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Original research

Are patients with GBA–Parkinson disease good candidates for deep brain stimulation? A longitudinal multicentric study on a large Italian cohort

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ABSTRACT

Background *GBA* variants increase the risk of developing Parkinson disease (PD) and influence its outcome. Deep brain stimulation (DBS) is a recognised therapeutic option for advanced PD. Data on DBS long-term outcome in *GBA* carriers are scarce.

Objective To elucidate the impact of *GBA* variants on long-term DBS outcome in a large Italian cohort.

Methods We retrospectively recruited a multicentric Italian DBS-PD cohort and assessed: (1) *GBA* prevalence; (2) pre-DBS clinical features; and (3) outcomes of motor, cognitive and other non-motor features up to 5 years post-DBS.

Results We included 365 patients with PD, of whom 73 (20%) carried *GBA* variants. 5-year follow-up data were available for 173 PD, including 32 mutated subjects. GBA-PD had an earlier onset and were younger at DBS than non-GBA-PD. They also had shorter disease duration, higher occurrence of dyskinesias and orthostatic hypotension symptoms.

At post-DBS, both groups showed marked motor improvement, a significant reduction of fluctuations, dyskinesias and impulsive-compulsive disorders (ICD) and low occurrence of most complications. Only cognitive scores worsened significantly faster in GBA-PD after 3 years. Overt dementia was diagnosed in 11% non-GBA-PD and 25% GBA-PD at 5-year follow-up.

Conclusions Evaluation of long-term impact of *GBA* variants in a large Italian DBS-PD cohort supported the role of DBS surgery as a valid therapeutic strategy in GBA-PD, with long-term benefit on motor performance and ICD. Despite the selective worsening of cognitive scores since 3 years post-DBS, the majority of GBA-PD had not developed dementia at 5-year follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *GBA* variants are the most common genetic risk factor for Parkinson disease (PD) worldwide. Data on clinical outcome of GBA-PD carriers after deep brain stimulation (DBS) are scarce, but an increased prevalence of cognitive deterioration has been reported.

WHAT THIS STUDY ADDS

⇒ By comparing baseline and up to 5-year post-DBS follow-up data in patients with GBA-PD versus non-GBA-PD, DBS surgery emerged as a valid therapeutic strategy also in GBA-PD, with prolonged motor benefit and low burden of non-motor complications which were overall comparable to non-GBA-PD. We confirmed a more evident worsening of cognitive scores in GBA-PD, although the majority of them had not developed dementia up to 5 years after surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study adds novel information on DBS long-term clinical outcome in GBA-PD, helping management and selection of patients for this advanced therapeutic procedure.

INTRODUCTION

Parkinson disease (PD) is one of the most common neurodegenerative diseases, with a lifetime prevalence of 3–4% and heavy socioeconomical burden. The PD clinical course is variable, both in terms of progression of the motor phenotype and occurrence of non-motor symptoms. Genetic causes are known to play a key role in PD pathogenesis and can influence the clinical course of the disease. The most relevant genetic risk factor is the *GBA* gene, encoding for the lysosomal hydrolase glucocerebrosidase and

recessively mutated in Gaucher disease.[1 2] Heterozygous *GBA* variants are found in ~10% of patients with PD worldwide.[2] In a large Italian multicentre study, we detected *GBA* variants in 14% of unselected patients with PD and up to 20% of those with early onset.[3] Of note, *GBA* mutations not only increase the risk of developing PD but can also influence the resulting phenotype. Overall, patients with GBA-PD have an earlier disease onset, more prevalent non-motor features and a greater risk of cognitive decline than non-mutated PD (non-GBA-PD).[3–5] While this can be influenced by the specific type of *GBA* variant (with severe and complex variants resulting in worse prognosis than mild and risk ones), attempts to define the disease outcome at the individual level still remain difficult.[6 7]

Despite decades of research aiming at developing strategies to slow down neurodegeneration, to date the therapeutic approach of PD remains symptomatic. Deep brain stimulation (DBS) is considered one of the best therapeutic options for complicated stages,[8 9] although unable to modify disease progression. In a subset of patients, DBS surgery may be complicated by long-term side effects such as neuropsychiatric manifestations and cognitive decline, particularly when targeting the subthalamic nucleus (STN).[10 11]

