

## A clinical and family history study of Parkinson's disease in heterozygous *glucocerebrosidase* mutation carriers

Type I Gaucher disease (GD), the most common lysosomal storage disorder, is caused by recessive *glucocerebrosidase* mutations.<sup>1</sup> Both patients with Type I GD and heterozygous *glucocerebrosidase* mutation carriers have increased Parkinson's disease (PD) risk.<sup>1</sup> Non-motor symptoms (NMS) are more frequent in PD with heterozygous *glucocerebrosidase* mutations (PD-GBA).<sup>2</sup> We used the non-motor symptoms scale (NMSS) and Parkinson's disease questionnaire (PDQ-39) to quantify NMS in PD-GBA.<sup>3</sup> The age related PD risk in heterozygous *glucocerebrosidase* carriers has been reported in familial PD.<sup>4</sup> Here, we calculate PD risk in obligate carrier relatives (parents) of Type I GD patients.

### Patients and methods

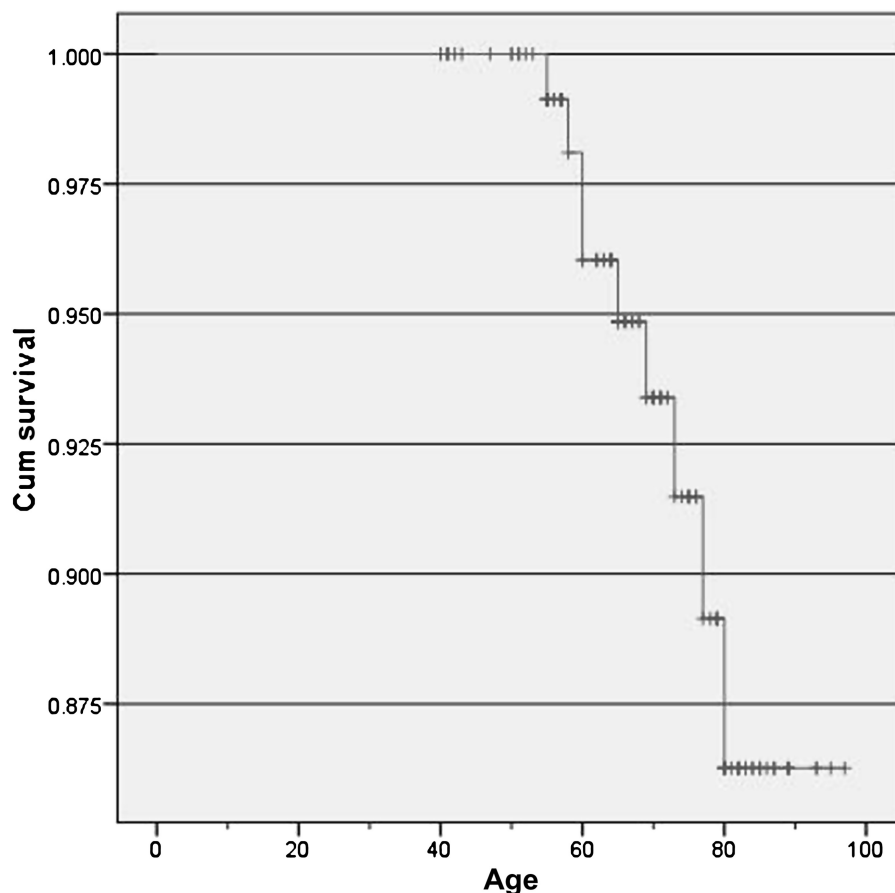
PD-GBA patients were identified by Sanger sequencing of the *glucocerebrosidase* gene in 220 sporadic PD (PD-S) patients. The G2019S mutation in *LRRK2* had previously been excluded. A control group of *glucocerebrosidase* mutation negative PD-S were selected from the same cohort. Each participant had the following administered: 40 item smell identification test (SIT), Montreal Cognitive assessment (MoCA), Parts I–IV of Unified Parkinson's Disease Rating Scale (UPDRS), NMSS, PDQ-39 and Rapid Eye Movement (REM) Sleep Behaviour Disorder Questionnaire (RBDQ). Statistical analysis was performed using SPSS (version 17). The proportion of participants with a MoCA score <26/30 (signifying mild cognitive impairment) or RBDQ >6/10 (signifying possible REM sleep behaviour disorder) was compared using the  $\chi^2$  test.<sup>3</sup> In parallel, family history data were obtained from 83 Type I GD patients, detailing age of onset of PD in their parents (n=166, who are obligate carriers). Age related risk of PD was calculated with

