Evolution of prodromal clinical markers of Parkinson disease in a *glucocerebrosidase* mutation positive cohort

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Abstract

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—The purpose of this study was the longitudinal clinical evaluation of a *GBA* mutation positive cohort and the evolution of the prodromal features of PD.

Design—Individuals were participants in a study of the aetiology and prodrome of PD and have been re-evaluated in this 2 year follow-up report.

Setting—Clinic-based.

Participants—Type 1 GD patients and heterozygous *GBA* mutation positive carriers were recruited in 2010 from the Lysosomal Storage Disorder Unit at the Royal Free Hospital, London. Thirty previously diagnosed Type 1 GD patients, twenty-eight heterozygous *GBA* mutation carriers and twenty-six genetically unrelated controls were included. For both GD and carrier subjects, exclusion criteria included a diagnosis of PD or dementia and for controls, any existing neurological disease.

Main Outcome(s) and Measure(s)—Assessment was performed for clinical markers including hyposmia, rapid eye movement sleep behaviour disorder (RBD), depression, autonomic dysfunction, cognitive function and parkinsonian motor signs (UPDRS part III).

Results—Over 2 years, depression scores were significantly worse in heterozygotes ($P = \cdot 01$), RBD scores were significantly worse in GD patients ($P < \cdot 001$) and heterozygotes ($P < \cdot 001$), and UPDRS III scores were significantly worse in GD patients ($P < \cdot 001$) and heterozygotes ($P < \cdot 001$). In controls, there was a small but significant deterioration in the UPDRS II score ($P = \cdot 006$). At 2 years, olfactory and cognitive assessment scores were lower in GD patients and heterozygotes compared to controls, but did not differ significantly from baseline. When the results from GD patients and heterozygotes were combined, there was a significant deterioration from baseline in RBD, BDI, UPDRS II and III scores (in all, $P < \cdot 01$), and at 2 years, significant differences in UPSIT, UMSARS, MMSE, MoCA, UPDRS II and UPDRS III scores when compared to controls (in all, $P < \cdot 05$).

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

Keywords

Parkinson's disease; Gaucher disease; neurodegeneration

INTRODUCTION

Homozygous *GBA* mutations cause Gaucher disease (GD), a lysosomal storage disorder. It is presently estimated that homozygous or heterozygous *GBA* mutations confer an increased risk for Parkinson disease (PD) of 20-30 fold[1,2] and at least 7% of PD patients have *GBA* mutations[2,3], and this is higher in the Ashkenazi Jewish population[4]. The penetrance of *GBA* mutation carriers to develop PD has been estimated as 13·7% at age 60 years and 29·7% at age 80 years[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 (DLB) are 8 times more likely to carry a mutation in *GBA* than healthy controls, suggesting 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, with deposits found in the olfactory bulb, peripheral nervous system, enteric nervous system (ENS), cardiac, and pelvic plexuses, etc[7]. This pathology probably underlies the early non-motor 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 this study, we have used early clinical markers to quantify non-motor symptoms such as hyposmia, rapid eye movement sleep behaviour disorder (RBD), depression, cognition, and autonomic dysfunction.

The aim of this 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 previously[11] and the results presented here represent the two year follow up.

METHODS

Participants

Type 1 GD patients were recruited from the Lysosomal Storage Disorder Unit at the Royal Free London NHS Foundation Trust in 2010. Potential heterozygous *GBA* mutation positive carrier relatives (parents: 78·6%; siblings: 10·7%; children >21 years: 10·7%) and genetically unrelated controls (spouses/partners) were identified by taking a detailed family history from each GD patient, and recruited with consent. Individuals were also recruited from the UK Gaucher Disease Association. In all, this unique cohort included one hundred and thirty-five participants. Among them, ninety participants have been followed longitudinally with target follow-up assessments at two year intervals beginning in 2012. For both GD and carrier subjects, exclusion criteria included a diagnosis of PD or dementia and for controls, any existing neurological disease. The diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank Criteria[12]. Dementia was diagnosed according to DSM-IV criteria in patients with a Mini-Mental State Examination score of 24. 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. The study was approved by the Hampstead Research Ethics Committee (reference number 10/H0720/21). All individuals provided written informed consent.

