npj | parkinson's disease

Article

Published in partnership with the Parkinson's Foundation

https://doi.org/10.1038/s41531-025-01140-7

Unraveling the role of *GBA1* genotype in axial signs response to subthalamic deep brain stimulation

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GBA1 variants represent the most common genetic risk factor for Parkinson's disease (PD) and are associated with higher risk of developing cognitive decline and axial motor impairment. While cognitive outcomes following subthalamic deep brain stimulation (STN-DBS) have recently received growing attention, axial signs progression remains poorly defined in this population. In this retrospective multicentric study, we analyzed a cohort of 353 PD patients who underwent bilateral STN-DBS surgery (75 GBA+ and 253 GBA−). 5-year follow-up data were available for 233 patients, including 43 mutated subjects. Lower off-medication UPDRS III score and levodopa responsiveness at baseline were identified as independent predictors of axial signs worsening after DBS, while *GBA1* genotype was not identified as risk factor. The presence of *GBA1* variants did not exert a detrimental effect on axial signs in PD patients up to five years following STN-DBS, supporting its consideration as a valid therapeutic option in this genetic subgroup.

Clinical and genetic predictors of deep brain stimulation (DBS) response in Parkinson's disease (PD) patients have been a field of great interest in the last few years[1–3]. Identifying predictors of clinical outcomes is a pivotal approach to provide optimal pre-operative counseling and a "personalized" stimulation for each patient. A number of studies investigated the influence of genetics on clinical outcomes of DBS, with considerable interest being directed towards patients with pathogenic variants in the *GBA1* gene, the most common genetic risk factor for PD[4]. Various Authors reported that these patients may experience an earlier cognitive decline following subthalamic (STN)-DBS, when compared to non-mutated patients[5–7]. In light of these findings, Pal et al. suggested that DBS candidates should be screened for *GBA1* pathogenic variants as part of the presurgical decision-making process and provided with appropriate counseling regarding potential risks associated with STN-DBS[5]. On the other hand, data from a large Italian cohort of PD patients with and without *GBA1* pathogenic variants supports STN-DBS did not impact on the rate of cognitive decline, suggesting that it remains a valid therapeutic strategy for this PD genetic subgroup[8]. Although cognitive outcomes of STN-DBS are still debated, motor outcomes appear to be comparable between PD patients carriers and non-carriers of *GBA1* pathogenic variants[5,6]. However, none of these studies specifically assessed axial motor signs, which may present more rapid deterioration and are often associated with cognitive decline in GBA−PD population[9].

Axial signs are highly disabling symptoms in advanced PD and were shown to predict mortality in patients with STN-DBS[10]. They are often refractory to medical and surgical treatments[11] and tend to worsen in the long-term follow-up after STN-DBS, exhibiting a distinct progression compared to appendicular motor signs[12]. Notably, there is a relationship between axial impairment and cognitive dysfunction in PD patients, regardless of DBS treatment[13]. Given the high prevalence of these disturbances in *GBA1* patients[14] and the suggested detrimental effect of *GBA1*

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pathogenic variants on cognitive outcome of STN-DBS[5], a definition of the course of axial motor signs after surgery in this population is of great relevance. To our knowledge, only one report specifically assessed the outcome of axial motor signs after STN-DBS in three PD patients carriers of *GBA1* pathogenic variants[15]. The authors observed a more severe axial motor impairment in these patients, despite sustained control of motor fluctuations and stable reduction of the dopaminergic medications. They suggested that axial signs worsen in these patients as a result of the more severe neurodegeneration in non-dopaminergic pathways in *GBA1*-associated PD. Based on report and the reviewed literature, we hypothesized that *GBA1* pathogenic variants would negatively influence the response of axial motor signs to DBS.

The main aim of this study is to elucidate the role of *GBA1* genotype in the outcome of axial motor signs after STN-DBS.

Results

A total of 353 PD patients with bilateral STN-DBS were included in the study. Mean age at DBS surgery was 56.54 ± 7.68 years, disease duration 10.46 ± 4.61 years, male/female ratio 236/117. Genetic testing detected *GBA1* pathogenic variants in 75 (21%) patients. Table 1 describes the baseline demographic and clinical data of the patients.

At baseline, GBA+ subjects were younger and had a shorter disease duration compared with the GBA− subjects (Table 1). Motor and cognitive performances and dopaminergic therapy did not differ significantly between the two groups, except for the UPDRS III score in off-medication condition, which was higher in GBA+ patients (39.7 ± 13.74 GBA+ versus 36.39 ± 11.87 GBA−, $p = 0.037$).

All subjects completed the 1-year follow-up, while 310 (63 GBA+ and 247 GBA−) and 233 (43 GBA+ and 190 GBA−) patients reached T3 and T5 assessments, respectively. For all these patients motor scores were available in the on-medication state, while motor scores in the off-medication state were available for 229 patients at T1 (55 GBA+ and 174 GBA−), 139 patients at T3 (36 GBA+ and 103 GBA−) and 75 patients at T5 (21 GBA+ and 54 GBA−). Motor, cognitive and pharmacological data of the two groups of subjects at each time point are displayed in online Supplementary Table S1.