Kaplan–Meier analysis. Parents with PD were also enrolled into the phenotyping study.

### RESULTS

Of 220 PD patients sequenced, 12 (5.5%) had a heterozygous *glucocerebrosidase* mutation, and nine were available for follow-up. Three parents of GD patients with PD were recruited, giving a cohort of 12 PD-GBA patients (5/12 female subjects, mean age 65 (range 49–81 years), 1/12 (8%) Ashkenazi Jewish mean disease duration 8 years (range 2–15)). Twenty out of 208 PD patients without *glucocerebrosidase* mutations (7/20 female subjects, mean age 65 (range 50–83 years), 2/20 Ashkenazi (10%) disease duration 9 years (range 2–20 years)) were selected as controls matched for age, sex and disease duration. Mutations in the PD-GBA group who underwent clinical phenotyping were: N370S (5/12, 42%), L444P (2/12, 16%), recombinant alleles (2/12, 16%), R496H (1/12, 8.3%), V460L (1/12, 8.3%) and IVS2+1 (1/12, 8.3%). The groups were matched for use of levo-dopa (75% vs 60%, p=0.067) and UPDRS parts I (PD-GBA median 8 vs PD-S 9, p=0.95), II (17 vs 18, p=0.067), III (33 vs 34, p=0.13) and IV scores (1 vs 0, p=0.13). No patient had deep brain stimulation but two

PD-GBA patients were on selective serotonin reuptake inhibitors for depression. All PD-GBA and PD-S had olfactory dysfunction on the SIT with no difference between group medians (16/40 vs 15, p=0.503). Using a cut-off score of 26/30 on the MoCA, significantly more PD-GBA had cognitive impairment than PD-S (7/12 (58%) vs 5/20 (25%), p=0.014). PD-GBA scores for abstraction (mean 1.4 vs 2, p=0.023) and orientation (mean 5 vs 5.8, p=0.016) were significantly lower, and there was a trend for PD-GBA attention scores to be lower (mean 4.8 vs 5.5, p=0.055). The overall NMSS score was higher for PD-GBA than PD-S (median 104 (IQR 69–134) vs 38 (16–60), p=0.002). PD-GBA reported more symptoms per participant than PD-S (median 13 (range 1–19) vs median 7 (range 1–14), p=0.0012). The following were more common in PD-GBA: falls with loss of consciousness (25% vs 0%, p=0.04), fatigue (92% vs 30%, p=0.001), unexplained pain (58% vs 10%, p=0.005), loss of interest in life (66% vs 5%, p=0.0004), anxiety (66% vs 20%, p=0.02) and apathy (50% vs 10%, p=0.03). PDQ-39 summary index scores were worse in PD-GBA than PD-S (mean 37 (SD 25) vs mean 21 (SD 13), p=0.032). Subsections in which PD-GBA



**Figure 1** Kaplan–Meier analysis of age related risk of developing Parkinson's disease. Risk is derived from family history data on 166 obligate carriers of *glucocerebrosidase* mutations (parents of Type I Gaucher disease patients), combined for men and women. Overall lifetime RR of Parkinson's disease was 30 (95% CI 7 to 122) in carriers compared to the London population.

had worse scores were emotion (mean 12.5 vs 3.3,  $p=0.008$ ) and discomfort (mean 21.5 vs mean 6.3,  $p=0.01$ ) with cognition (mean 25 vs mean 12.5,  $p=0.075$ ) and ADL (mean 38.4 vs 21,  $p=0.052$ ) being non-significantly worse. Using a cut-off score of 6/10, more PD-GBA participants screened positive for REM sleep disorder than PD-S (7/12 (58%) vs 1/20 (5%),  $p=0.0016$ ).

