk for the development of PD and to identify biomarkers or symptoms indicating progression to early PD. The first clinical evaluation of this cohort has been published,[11] and the results presented here represent the 2-year follow-up.

Methods

Participants

Patients with type 1 GD were recruited from the Lysosomal Storage Disorder Unit at the Royal Free Hospital in London, England, in 2010. Potential heterozygous *GBA* mutation–positive relatives (78.6% of parents, 10.7% of siblings, and 10.7% of children >21 years of age) and genetically unrelated controls (spouses or partners) were identified by obtaining a detailed family history from each patient with GD, and these heterozygotes and controls were then recruited to participate in our study. Participants were also recruited from the UK Gauchers Association. In all, this unique cohort included 135 participants. Among them, 90 participants have been followed up longitudinally, with target follow-up assessments at 2-year intervals beginning in 2012. Exclusion criteria included a diagnosis of PD or dementia for both the patients with GD and the *GBA* mutation carriers and any existing neurological disease for the controls. The diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank Criteria.[12] Dementia was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for patients with a Mini-Mental State Examination (MMSE) score of 24 or less. The *GBA* mutation status in all participants was confirmed by Sanger sequencing of the *GBA* gene, as previously described.[11] The senior researcher was blinded to genotype. Our study was approved by the Hampstead Research Ethics Committee (reference 10/H0720/21). All participants provided written informed consent.

Follow-up Evaluation

Of the 90 participants who were evaluated at baseline (2010-2011),[11] 4 (4.4%) were lost to follow-up because they either declined to participate (n = 2) or could not be contacted (n = 2). In addition, 2 participants (2.2%) died (one died of pneumonia, and the other died of breast cancer). Therefore, 84 participants (93.3%) (30 participants who previously received a diagnosis of type 1 GD, 28 heterozygous *GBA* mutation carriers, and 26 controls) completed the follow-up evaluation that comprised a structured clinical workup, a standardized clinical history, and a complete neurological assessment, which included the use of the Unified Parkinson's Disease Rating Scale for activities of daily living and the motor subscale (UPDRS parts II and III, respectively), the University of Pennsylvania Smell Identification Test (UPSIT) for olfactory function, the MMSE and the Montreal Cognitive Assessment (MoCA) for cognitive function, the Rapid Eye Movement Sleep Behaviour Disorder Questionnaire (RBDQ), the Beck Depression Inventory (BDI) for depression, and a subscale of the Unified Multiple System Atrophy Rating Scale (UMSARS) for autonomic dysfunction. Anosmia was interpreted using age- and sex-adjusted normative scores (http://sensonics.com/). All participants were examined independently by a physician trained in movement disorders (M.B.). All procedures were performed and scored identically at follow-up to those performed at baseline. A senior neurologist who is an expert on movement disorders (A.H.V.S.) evaluated participants whenever there was a significant difference between follow-up and baseline UPDRS scores.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 21. To assess the differences between the group mean values across the 2 different time points, we performed a 2-way analysis of covariance with the factors "group" (eg, patients with GD vs carriers vs controls) and "time" (time 1 vs time 2). The covariates age, sex, education, and family relationship were added to the design matrix in order to account for differences in these mean values between the groups. Post hoc tests were used to compare the groups at follow-up. Paired *t* tests were used to compare the scores within each group before and after follow-up. Differences in age, sex, and ethnicity between groups were checked using the 1-way analysis of variance and the χ^2 test. We also accounted for performing multiple statistical tests across our dependent variables (the UPSIT, UMSARS, RBDQ, MMSE, MoCA, UPDRS part II, UPDRS part III, and BDI scores) by defining a significance threshold for statistical tests of $P < .05$ and by correcting this for multiple comparisons using the Benjamini-Hochberg false discovery rate. In brief, this procedure involves ordering all *P* values in ascending order and applying a sequential threshold.