Follow-up evaluation

Of ninety individuals who were evaluated at baseline (2010-2011)[11], four participants (4·4%) were lost to follow-up because they either declined to participate (n=2) or were uncontactable (n=2). In addition, two deaths (2·2%) had occurred: one caused by pneumonia, and one by breast carcinoma. Therefore, eighty-four (93·3%) participants (thirty previously diagnosed Type 1 GD patients, twenty-eight heterozygous *GBA* mutation carriers, and twenty-six controls) completed the follow-up evaluation that comprised: a structured clinical work-up, a standardised clinical history, complete neurological assessment including the Unified Parkinson's Disease Rating Scale activities of daily living and motor subscale (UPDRS parts II and III), olfactory function using the University of Pennsylvania Smell Identification Test (UPSIT), cognitive function using the Mini-Mental State Examination (MMSE) and Montreal Cognitive assessment (MoCA), RBD with the RBD Questionnaire (RBDQ), depression using the Beck's Depression Inventory (BDI), and autonomic dysfunction using a subscale of the Unified Multiple System Atrophy Rating Scale (UMSARS). Anosmia was interpreted using age- and sex-adjusted normative scores (www.sensonics.com). All participants were examined independently by a movement disorders-trained physician (M.B.). All procedures were performed and scored identically at follow-up to those carried out at baseline. A senior neurologist expert on movement disorders (A.H.V.S.) evaluated individuals where there was a significant difference between UPDRS scores measured at follow-up and at baseline.

Statistical analysis

The data was analysed using IBM SPSS Statistics (version 21). To assess the differences between the group means across the two different time points, we performed a two-way ANCOVA with factors Group (e.g. Gaucher vs. Carrier vs. Control) and Time (Time 1 vs.

Time 2). The covariates age, gender, education, and family relationship were added to the design matrix, in order to account for differences in these 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 One-way ANOVA and the Chi-squared test. We also accounted for performing multiple statistical tests across our dependent variables (UPSIT, UMSARS, RBDQ, MMSE, MoCA, UPDRS II, UPDRS III, BDI) by defining a significance threshold for statistical tests of $P < \cdot05$, and correcting this for multiple comparisons using the Benjamini-Hochberg FDR (False Discovery Rate). In brief, this procedure involves ordering all P values in ascending order and applying a sequential threshold.

RESULTS

The eighty-four participants (40 men [47·6%]) had a mean follow-up duration of 1·9±0·2 years (range, 1·5-2·3 years). The demographic, clinical and genetic characteristics, with statistical comparisons, of the cohort are shown in Table I. Participants with Type 1 GD did not differ significantly from heterozygous *GBA* positive carriers or controls in terms of age, sex, and ethnicity (One-way ANOVA and Chi-squared test, in all $P > \cdot05$). Both Type 1 GD patients and heterozygous *GBA* mutation carriers were significantly more likely to have a family history of PD than controls ($P = \cdot03$). As described previously[11], the most common genotype in GD patients was N370S/L444P (11/30; 36·7%). No GD patients had features of Type III disease such as generalized seizures or progressive myoclonic epilepsy. In carriers, the most common genotype was N370S (14/28; 50%).

GBA mutation positive individuals show significant deterioration in clinical markers

The results of prodromal clinical features of PD at baseline and follow-up are reported in Table II (see also Figure 1 and Figure 2). Please refer to Table II for the exact P values. There was a significant deterioration in RBDQ, UPDRS II and III scores for GD patients over the mean two years of follow-up. Over the same period, the *GBA* mutation carriers showed a significant deterioration in RBDQ, UPDRS II and III, and BDI scores. There was a marginal but significant deterioration only in the UPDRS II score in the matched controls. There was no difference between baseline and follow-up scores for all groups for assessments of olfaction, cognition and autonomic dysfunction.