Data on 166 parents of Type I GD patients were available (17/83 (20%) families Ashkenazi Jewish, 5/83 (6%) Eastern European and the remainder Caucasian UK citizens, no consanguineous families). A PD case was defined by the proband reporting a definite medical diagnosis in their parents. Ten cases of PD were identified, and three were examined in person to confirm diagnosis (these are included in the cohort of 12 PD-GBA described above). Of the 10 cases of PD in relatives, five were male subjects (50%) and mean age of onset was 67 (SD 8.6 years). Figure 1 shows a Kaplan–Meier analysis for developing PD for men and women combined. Age related risk of PD peaked at age 80 (15%). Based on the London population,<sup>5</sup> 0.33 cases of PD would be expected in our cohort of 166 (derived from lifetime prevalence of 2/1000 for men and women). This gave a lifetime RR of 30 (95% CI 7 to 122).

## DISCUSSION

Here, we confirm reports of more severe cognitive dysfunction, depression and anxiety in PD-GBA.<sup>2</sup> Using the NMSS and PDQ-39, we demonstrate for the first time a greater burden of NMS, with lower quality of life in PD-GBA. The number of NMS per patient and severity of symptoms were significantly higher, even though both groups were at a similar stage and duration of PD. Interestingly, a positive result on the RBD screening questionnaire was significantly more common in PD-GBA, suggesting REM sleep behaviour disorder may be more prevalent in PD-GBA. This needs confirmation with sleep studies. The midbrain raphe is involved in sleep regulation and is more frequently abnormal on transcranial sonography in PD-GBA than PD-S.<sup>2</sup> This may explain the apparently increased REM sleep behaviour disorder in PD-GBA. Olfactory dysfunction in PD-GBA and PD-S was

equivalent. This contrasts with LRRK2 and Parkin mutation associated PD in which olfactory dysfunction is less severe than in PD-S.<sup>3</sup> This suggests that the pathological process in PD-GBA and PD-S involves olfactory pathways to a similar extent. The more severe cognitive dysfunction in PD-GBA implies that there may be more widespread cortical pathology than in PD-S. Our clinical findings of more severe NMS correlate with pathological studies indicating that PD-GBA may be associated with more widespread Lewy body pathology.<sup>1</sup>

Lifetime RR of PD in our cohort of 166 obligate carriers was 30, with a cumulative risk of 5% at age 60 rising to 15% at age 80. This risk is similar to that for Type I GD patients.<sup>1</sup> The risk in our cohort is less than the 13.7% (age 60) and 29.7% (age 80) reported in familial PD-GBA.<sup>4</sup> It may be that additional genetic or environmental factors in these PD-GBA families are contributing to an increased risk compared with our GD families. Taken together, these studies confirm a high, age related risk of PD in heterozygous carriers which may differ with ethnic group and family history of GD. This will help to inform genetic counselling of parents of patients with Type I GD.

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**Contributors** Author roles 1. Research project: A. Conception, B. Organisation, C. Execution; 2. Statistical analysis: A. Design, B. Execution, C. Review and critique; 3. Manuscript preparation: A. Writing of the first draft, B. Review and critique. Alisdair McNeill: 1A, 1B, 1C, 2A, 2B, 3A; Raquel Duran: 1C, 2C, 3B; Anthony Schapira: 1A, 2C, 3B; D Hughes: 1B, 2C, 3B; A Mehta: 1B, 2C, 3B.

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