Table 1. Demographic, Clinical, and Genetic Characteristics of the Study Cohort[a]

Characteristic	Patients With Type 1 GD (n = 30)	Heterozygous *GBA* Mutation Carriers (n = 28)	Controls (n = 26)	*P* Value
Age, mean (SEM), y	61.0 (2.1)	63.6 (2.0)	61.7 (2.2)	.19[b]
Sex, No.				
Male	14	12	14	.29[c]
Female	16	16	12	
Ethnicity, No.				
Ashkenazi Jewish	10	5	6	.38[c]
White British	20	23	20	
Family history of PD, %	16.7	7.1	0.0	.03[c,d]
Most frequent genotype	N370S/L444P	N370S		
GD treatment				
ERT	25	0	0	
SRT	2	0	0	
None	3	0	0	

Abbreviations: ERT, enzyme replacement therapy; GD, Gaucher disease; PD, Parkinson disease; SRT, substrate reduction therapy.

[a] Significance was taken at the 5% level.

[b] Determined by use of 1-way analysis of variance.

[c] Determined by use of the χ^2 test.

[d] Significant difference.

Results

The 84 participants (40 men [47.6%]) had a mean (SD) follow-up duration of 1.9 (0.2) years (range, 1.5-2.3 years). The demographic, clinical, and genetic characteristics, along with statistical comparisons, of the cohort are shown in **Table 1**. The participants with type 1 GD did not differ significantly from the heterozygous *GBA* mutation carriers or the controls in terms of age, sex, and ethnicity (all $P > .05$, determined by use of 1-way analysis of variance and the χ^2 test). Both the patients with type 1 GD and the heterozygous *GBA* mutation carriers were significantly more likely than the controls to have a family history of PD ($P = .03$). As described previously,[11] the most common genotype in patients with type 1 GD was N370S/L444P (11 of 30 patients [36.7%]). None of the patients with type 1 GD had features of type III GD (such as generalized seizures or progressive myoclonic epilepsy). For the carriers, the most common genotype was N370S (14 of 28 carriers [50.0%]).

GBA Mutation–Positive Individuals With Significant Deterioration

The scores with regard to the prodromal clinical features of PD at baseline and follow-up are reported in **Table 2** (see also **Figure**). Please refer to Table 2 for the exact *P* values. There was a significant deterioration for GD patients over the mean 2 years of follow-up as reflected in the RBDQ, UPDRS part II, and UPDRS part III scores. Over the same period, the *GBA* mutation carriers showed a significant deterioration as reflected in the RBDQ, UPDRS part II, UPDRS part III, and BDI scores. There was a marginal but significant deterioration only in the matched controls with regard to the UPDRS part II score. There was no difference between baseline and follow-up scores for all groups for assessments of olfaction, cognition, and autonomic dysfunction.

At the 2-year follow-up, the patients with GD showed a significant difference in mean UPSIT, MMSE, MoCA, UPDRS part II, and UPDRS part III scores when compared with controls. Similarly, at 2 years, *GBA* mutation carriers showed a significant difference in mean follow-up UPSIT, MMSE, and MoCA scores when compared with controls. When the patients with GD and the *GBA* mutation carriers were compared at baseline, there was a significant difference in the mean BDI score. At the 2-year follow-up, the patients with GD demonstrated significantly worse mean BDI, UPDRS part II, and UPDRS part III scores compared with the carriers. There was no significant difference in mean UPSIT, UMSARS, MMSE, MoCA, or RBDQ scores between the patients with GD and the carriers at follow-up.

When the results from individuals with homozygous or heterozygous mutations in *GBA* were combined in a secondary, pooled analysis (**Table 3**; eFigures 1 and 2 in the Supplement), a significant deterioration in *GBA* mutation–positive individuals over the 2 years of follow-up was found with regard to mean RBDQ, BDI, UPDRS part II, and UPDRS part III scores. At baseline, *GBA* mutation–positive individuals showed significant differences in mean UPSIT and MoCA scores when compared with controls.[11] At the 2-year follow-up, *GBA* mutation–positive individuals showed significant differences in mean UPSIT, UMSARS, MMSE, MoCA, UPDRS part II, and UPDRS part III scores when compared with controls.