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

When the results from individuals with homozygous or heterozygous mutations in *GBA* were combined in a secondary, pooled analysis (see Table III and eFigures 1 and 2 in the

Supplemental material), there was a significant deterioration in mean RBDQ, BDI, UPDRS II and III scores in *GBA* mutation positive individuals over the two years of follow-up. At baseline, *GBA* mutation positive individuals showed significant differences in mean UPSIT and MoCA scores when compared to controls[11]. At 2 years follow-up, *GBA* mutation positive individuals showed significant differences in mean UPSIT, UMSARS, MMSE, MoCA, UPDRS II and UPDRS III scores when compared to controls.

Specific GD patients and GBA heterozygotes show parkinsonian motor signs and significant deterioration across more than one clinical marker

At baseline, three GD patients had parkinsonian motor signs, but insufficient for a diagnosis of PD. As described previously[11], GD05 (male, 78 years old, Ashkenazi Jewish) had bilateral rigidity with activation manoeuvre, asymmetric bradykinesia of all limbs, and gait impairment. GD18 (male, 83 years old, Ashkenazi Jewish) had left arm rest tremor and bilateral arm rigidity with activation manoeuvre. GD27 (male, 69 years old, 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 study subjects had worsened but did not meet the diagnostic criteria for PD[13]. GD05 had developed a tremor in both hands (intermittent, present at rest and worse on intention). GD18 now had bilateral rigidity without activation manoeuvre and gait impairment. GD27 had developed a head tremor and the postural and kinetic tremor of the upper limbs had worsened (now present at rest). In addition, one subject that did not have parkinsonian signs at baseline had developed them at follow-up. GD11 (male, 73 years old, 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, two *GBA* carriers had parkinsonian motor signs at baseline. As described previously[11], C17 (female, 78 years old, White British) had bilateral rigidity, mask-like facies, and bradykinesia while C31 (male, 78 years old, White British) had masked facies, bilateral rigidity with activation manoeuvre, left arm kinetic tremor, and flexed posture. At follow-up, the parkinsonian signs present in these study subjects remained unchanged from baseline.

When specific GD patients and *GBA* heterozygotes with features of parkinsonism (6/58; 10·3%) were excluded, the follow-up data remained significant. The remaining GD patients and carriers (52/58; 89·7%) still showed a significant deterioration in RBDQ, UPDRS II and III, and BDI scores after two years (see eTable 1 in the supplemental material).

Premotor signs present at baseline that could predict parkinsonian motor signs

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

DISCUSSION

This 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 pre-motor PD, and motor features of PD have both evolved since the initial testing, and 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 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 smell impairment is not simply a consequence of aging but rather is a prodromal phenomenon that may predict PD[15]. In the cohort studied, both Type 1 GD patients and heterozygous mutation carriers were, as a group, hyposmic at baseline[11]. At 2 years, follow-up olfactory scores in GD patients and heterozygous carriers remained significantly lower than those reported for controls, but unchanged from baseline. This could reflect the short length of the follow-up period, considering olfactory impairment may progress slowly.

An impaired sense of smell does appear to correlate with other modalities in the prodromal phase of PD e.g. RBD[16]. Due 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 in those without existing neurological or sleep disorders, a high specificity, and therefore, represents a good tool to detect subjects 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 to controls. It is arguable whether a score of five or six should be the cut off point for a scale that is structured to determine if there is RBD or not. It should be noted, however, that the proportion of RBDQ scores greater than five was higher in *GBA* mutation positive individuals compared to controls at follow-up, albeit this difference did not reach significance ($P = 0 \cdot 39$, Chi-squared test).