To date, patients' selection criteria to DBS surgery are based on clinical features (presence of motor fluctuation and absence of dementia and psychiatric conditions), a sustained response to levodopa and normal neuroimaging,[12] while the genetic background has not been considered so far in the decision-making process. Of note, a study investigating the role of *GBA*, *LRKK2* and *PRKN* mutations on the early cognitive outcome after STN-DBS demonstrated a greater deterioration of cognitive profile after 1-year post-surgery in *GBA* carriers only.[13] More recently, a larger multicentre study described a more rapid cognitive decline in GBA-PD subjects who underwent STN-DBS, compared with both non-mutated and non-operated patients.[14] Despite these evidences, data on the impact of *GBA* mutations on long-term DBS clinical effects are still scarce and recommendations for this procedure in GBA-mutated patients remain inconclusive.[15]

To address this key issue, we performed a deep clinical characterisation of a large cohort of Italian patients with PD who underwent DBS surgery and then *GBA* genetic testing. Baseline and follow-up data at 1, 3 and 5 years were collected to describe the clinical phenotype of GBA-mutated and non-mutated patients, as well as their motor and non-motor outcome, with special focus on cognitive profile.

METHODS

Subjects

This is a multicentric Italian study involving nine tertiary level Movement Disorder Centres across Italy in the frame of the PARKNET consortium. An ongoing research project is in place within PARKNET aimed at recruiting patients with PD and recording clinical and genetic data, both on *GBA* and other PD-related genes (see online supplemental file 1). Ethics approval was obtained by the respective Ethics Committee of each participating centre and all patients gave written informed consent.

From this large cohort, we retrospectively selected PD subjects who underwent DBS according to standardised criteria[15] between years 2005 and 2021, and who fulfilled the following criteria:

- Availability of detailed clinical data at presurgery and at least 1-year post-surgery. When available, 3 and 5 years follow-up data were also recorded.
- Genetic testing for GBA and major PD-related genes already performed at time of recruitment.
- Absence of pathogenic or likely pathogenic variants in PD-related genes other than *GBA*.

Based on the presence or absence of *GBA* variants, patients were stratified into GBA-PD and non-GBA-PD groups. *GBA* variants were classified into five classes (mild, severe, complex, risk and unknown) as reported.[3 16]

Clinical assessment

Clinical data were retrospectively collected and obtained from available clinical records. Demographic, motor and non-motor features were recorded prior to DBS surgery (mean 2.5±1.5 months) (baseline-T0) and after 1 (T1), 3 (T3) and, when available, 5 years (T5) post-surgery.

Demographic data included sex, age at baseline, at disease onset and at DBS, disease duration at DBS, years of education, family history of first-degree PD relatives and DBS target.

At baseline, occurrence of mild cognitive impairment (MCI), REM behaviour sleep disorders (RBD) or axial dystonia was noted.

At each time point, the following data were collected: MDS-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) scores in ON and OFF medication phase (stim-ON after surgery), Hoehn and Yahr (HY) stage, Mini-Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA), levodopa equivalent daily dose (LEDD) calculated for all drugs, presence of motor fluctuations (wearing-off, unpredictable 'on-off' fluctuations), dyskinesias, freezing of gait and autonomic symptoms (including symptomatic orthostatic hypotension). Impulse control disorders (ICD) were assessed using structured interviews performed during clinical examinations and recorded in the patients' clinical charts. As post-surgery complications, we evaluated the occurrence of dementia, depression, hallucinations, inability to walk, freezing of gait, recurrent falls and urinary incontinence.

MMSE and MoCA scores were both converted to Mattis Dementia Rating Scale (MDRS) scores following a validated method.[17] MCI and dementia were clinically diagnosed according to PD-MCI and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria.[18 19]

Statistics

Statistical analysis was performed using 'Stata' V.13.0 (StataCorp, Texas, USA). We set statistical significance at $p<0.05$ for all statistical tests performed.

For each time point, data comparison between GBA-PD and non-GBA-PD was performed with Wilcoxon-Mann-Whitney test for numerical variables and $\chi 2$ test for categorical variables.

GBA-PD subjects were further divided according to mutation severity in mild, risk, severe, complex and unknown.[3 16] Severe and complex variants were merged for statistical analysis (here after, referred to as the 'severe/complex' group), while unknown variants were excluded from comparison.