Specific Patients With GD and *GBA* Heterozygotes With Parkinsonian Motor Signs and Significant Deterioration

At baseline, 3 patients with GD had parkinsonian motor signs, but this was insufficient for a diagnosis of PD. As described previously,[11] patient GD05 (male, 78 years of age, and Ashkenazi Jewish) had bilateral rigidity with activation maneuver, asymmetric bradykinesia of all limbs, and gait impairment. Patient GD18 (male, 83 years of age, and Ashkenazi Jewish) had a left-arm rest tremor and bilateral arm rigidity with activation maneuver. Patient GD27 (male, 69 years of age, and white British) had flexed posture, bilateral rigidity, and postural and kinetic tremor of the upper limbs. At follow-up, the parkinsonian signs present at baseline in these patients had worsened but did not meet the diagnostic criteria for PD.[13] Patient GD05 had developed a tremor in both hands (intermittent, present at rest, and worse on intention). Patient

Table 2. Baseline and Follow-up Clinical Markers in a Group Comparison Between Patients With Type 1 GD, Heterozygous *GBA* Mutation Carriers, and Controls[a]

Marker	Mean (SEM) Score			Between-Group *P* Value[b]		
	Patients With GD (n=30)	Carriers (n=28)	Controls (n=26)	Patients With GD vs Controls	Carriers vs Controls	Patients With GD vs Carriers
University of Pennsylvania Smell Identification Test score						
Baseline	32.57 (0.96)	31.11 (0.93)	35.32 (0.40)			
Follow-up	31.21 (0.98)	30.22 (1.10)	33.95 (0.62)	.003[d]	.001[d]	.52
Within-group *P* value[c]	.03	.29	.13			
Unified Multiple System Atrophy Rating Scale score						
Baseline	0.40 (0.15)	0.37 (0.15)	0.08 (0.06)			
Follow-up	0.63 (0.16)	0.53 (0.16)	0.13 (0.07)	.004[d]	.02[d]	.99
Within-group *P* value[c]	.11	.59	.32			
Rapid Eye Movement Sleep Behaviour Disorder Questionnaire score						
Baseline	0.93 (0.31)	0.10 (0.10)	0.25 (0.14)			
Follow-up	2.93 (0.55)	2.30 (0.40)	1.08 (0.30)	.04	.99	.23
Within-group *P* value[c]	<.001[d]	<.001[d]	.07			
Mini-Mental State Examination score						
Baseline	29.23 (0.17)	29.23 (0.18)	29.28 (0.16)			
Follow-up	28.40 (0.48)	28.63 (0.32)	29.50 (0.21)	.01[d]	.03[d]	.99
Within-group *P* value[c]	.08	.05	.30			
Montreal Cognitive Assessment score						
Baseline	25.93 (0.53)	25.55 (0.58)	27.32 (0.23)			
Follow-up	26.33 (0.75)	26.21 (0.57)	27.73 (0.26)	.001[d]	.001[d]	.99
Within-group *P* value[c]	.07	.38	.20			
Unified Parkinson's Disease Rating Scale part II score						
Baseline	1.45 (0.82)	0.33 (0.21)	0.00 (0.00)			
Follow-up	2.72 (0.66)	1.33 (0.30)	0.58 (0.19)	<.003[d]	.99	.009[d]
Within-group *P* value[c]	.003[c]	<.001[c]	.006[d]			
Unified Parkinson's Disease Rating Scale part III score						
Baseline	4.29 (1.45)	1.97 (0.65)	0.21 (0.17)			
Follow-up	7.82 (1.91)	4.50 (0.75)	0.92 (0.37)	<.001[d]	.04	.006[d]
Within-group *P* value[c]	<.001[d]	<.001[d]	.06			
Beck Depression Inventory score						
Baseline	2.68 (1.78)	0.65 (0.41)	0.33 (0.33)			
Follow-up	5.84 (1.14)	2.88 (0.68)	0.58 (0.43)	.04	.99	.03[d]
Within-group *P* value[c]	.04	.01[d]	.11			

Abbreviation: GD, Gaucher disease.

[a] Significance was taken at the 5% level for all variables. Only values that survived multiple comparisons with the false discovery rate procedure were denoted significant. Reported *P* values compare the mean (SEM) scores for clinical markers within groups (baseline and follow-up) and between groups (patients with type 1 GD, carriers, and controls) at follow-up.

[b] Two-way analysis of covariance with Bonferroni correction.