Depression can precede the onset of the motor symptoms of PD and is a presenting complaint in 12-22% of patients[19]. There was an increase in the report 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 long-term chronic illnesses[20]. In addition, BDI scores of 1-10 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 DLB[23]. There are several lines of evidence now for greater cognitive impairment in those with established GBA-PD versus sporadic PD[24,25,26], and this may reflect a higher burden of LB disease in GBA-related parkinsonism[27,28]. Interestingly, in a subgroup of six *GBA* mutation positive individuals with parkinsonian motor signs, mild cognitive impairment (MoCA score </=24 in 5/6, 83·3%) was the main premotor sign present at baseline that could have predicted their

motor deterioration. Compared to 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.

Control subjects showed a small but significant change in the UPDRS part II score from baseline. Particular aspects of the UPDRS II that had worsened in controls included: 2.11 (getting out of a bed, a car or a deep chair), 2.12 (walking e.g. use of a walking aid), 2.5 (dressing e.g. 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 (ADL) in aging controls. We believe what drove the changes in the controls were a small group of individuals (n=6) who were older (mean age 70·5 years (range 62·6-77·8). When compared, a significantly higher follow-up UPDRS part II score in GD patients distinguished these individuals from age-matched controls.

There were some *GBA* mutation positive individuals (10%) with significant motor findings identified using the UPDRS part III, which did not overlap with normal physiology (e.g. 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 that are progressing towards clinical PD.

We considered the effect of concurrent medications. The majority of Type 1 GD patients (83%) were receiving enzyme replacement therapy (ERT). This does not cross the blood brain barrier and has no reported neurological side effects. Furthermore, ERT has no known impact on dysautonomia. Substrate reduction therapy (SRT) can induce memory problems[30]. However, only 2 GD patients were receiving SRT when evaluated at baseline and at follow-up, and neither had cognitive impairment.

Our 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 focussed 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 follow 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 the study was that not all investigators were blind to the genetic status of individuals. To minimise any observer bias, standardised scores were used and all follow-up data were re-examined. 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 accurately to 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 PD prediction.

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 with GBA-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, suggest that clinical markers in some individuals of this *GBA* mutation positive cohort have evolved, in a pattern consistent with the clinical prodrome of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Full financial disclosures of all authors for the past year

Anthony Schapira

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Honoraria/payment	None	Donation of medical equipment	None
Advisory Boards	None	Patents planned, pending, or issued	None
Speakers' bureaus	None	Other	None

Statements

Michelle Beavan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Written permission has been obtained from all persons named in the Acknowledgment section.

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Figure 1.

Clinical markers show progression in *GBA* mutation positive individuals in a two-year follow-up study.

Figures demonstrate mean baseline and follow-up scores for olfaction (A), mean baseline and follow-up scores for autonomic dysfunction (B), mean baseline and follow-up MoCA scores (C) and mean baseline and follow-up MMSE scores (D) for Type 1 GD patients and heterozygous *GBA* positive carriers compared to controls. Means are plotted together with the SEM.
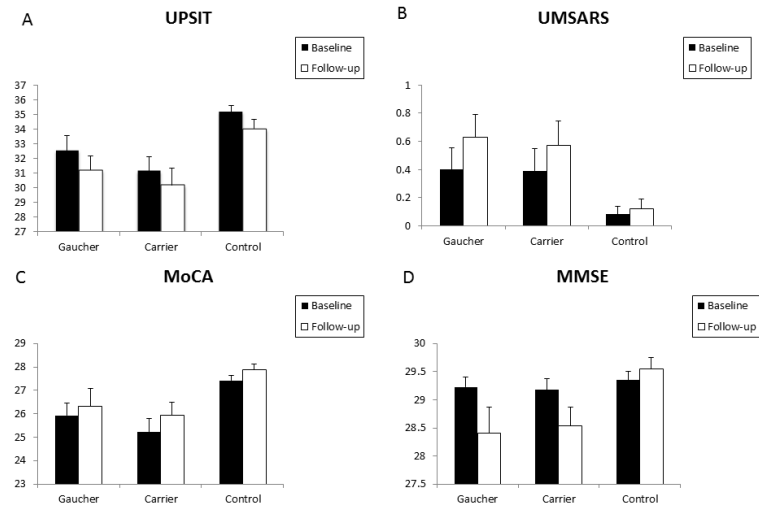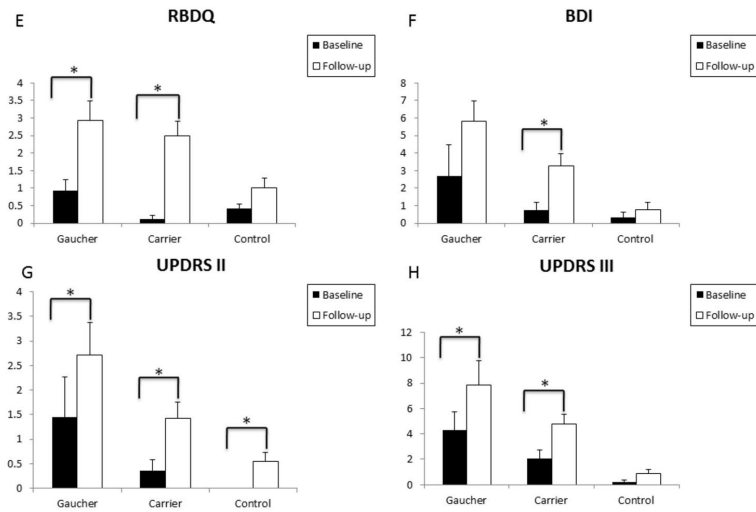
Figure 2.
Clinical markers show progression in *GBA* mutation positive individuals in a 2-year follow-up study.