Comparison among GBA-PD subgroups at T0 and T1 was performed using Kruskal-Wallis test followed by Dunn's Pairwise test (Bonferroni adjustment) and $\chi 2$ test, for numerical and categorical variables, respectively. Intra-group analysis (T0 vs T1) was separately performed in each subgroup as reported above.

Longitudinal analysis of the PD group was performed over 5 years using a generalised linear mixed-effect model, with groups as independent variables and age, sex, ears of education and disease duration as covariates. Due to the small sample size of

Table 1 Demographic characteristic at baseline of non-GBA-PD and GBA-PD groups

	non-GBA-PD (*n=292*)	GBA-PD (*n=73*)	P value
Age (years)	64.27±7.6	60.0±9.0	0.001
Age at onset (years)	47.0±8.2	44.5±8.2	0.01
Age at DBS (years)	58.15±7.6	53.9±8.5	0.001
Sex (% males)	68.1	61.6	ns
Disease duration at DBS (years)	10.8±4.0	9.0±3.7	0.005
Education (years)	11.5±3.8	11.5±3.7	ns
DBS target - STN versus GPi (% STN)	94.2	91.8	ns
Family history for PD (% yes)	54/265 (20.4)	26/70 (36.1)	0.003

Data are reported as means (±SD). P value<0.05 significance difference (GBA-PD vs non-GBA-PD).
GPi: globus pallidus internus
STN: subthalamic nucleus
DBS, deep brain stimulation; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; Gpi, globus pallidus internus; ns, non-significant; PD, Parkinson disease; RBD, REM behaviour sleep disorders; STN, subthalamic nucleus.

GBA-PD subgroups, longitudinal analysis of subgroups was not assessed.

Finally, we performed an exploratory analysis to compare the clinical characteristics of subjects who developed dementia at 5 years within the two PD groups, and assessed whether any preoperative features could predict the risk of cognitive deterioration after DBS implant (see online supplemental file 1 for details).

RESULTS

Characteristics of patients with Italian PD accessing DBS

We analysed data of 365 PD subjects (244/121 male/female, age 63.4±8.0 years, age at onset 46.5±8.2 years, PD duration 10.4±4.0 years) who underwent bilateral DBS surgery (342 targeting bilateral STN). On genetic testing, which was nearly always performed after surgery, *GBA* variants were detected in 73 (20%) patients (table 1).

At pre-DBS evaluation, GBA-PD subjects (45/28 male/female) were younger, had earlier age at PD onset and at time of DBS surgery and a slightly shorter disease duration compared with the non-GBA-PD group (table 1). GBA-PD also had a higher prevalence of positive family history of PD compared with non-GBA-PD. Motor and cognitive performances, as well as other non-motor symptoms, were comparable between the two groups, except for dyskinesias and orthostatic hypotension symptoms that were significantly more prevalent in GBA-PD (online supplemental table S1).

Among GBA-PD subjects, 33 patients carried severe/complex variants (45.2%), 17 had mild variants (23.3%) and 15 carried risk alleles (20.6%). In 8 patients (10.9%), the severity of the variants could not be assessed (unknown variants) (online supplemental table S2). The pre-DBS clinical profile of *GBA* subgroups (stratified according to mutation severity) were comparable (online supplemental table S3).

All subjects completed the 1-year follow-up, while 230 (180 non-GBA-PD and 50 GBA-PD) and 173 (141 non-GBA-PD and 32 GBA-PD) DBS-PD subjects reached T3 and T5 assessments, respectively.

Response to DBS after 1-year follow-up

At 1-year evaluation post-DBS, both non-GBA-PD and GBA-PD presented marked improvement of their motor symptoms (as shown by lower MDS-UPDRS-III-OFF med scores), with a significant reduction in dyskinesias, motor fluctuations and wearing-off phenomena and a marked decrease of LEDD intake (figure 1A–B and online supplemental table S4).

Regarding cognition, MDRS scores showed no significant differences between non-GBA-PD and GBA-PD, although the latter group presented a slight, although significant reduction of the score compared with the baseline. A diagnosis of dementia at this time point was made in <3% subjects (five non-GBA-PD and three GBA-PD) (figure 1A–C and online supplemental table S4).