[c] Determined by use of paired *t* test.

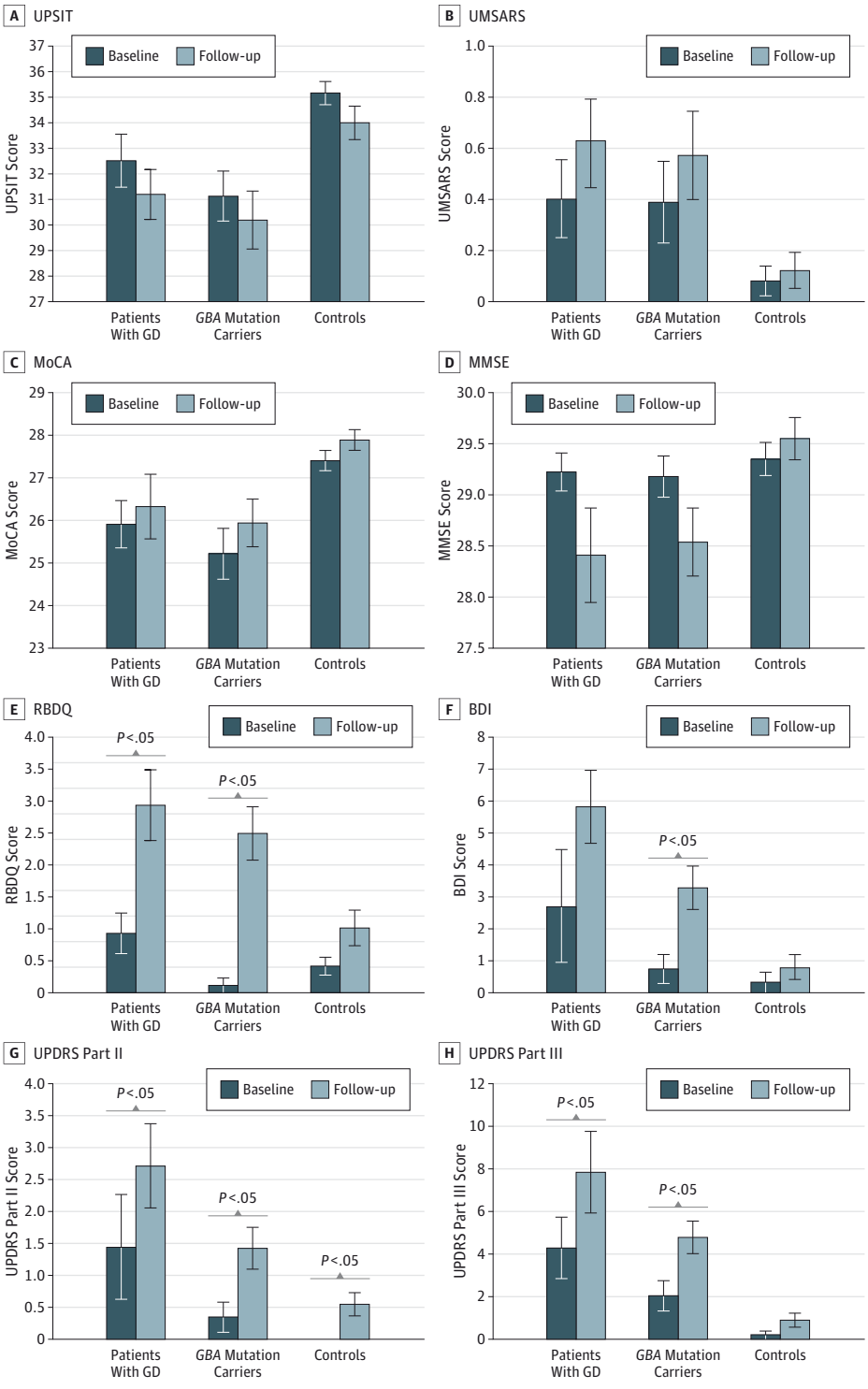
[d] Statistically significant difference.