Figures demonstrate a statistically significant increase in depressive symptoms for carriers at the follow-up evaluation (F), a statistically significant increase in mean follow-up RBDQ scores (E) and UPDRS III scores (H) in Type 1 GD patients and heterozygous *GBA* mutation positive carriers compared to controls, and a statistically significant increase in mean follow-up UPDRS II scores in Type 1 GD patients, heterozygous *GBA* mutation positive carriers, and controls (G). Means are plotted together with the SEM.

Table I

Demographic, clinical and genetic characteristics of the study cohort

Characteristic	Type 1 GD patients (n=30)	Heterozygous *GBA* mutation carriers (n=28)	Controls (n=26)	*P* value
Age, years	61·0 (2·1)	63·6 (2·0)	61·7 (2·2)	·19[a]
Gender (F/M)	16/14	16/12	12/14	·29[b]
Ethnicity (Ashkenazi/White British)	10/20	5/23	6/20	·38[b]
Family history of PD, (%)	16·7	7·1	0·0	·03[bc]
Most frequent genotype	N370S/L444P	N370S	-	-
GD treatment (ERT/SRT/none)	25/2/3	-	-	-

Results are presented as mean and SEM. Significance was taken at the 5% level.

Abbreviations: ERT Enzyme Replacement Therapy. SRT Substrate Reduction Therapy.

[a]One-way ANOVA.

[b]Chi-squared test.

[c]Significant difference

Table II

Baseline and follow-up clinical markers in a group comparison between Type 1 GD patients, carriers and controls.

		Type 1 GD patients (n=30)	Heterozygous *GBA* mutation carriers (n=28)	Controls (n=26)	*P* (between)[b]		
					P[1]	P[2]	P[3]
UPSIT	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[c]	·001[c]	·52
	P (within)[a]	·03	·29	·13			
UMSARS	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[c]	·02[c]	1·00
	P (within)[a]	·11	·59	·32			
RBDQ	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	1·00	·23
	P (within)[a]	<·001[c]	<·001[c]	·07			
MMSE	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[c]	·03[c]	1·00
	P (within)[a]	·08	·05	·30			
MoCA	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[c]	·001[c]	1·00
	P (within)[a]	·07	·38	·20			
UPDRS II	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[c]	1·00	·009[c]
	P (within)[a]	·003[c]	<·001[c]	·006[c]			
UPDRS III	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[c]	·04	·006[c]
	P (within)[a]	<·001[c]	<·001[c]	·06			
BDI	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	1·00	·03[c]
	P (within)[a]	·04	·01[c]	·11			

Abbreviations: *UPSIT* Smell Identification Test, *UMSARS* Unified Multiple System Atrophy Rating Scale, *MoCA* Montreal Cognitive assessment, *MMSE* Mini-Mental State Examination, *RBDQ* Rapid Eye Movement Sleep Behaviour Disorder Questionnaire, *UPDRS* Unified Parkinson's Disease Rating Scale, *BDI* Becks Depression Inventory.