Among other non-motor features, the presence of ICD was significantly reduced in both groups compared with pre-DBS stage. The occurrence of complications such as recurrent falls, inability to walk, depression, hallucinations and urinary dysfunctions was low and comparable between the two groups (figure 1C and online supplemental table S4).

When patients with GBA-PD were stratified by mutation type, all subgroups showed a similar motor response to surgery, with significant reduction of both MDS-UPDRS-III OFF-med scores and LEDD, and a comparable significant improvement in dyskinesias and motor fluctuations respect to baseline (online supplemental table S5). T1 MDRS scores similarly worsened across subgroups, although not significantly compared with baseline. Of the three subjects who had developed dementia, two carried a mild and one a severe variant. No differences among GBA-PD subgroups were observed regarding other non-motor symptoms and complications (online supplemental table S5).

Long-term outcome at 3 and 5 years from DBS surgery

At 3 and 5 years follow-ups, GBA-PD and non-GBA-PD showed comparable MDS-UPDRS (OFF med and ON med phase), HY scores and LEDD intake. Presence of wearing-off and dyskinesias were also similar in both groups, except for the 'on-off' phenomenon, which was significantly more prevalent at 5 years in the GBA-PD group (online supplemental table S6).

When comparing T3 and T5 outcome to baseline, we observed a prolonged motor benefit from DBS in both PD groups, documented by a still significant reduction in MDS-UPDRS-OFF med score, dyskinesias, wearing off and 'on-off' phenomenon and LEDD intake (figure 2 and online supplemental table S6).

Compared with 1-year post-DBS, both PD groups showed a slight global motor and non-motor worsening. Of note, GBA-PD showed a more sustained benefit on selected variables, such as dyskinesias, LEDD intake and freezing of gait, which remained stable or increased only later compared with non-GBA-PD.

A deterioration of cognitive MDRS scores post-DBS was observed in both PD groups when compared with baseline as well as to 1-year follow-up, with a significantly more marked worsening of GBA-PD already at 3 years post-DBS. After 5 years from surgery, 8 of 32 (25%) patients with GBA-PD versus 15 of 140 (11%) patients with non-GBA-PD developed dementia, a difference that resulted statistically significant (figure 2 and online supplemental table S6).

Regarding other non-motor symptoms and complications, longitudinal analysis did not reveal major differences between PD groups, except for hallucinations that were significantly more common in GBA-PD only at 3-year follow-up. Notably, we observed a significant long-term reduction of ICD in both groups (figure 2 and online supplemental table S6)