GD18 now had bilateral rigidity without activation maneuver or gait impairment. Patient GD27 had developed a head tremor, and the postural and kinetic tremor of his upper limbs had worsened (now present at rest). In addition, 1 patient who did not have parkinsonian signs at baseline had developed them at follow-up. Patient GD11 (male, 73 years of age, and Ashkenazi Jewish) had developed a very slight tremor of his right thumb (non-pill-rolling) present at rest but with no other features of parkinsonism.

Similarly, 2 *GBA* carriers had parkinsonian motor signs at baseline. As described previously,[11] patient C17 (female, 78 years of age, and white British) had bilateral rigidity, masklike facies, and bradykinesia, whereas patient C31 (male, 78 years of age, and white British) had masked facies, bilateral rigidity with activation maneuver, left-arm kinetic tremor, and flexed posture. At follow-up, the parkinsonian signs present in these patients remained unchanged from baseline.

When specific patients with GD and specific *GBA* heterozygotes, both with features of parkinsonism (6 of 58 participants [10.3%]), were excluded, the follow-up data remained significant. The remaining patients with GD and the remaining *GBA* mutation carriers (52 of 58 of participants [89.7%]) still showed a significant deterioration as reflected in the RBDQ, UPDRS part II, UPDRS part III, and BDI scores after 2 years (eTable 1 in the Supplement).

Figure. Clinical Markers Showing Progression in *GBA* Mutation–Positive Individuals in a 2-Year Follow-up Study



Mean baseline and follow-up scores for olfaction (A), autonomic dysfunction (B), Montreal Cognitive Assessment (MoCA) scores (C), and Mini-Mental State Examination (MMSE) scores (D) for patients with type 1 Gaucher disease (GD) and for heterozygous *GBA* mutation–positive carriers compared with controls. Error bars indicate SEM. E, A statistically significant increase is demonstrated in the mean follow-up Rapid Eye Movement Sleep Behaviour Disorder Questionnaire (RBDQ) scores. F, A statistically significant increase in depressive symptoms is demonstrated for carriers at the follow-up evaluation. G, A statistically significant increase is demonstrated in the mean follow-up Unified Parkinson's Disease Rating Scale (UPDRS) part II scores for patients with type 1 GD, heterozygous *GBA* mutation–positive carriers, and controls. H, A statistically significant increase is demonstrated in the mean follow-up UPDRS part III scores for patients with type 1 GD and for heterozygous *GBA* mutation–positive carriers compared with controls. Error bars indicate SEM. BDI indicates Beck Depression Inventory; UMSAR, Unified Multiple System Atrophy Rating Scale; and UPSIT, University of Pennsylvania Smell Identification Test.

Premotor Signs Present at Baseline That Could Predict Parkinsonian Motor Signs

When the clinical markers of specific patients with GD (patients GD05, GD11, GD18, and GD27) and specific *GBA* heterozygotes (patients C17 and C31), both with parkinsonian motor signs, were compared with those of *GBA* mutation–positive individuals without features of parkinsonism, there were significant differences in age ($P = .002$) and cognition ($P = .009$) at baseline (eTable 2 and 3 in the Supplement). Baseline UPSIT scores were also noted to be lower for those individuals with features of parkinsonism, but this difference did not reach statistical significance.

Table 3. Baseline and Follow-up Clinical Markers in a Pooled Analysis Comparing All *GBA* Mutation–Positive Individuals vs Controls[a]