Results are presented as mean and SEM. Significance was taken at the 5% level for all variables. Only values which survived multiple comparisons with the FDR procedure were denoted significant.

Reported *P* values compare the mean values for clinical markers within groups (baseline and follow-up) and between groups (Type 1 GD, carriers and controls) at follow-up.

[1] Controls versus Type 1 GD patients.

[2]Controls versus heterozygote *GBA* mutation carriers.

[3]Type 1 GD patients versus heterozygote *GBA* mutation carriers.

[a]Paired t-test.

[b]Two-way ANCOVA with Bonferroni correction.

[c]Statistically significant difference.

Table III

Baseline and follow-up clinical markers in a pooled analysis comparing all *GBA* mutation positive individuals versus controls.

		Type 1 GD patients and Heterozygous *GBA* mutation carriers combined scores (n=58)	Controls (n=26)	*P* (between)[b] *P* [1]
UPSIT	Baseline	31·85 (0·67)	35·32 (0·40)	
	Follow-up	30·71 (0·73)	33·95 (0·62)	<·001[c]
	P (within)[a]	·02	·13	
UMSARS	Baseline	0·38 (0·11)	0·08 (0·06)	
	Follow-up	0·58 (0·11)	0·13 (0·07)	·001[c]
	P (within)[a]	·15	·32	
RBDQ	Baseline	0·51 (0·20)	0·25 (0·14)	
	Follow-up	2·63 (0·33)	1·08 (0·30)	·06
	P (within)[a]	<·001[c]	·07	
MMSE	Baseline	29·23 (0·12)	29·28 (0·16)	
	Follow-up	28·51 (0·27)	29·50 (0·21)	·002[c]
	P (within)[a]	·02	·30	
MoCA	Baseline	25·7 (0·38)	27·32 (0·23)	
	Follow-up	26·3 (0·45)	27·73 (0·26)	<·001[c]
	P (within)[a]	·06	·20	
UPDRS II	Baseline	0·88 (0·39)	0·00 (0·00)	
	Follow-up	2·01 (0·36)	0·58 (0·19)	·02[c]
	P (within)[a]	<·001[c]	·006[c]	
UPDRS III	Baseline	3·09 (0·75)	0·21 (0·17)	
	Follow-up	6·10 (0·95)	0·92 (0·37)	<·001[c]
	P (within)[a]	<·001[c]	·06	
BDI	Baseline	1·72 (0·94)	0·33 (0·33)	
	Follow-up	4·44 (0·71)	0·58 (0·43)	·09
	P (within)[a]	·002[c]	·11	

Abbreviations: *UPSIT* Smell Identification Test, *UMSARS* Unified Multiple System Atrophy Rating Scale, *MoCA* Montreal Cognitive assessment, *MMSE* Mini-Mental State Examination, *RBDQ* Rapid Eye Movement Sleep Behaviour Disorder Questionnaire, *UPDRS* Unified Parkinson's Disease Rating Scale, *BDI* Becks Depression Inventory.

Results are presented as mean and SEM. Significance was taken at the 5% level for all variables. Only values which survived multiple comparisons with the FDR procedure were denoted significant.

Reported *P* values compare the mean values for clinical markers within groups (baseline and follow-up) and between groups (Controls and *GBA* mutation positive individuals) at follow-up.

[1] Controls versus *GBA* mutation positive individuals.

[a]Paired t-test.

[b]Two-way ANCOVA with Bonferroni correction.

[c]Statistically significant difference.