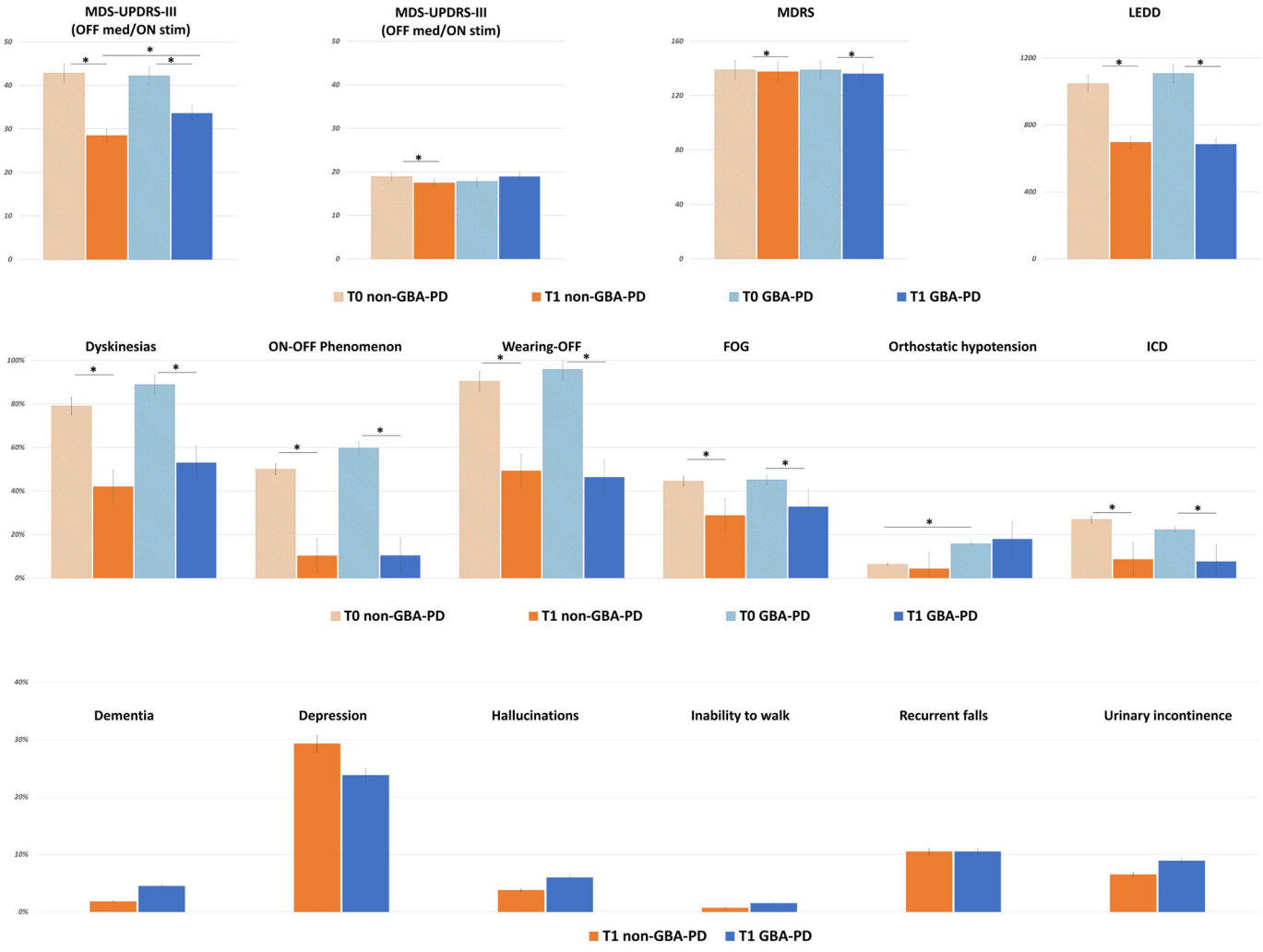

Figure 1 Clinical motor and non-motor parameters at T1 of non-GBA-PD and GBA-PD groups. (A–B) Between-group comparison (GBA-PD vs non-GBA-PD) and within-group comparison (T0 vs T1) of clinical motor and non-motor parameters. (C) Between-group comparison (GBA-PD vs non-GBA-PD) of motor and non-motor complications at T1. *, p value<0.05 significance difference. FOG, freezing of gait; ICD, impulse control disorders; LEDD, levodopa equivalent daily dose; MDS-UPDRS-III, MDS-Unified Parkinson's Disease Rating Scale part III; MDRS, Mattis Dementia Rating Scale; PD, Parkinson disease.

DISCUSSION

Mutations in *GBA* are the most relevant genetic risk factor for PD,[20] and are associated to earlier onset, more rapid disease progression, earlier cognitive decline and increased burden of non-motor symptoms.[3] In this light, the choice of the most appropriate therapeutic approach, as well as the best timing for addressing patients to advanced therapies such as DBS, is of the utmost importance. Although DBS surgery does not stop the progression of neurodegeneration, it changes drastically the clinical course of the disease, both improving motor functions and quality of life of patients.[21] Recent evidence suggested that *GBA* variants can influence the response to DBS[14 22–24]; however, the post-DBS long-term clinical outcome of GBA-PD subjects is still poorly investigated and the balance of risks versus benefits remains an open question.[15]

Here we evaluated the prevalence of *GBA* variants and their impact on the DBS outcome in a large and clinically well-characterised cohort of Italian PD subjects. On stratification according to *GBA* genotype, we described the clinical phenotype of GBA-PD at pre-DBS and up to 5 years post-surgery and compared them with the non-GBA-PD group.