Marker	Patients With Type 1 GD and Heterozygous *GBA* Mutation Carriers (n = 58)	Controls (n = 26)	Between-Group *P* Value (Controls vs Carriers)[b]
University of Pennsylvania Smell Identification Test score			
Baseline	31.85 (0.67)	35.32 (0.40)	
Follow-up	30.71 (0.73)	33.95 (0.62)	<.001[d]
Within-group *P* value[c]	.02	.13	
Unified Multiple System Atrophy Rating Scale score			
Baseline	0.38 (0·11)	0.08 (0.06)	
Follow-up	0.58 (0·11)	0.13 (0.07)	.001[d]
Within-group *P* value[c]	.15	.32	
Rapid Eye Movement Sleep Behaviour Disorder Questionnaire score			
Baseline	0.51 (0.20)	0.25 (0.14)	
Follow-up	2.63 (0.33)	1.08 (0.30)	.06
Within-group *P* value[c]	<.001[d]	.07	
Mini-Mental State Examination score			
Baseline	29.23 (0.12)	29.28 (0.16)	
Follow-up	28.51 (0.27)	29.50 (0.21)	.002[d]
Within-group *P* value[c]	.02	.30	
Montreal Cognitive Assessment score			
Baseline	25.7 (0.38)	27.32 (0.23)	
Follow-up	26.3 (0.45)	27.73 (0.26)	<.001[d]
Within-group *P* value[c]	.06	.20	
Unified Parkinson's Disease Rating Scale part II score			
Baseline	0.88 (0.39)	0.00 (0.00)	
Follow-up	2.01 (0.36)	0.58 (0.19)	.02[d]
Within-group *P* value[c]	<.001[d]	.006[c]	
Unified Parkinson's Disease Rating Scale part III score			
Baseline	3.09 (0.75)	0.21 (0.17)	
Follow-up	6.10 (0.95)	0.92 (0.37)	<.001[d]
Within-group *P* value[c]	<.001[d]	.06	
Beck Depression Inventory score			
Baseline	1.72 (0.94)	0.33 (0.33)	
Follow-up	4.44 (0.71)	0.58 (0.43)	.09
Within-group *P* value[c]	.002[d]	.11	

Abbreviation: GD, Gaucher disease.

[a] Significance was taken at the 5% level for all variables. Only values that survived multiple comparisons with the false discovery rate procedure were denoted significant. Reported *P* values compare the mean (SEM) scores for clinical markers within groups (baseline and follow-up) and between groups (controls and *GBA* mutation–positive individuals) at follow-up.

[b] Two-way analysis of covariance with Bonferroni correction.

[c] Determined by use of paired *t* test.

[d] Statistically significant difference.

Discussion

Our study was designed to investigate the progression of clinical biomarkers in a cohort of individuals at high risk for PD. Our results demonstrate that clinical features associated with premotor PD and motor features of PD have both evolved since the initial testing, and they support the hypothesis that some *GBA* mutation–positive individuals within this cohort are exhibiting clinical features of early neurodegeneration.

Olfactory abnormalities are found in those with PD with mutations in *GBA*,[14] but they are not a reported feature of GD or its treatment. It has been proposed that the earliest α-synuclein changes occur in the dorsal motor nucleus of the vagus and olfactory bulb,[8] and evidence suggests that an impaired sense of smell is not simply a consequence of aging but rather is a prodromal phenomenon that may predict PD.[15] In the cohort studied, both patients with type 1 GD and heterozygous mutation carriers were, as a group, hyposmic at baseline.[11] At 2 years, follow-up olfactory scores for patients with GD and for heterozygous carriers remained significantly lower than those reported for controls, but they remained unchanged from baseline. This could reflect the short length of the follow-up period, considering that olfactory impairment may progress slowly.

An impaired sense of smell does appear to correlate with other modalities in the prodromal phase of PD (eg, RBD).[16] Owing to its high specificity and long latency to clinical disease, RBD is one of the strongest clinical predictors of neurodegenerative disease and a potential prodromal marker for preventative therapy.[17] The RBDQ carries a high sensitivity, and for those individuals without existing neurological or sleep disorders, it carries a high specificity and, therefore, represents a good tool to detect individuals with RBD.[18] We did identify a significantly increased frequency of symptoms of RBD at the follow-up assessment in *GBA* mutation–positive individuals compared with controls. It is arguable whether a score of 5 or 6 should be the cutoff point for a scale that is structured to determine whether there is RBD or not. It should be noted, how-

ever, that the proportion of RBDQ scores greater than 5 was higher among *GBA* mutation-positive individuals than among controls at follow-up, albeit this difference did not reach significance (P = .39, determined by use of the χ^2 test).