Heterozygous *GBA* variants were detected in 20% of PD-DBS, a proportion which is considerably higher than the average frequency of *GBA* carriers within the Italian population-representative PD cohort. Pal and collaborators found an even higher frequency of *GBA* carriers (37%) in their PD-DBS cohort. Other studies also reported a prevalence of genetic mutations about three times higher in patients with PD-DBS than non-operated counterparts, with *GBA* variants being the most prevalent genetic determinants.[25–27] Although no definite conclusions can be drawn from these studies, as none of them relied on a truly consecutive enrolment strategy, it seems that *GBA* carriers were generally more likely to undergo DBS surgery. Of note, Italian patients with GBA-PD were significantly younger and had earlier age at disease onset and shorter disease duration at DBS than non-GBA-PD, while showing a comparable HY stage as well as motor and non-motor features, with the sole exception of orthostatic hypotension, which was more prevalent in GBA-PD. Taken together, these observations support the hypothesis that *GBA* variants contribute to speed up the neurodegenerative process, resulting not only in earlier onset but also in a faster progression of motor symptoms, which would candidate patients to DBS earlier in their disease course.[28]

The motor response to DBS of GBA-PD was fully satisfactory at 1-year follow-up, with a marked improvement of motor outcome which was comparable to non-GBA-PD. This motor

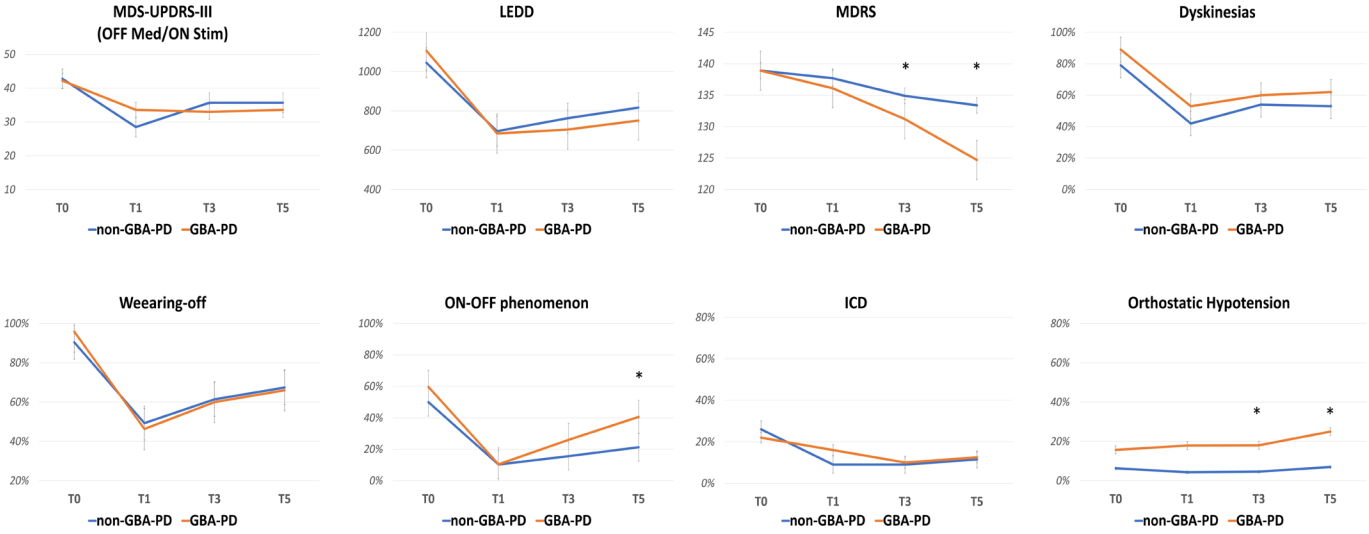

Figure 2 Evolution of clinical motor and non-motor parameters of non-GBA-PD and GBA-PD groups over time. The graphs show for GBA-PD (orange) and non-GBA-PD (blue) the mean of MDS-UPDRS-OFF med, MDRS and LEDD and the percentage of 'yes' of dyskinesias, on-off phenomenon, wearing-off, ICD and orthostatic hypotension at baseline (T0), T1, T3 and T5. *, p value<0.05 significance difference between-group comparison (GBA-PD vs non-GBA-PD) at T3 and T5. ICD, impulse control disorders; LEDD, levodopa equivalent daily dose; MDS-UPDRS-III, MDS-Unified Parkinson's Disease Rating Scale part III; MDRS, Mattis Dementia Rating Scale; PD, Parkinson disease.

benefit is in line with previous papers reporting a significant global motor improvement from STN-DBS implant in GBA-PD, especially in the short term.[22–24 29 30] The long-term assessment up to 5 years post-surgery confirmed the good clinical outcomes on motor performances in both PD groups. GBA-PD showed a prolonged benefit on control of motor fluctuation and dyskinesias, as well as a lower LEDD compared with pre-DBS.