Depression can precede the onset of the motor symptoms of PD and is a presenting complaint in 12% to 22% of patients.[19] There was an increase in the number of reports of depressive symptoms in *GBA* mutation-positive individuals at follow-up. Patients with GD can exhibit moderate to severe psychological complications, similar to patients with other chronic illnesses.[20] In addition, BDI scores of 1 to 10 are consistent with minimal depression, and the specificity of depression alone as a clinical marker of prodromal PD is low but may be usefully combined with other features.[21]

Mild cognitive impairment can occur as a prodrome to parkinsonism[22] or dementia with Lewy bodies.[23] There are several lines of evidence now for greater cognitive impairment in those with established *GBA*-related PD vs sporadic PD,[24-26] and this may reflect a higher burden of Lewy body disease in *GBA*-related parkinsonism.[27,28] Interestingly, in a subgroup of 6 *GBA* mutation-positive individuals with parkinsonian motor signs, mild cognitive impairment (MoCA score of ≤24 for 5 of 6 individuals [83.3%]) was the main premotor sign present at baseline that could have predicted their motor deterioration. Compared with controls, the remaining *GBA* mutation-positive individuals demonstrated significantly lower MMSE and MoCA scores at follow-up, albeit these were unchanged from baseline and still within the normal range for cognitive function.

Controls showed a small but significant change in the UPDRS part II score from baseline. Particular aspects of the UPDRS part II that had worsened for controls included a score of 2.11 for getting out of a bed, a car, or a deep chair; a score of 2.12 for walking (eg, use of a walking aid); and a score of 2.5 for dressing (eg, help with buttons). Subjective complaints of stiffness, tremors, and imbalance are associated with an increased risk for the development of PD.[29] However, we note that the UPDRS part II was not designed or validated as a tool for activities of daily living for aging controls. We believe that what drove the changes in the controls was a small group of individuals (n = 6) who were older (mean age, 70.5 years [range, 62.6-77.8 years]). A significantly higher follow-up UPDRS part II score for patients with GD distinguished these individuals from age-matched controls.

There were some *GBA* mutation-positive individuals (10.0%) with significant motor findings identified using the UPDRS part III that did not overlap with normal physiology (eg, bilateral postural tremor) or existing bone/joint abnormalities. These individuals did not meet the diagnostic criteria for PD but could represent a subgroup of *GBA* mutation-positive individuals who are progressing toward clinical PD.

We considered the effect of concurrent medications. The majority of patients with type 1 GD (83.0%) were receiving enzyme replacement therapy. This type of therapy does not cross the blood-brain barrier and has no reported neurological adverse effects. Furthermore, enzyme replacement therapy has no known effect on dysautonomia. Substrate reduction therapy can induce memory problems.[30] However, only 2 patients with GD were receiving substrate reduction therapy when evaluated at baseline and at follow-up, and neither had cognitive impairment.

To our knowledge, this study is the first to undertake the longitudinal follow-up of a large cohort of *GBA* mutation-positive individuals prior to the development of PD. Much of the work published thus far in the literature has focused on patients with established PD. This has been essential to make important comparisons between sporadic PD and *GBA*-related parkinsonism and to observe subtle differences. The opportunity to observe patients prospectively within a unique at-risk cohort such as this is essential for defining the optimal time to intervene with neuroprotective therapy.

One limitation of our study was that not all investigators were blinded to the genetic status of individuals. To minimize any observer bias, standardized scores were used, and all follow-up data were reexamined. Other potential criticisms are the use of prodromal markers and their sensitivity, specificity, and positive and negative predictive values. The presence of clinical markers alone may be insufficient to accurately predict a neurodegenerative disorder in the majority of cases. However, clinical markers may be used in combination with other biochemical or imaging markers for prodromal PD to develop a more reliable method for predicting PD.

Conclusions

The data from this cohort suggest that hyposmia is the earliest and most sensitive prodromal marker. Cognitive impairment is also an early feature, and this may relate to the increased cognitive impairment observed in *GBA*-related PD. Symptoms of RBD, the most specific clinical marker, are now present in *GBA* mutation-positive individuals. Depressive symptoms have also surfaced but must be interpreted with some caution, considering their low specificity as a marker for PD. There has also, and perhaps most importantly, been a significant decline on the UPDRS, which, together with impaired RBD and depression, suggests that clinical markers in some individuals of this *GBA* mutation-positive cohort have evolved, in a pattern consistent with the clinical prodrome of PD.

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Drafting of the manuscript: Beavan, McNeill.
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