DBS also had a positive impact on some non-motor symptoms, again with similar benefits in the two groups. In particular, we observed a significant improvement of ICD and no worsening of mood disorders or development of other neuropsychiatric symptoms, a positive effect which was sustained over time and likely related to the reduction of dopaminergic therapy. To our knowledge, this is the first observation of the neuropsychiatric outcome of DBS in GBA-PD, and this positive finding must be considered in the therapeutic management.

The nearly double prevalence of orthostatic hypotension in GBA-PD compared with non-GBA-PD at baseline remained evident even 5 years post-DBS. This is a novel important observation, which corroborates previous studies reporting a more frequent occurrence of global autonomic dysfunction in GBA-PD,[31–34] and a recent paper that systematically assessed blood pressure of patients with GBA-PD from supine to upright position.[35] The finding that orthostatic hypotension is not relieved by DBS should be taken into account when addressing these patients to advanced therapies by thoroughly evaluating its degree of severity, which could significantly impact the disease course.

A different consideration should be made regarding the cognitive profile of patients with GBA-PD who underwent DBS surgery. Lythe *et al* and Mangone *et al* first reported a higher prevalence of cognitive impairment and a faster cognitive decline following STN-DBS implant in a small group of GBA-PD subjects compared with non-carriers, with carriers of severe variants showing a more pronounced cognitive deterioration even after 1-year post-surgery.[22 24] More recently, Pal *et al* confirmed the negative impact on cognition of both STN-DBS and presence of *GBA* variants. In our study, a slight deterioration of MDRS scores emerged in the GBA-PD group already 1 year after DBS, although this was similar to non-GBA-PD. However, in the long-term evaluation, we observed a more pronounced worsening of cognitive scores in GBA-PD compared with non-GBA-PD, which was already significant 3 years post-DBS and became even more marked after 5 years, although the sample size was reduced at this last time point. While this postoperative decline of MDRS scores is in line with previous reports,[14 24] only a minority of GBA-PD subjects eventually developed a clinically defined dementia (8/32, 25%), although this proportion was higher than non-GBA-PD (15/140, 11%). The clinical characteristics of subjects who developed dementia at 5-year post-DBS were comparable among the two groups, with similar age at DBS, disease duration, LEDD intake, MDRS scores and motor and non-motor features.

A deterioration of cognitive performance, and in particular of executive functions, has been reported in PD subjects undergoing STN-DBS, in the absence of *GBA* mutations.[36 37] It was proposed that chronic stimulation of the STN, while determining a major improvement in motor performances, may negatively impact cognitive functions.[36 37] However, other factors independent from DBS which can influence the susceptibility to develop cognitive deficit cannot be excluded. In line with this hypothesis, a 3-year post-DBS follow-up study suggested that the development of dementia may relate more to the natural evolution of the disease rather than to a direct effect of DBS.[11] It is worth noting that all PD subjects in our cohort who eventually developed dementia had received an STN-DBS. To date, there is no evidence assessing motor and cognitive outcomes of GBA-PD subjects treated with STN-DBS versus GPi target. In our study, a statistical comparison of target efficacy and outcomes was not feasible due to the low number of patients with GPi target, especially in the GBA-PD group, and further studies are warranted to address this question.

In an exploratory analysis, we investigated whether any preoperative features could predict the risk of cognitive deterioration after DBS implant. In line with the literature, an older age at PD onset and at DBS surgery seemed to be associated with dementia in both PD groups. Interestingly, in our cohort the majority of GBA-PD subjects with dementia were women (75%), while this

was the opposite for non-GBA-PD (74% men). This observation must of course be taken with caution due to the small sample size of demented subjects, especially in the GBA-PD group, but it highlights for the first time a potential impact on gender as an additional player in determining the clinical outcome of GBA-PD. To date, evidence regarding the role of sex in GBA-PD is very limited,[38–40] and further research is needed in this regard.

In our GBA-PD cohort, the frequency of severe/complex mutations (45%) was nearly twice than that of mild (23%) and risk (21%) variants, fully in line with the previously reported frequency of these variants in Italy.[3] Pal and collaborators reported instead a much higher prevalence of risk (41%) and mild (40%) variants compared with severe ones (19%), likely reflecting a different distribution of variants across distinct populations and countries.[14] To date, no other report described the frequency of different classes of *GBA* variants in DBS-PD. Of note, in our study both the baseline and 1-year follow-up clinical picture were fully comparable across carriers of different classes of *GBA* variants, including MDRS scores and proportion of patients who developed dementia (at 5 years: 2 mild, 1 risk, 3 severe, 2 unknown). We believe these findings are not in contrast with the general knowledge that GBA-PD, especially when associated with severe/complex variants, is characterised by higher prevalence and earlier occurrence of non-motor features, but rather highlight the great inter-individual variability observed in *GBA* mutation carriers. Indeed, since patients were addressed to DBS based on clinical criteria only and regardless of their genetics status, those who eventually underwent surgery are likely to represent a 'sub-phenotype' of GBA-PD showing significant motor worsening but still a normal cognitive performance and lower burden of non-motor symptoms after several years from onset, regardless of the variant type. We were not able to compare the long-term effects of DBS in carriers of different *GBA* variants due to the small sample size, and replication in larger cohorts is needed to better describe the correlation between variant types and DBS response.

Our study has some limitations. First, the sample size is still limited, especially at 3-year and 5-year post-DBS, hampering a long-term outcome analysis across different variant types. Similarly, despite our cohort included patients who underwent either STN-DBS or GPi-DBS, the very low number of subjects with GPi target did not allow subgroup comparisons. Also, the lack of non-DBS cohorts does not allow discriminating the relative contribution of *GBA* genotype and of the surgical procedure itself to the cognitive decline, as suggested by Pal and collaborators.[14] Some clinical features such as symptomatic orthostatic hypotension and RBD were mainly recorded anamnestically and not measured through specific tests or scales, possibly resulting in over-estimated or under-estimated frequencies. Another limitation resides in the fact that 8 out of 73 patients with GBA-PD carried variants that were classified as 'unknown', whose pathogenetic impact still remains to be determined. However, repetition of statistical analyses on removal of these eight subjects from the GBA-PD group did not yield any substantial modification of results.

Finally, we are aware of the lack of direct measures of quality of life, which will undoubtedly need to be thoroughly evaluated in future studies.

In conclusion, this is the first report showing the impact of *GBA* genotype on DBS outcome over a prolonged follow-up in a large Italian cohort of DBS-treated PD subjects. Our findings support the role of DBS surgery as a valid therapeutic strategy also in patients with PD carrying *GBA* mutations, with long-term clinical benefit on motor performance, reduction of LEDD, motor complications and ICD that were comparable to non-mutated patients. Despite the worsening of cognitive scores in GBA-PD already evident 3 years after DBS, the majority of subjects still maintained a good cognitive profile after 5 years from surgery. Ultimately, in the era of personalised therapies, this study supports the potential relevance of including *GBA* testing as part of the diagnostic workout of any patient with PD, as knowledge of the *GBA* genotype could help towards a better clinical management since the early stages of the disease. This would address a more appropriate counselling on clinical outcome and a better choice and timing of both pharmacological and advanced therapies.

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Contributors Study concept and design: EMV on behalf of the PARKNET Study Group. Collection of data: MA, RZ, CAA, FC, RC, AC, FCol, FCog, ADF, GG, AI, GI, CL, MM, FM, RM, PM, EM, FS and FV. Analysis and interpretation of data: MA, RZ, CAA, GC, IP, ADF and EMV. Drafting of the manuscript: MA and EMV. Critical revision of the manuscript for important intellectual content: AA, MB, GC-B, RC, PC, ADF, RE, GG, AI, GI, LL, CT, FV, the PARKNET Study Group, CP and EMV. EMV acts as a guarantor for this study.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This is a multicentric Italian study involving nine tertiary level Movement Disorder Centres across Italy in the frame of the PARKNET consortium. Project code: PARK-Net 3 - 22033 - ID 3951. Participants gave informed consent to participate in the study before taking part.

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