Among GBA+ subjects, 28 patients carried severe/complex variants (37.3%), 16 had mild variants (21.3%) and 17 carried risk alleles (22.7%). In 14 patients (18.7%), the severity of the variants could not be assessed (unknown variants) (online Supplementary Table S2).

Outcome of axial motor signs in GBA+ and GBA− patients

In the on-medication condition, both groups of patients presented an improvement of the axial score at 1-year follow-up, although statistically non-significant, with a following significant deterioration at 3- and 5-year follow-ups (Fig. 1A, Table 2). Comparing the variation of axial score from the baseline to the three time points of follow-up after surgery, no difference was found between the two groups of patients at T1 (−0.12 ± 2.36 GBA+ versus −0.23 ± 2.15 GBA−, $p = 0.8$), T3 (1.12 ± 2.73 GBA+ versus 1.24 ± 2.55 GBA−, $p = 0.8$) and T5 (2.16 ± 2.88 GBA+ versus 2.57 ± 3.47 GBA−, $p = 0.6$).

In the off-medication condition, both groups of patients presented a significant improvement of the axial score at 1-year and 3-year follow-up; at 5 years, only the GBA+ cohort showed a significant improvement of the axial score (Fig. 1B, Table 2). Comparing the variation of axial score from the baseline at the three time points of follow-up after surgery, no significant difference was found between the two groups of patients at T1 (−4.23 ± 4.84 GBA+ versus −3.04 ± 4.05 GBA−, $p = 0.1$) and T3 (−3.17 ± 5.48 GBA+ versus −1.57 ± 4.58 GBA−, $p = 0.1$), while the two groups differed at T5, with a greater improvement of axial signs in GBA+ group (−3.54 ± 4.45 GBA+ versus −0.54 ± 4.43 GBA−, $p = 0.005$).

Repetition of statistical analyses excluding the 14 subjects with *GBA1* unknown variants (9 patients at 5-year follow-up) did not yield any substantial modification of the results.

Predictors of axial signs worsening

In the whole sample of patients, the preoperative independent variables incorporated into the final Cox regression models are reported in Table 3.

The multivariable Cox regression models identified the lower UPDRS III score in the off-medication condition as predictor of axial motor signs worsening after STN-DBS in both on-medication (HR = 0.98, 95% CI 0.97–0.99) and off-medication (HR = 0.93, 95% CI 0.90–0.96) conditions, and the lower levodopa responsiveness as predictor of axial motor signs worsening after STN-DBS in off-medication condition (HR = 0.98, 95% CI 0.96–0.99). Variance inflation factor (VIF) was 1.002 for the variables "UPDRS III score in the off-medication condition" and "levodopa responsiveness". *GBA1* status was not identified as a risk factor of axial signs worsening, as also shown in Fig. 2 which depicts the Kaplan–Meier curves of axial worsening in both on- and off-medication conditions within the two groups of GBA+ and GBA− patients. The log-rank test did not show significant differences between the curves of GBA+ and GBA− patients in axial score worsening after surgery in both on-medication ($\chi^2 = 0.043$, $p = 0.8$) and off-medication ($\chi^2 = 0.021$, $p = 0.9$) conditions (Fig. 2).

Stimulation parameters and dopaminergic therapy in GBA+ and GBA− patients

Stimulation parameters of both hemispheres and LEDD did not significantly differ between GBA+ and GBA− patients at T1, T3, and T5, with the exception of a slightly higher stimulation amplitude in the left STN for GBA+ patients at T3 (3.15 ± 0.96 mA in GBA+ vs. 2.82 ± 0.88 mA in GBA−, $p = 0.025$) (Table S3). Comparing the variation of LEDD from the baseline at the three time points of follow-up after surgery, no difference was found between the two groups of patients at T1 (−416.99 ± 361.47 GBA+ versus −408.96 ± 396.72 GBA−, $p = 0.5$), T3 (−335.7 ± 460.7 GBA+ versus −355.96 ± 417.76 GBA−, $p = 0.9$) and T5 (−266.32 ± 394.35 GBA+ versus −246.2 ± 474.99 GBA−, $p = 0.6$).

Outcome of axial motor signs in GBA severe patients

Twenty-eight patients with severe/complex variants of *GBA1* completed the 1-year follow-up, while 15 and 8 patients completed the 3-year and 5-year follow-ups, respectively. Demographic and clinical data of GBA severe patients at T0, T1, T3 and T5 are displayed in online Supplementary Table S4.

A comparison of the on-medication axial score variation from the baseline to the three time points of follow-up after surgery between GBA severe and GBA− patients found no difference at T1 (−0.46 ± 2.04 GBA severe versus −0.23 ± 2.15 GBA−, $p = 0.5$), T3 (1.0 ± 2.32 GBA severe versus 1.24 ± 2.55 GBA−, $p = 0.6$) and T5 (1.47 ± 2.47 GBA severe versus 2.57 ± 3.47 GBA−, $p = 0.2$). Comparing the Kaplan-Meier curves of axial worsening in the on-medication condition, the log-rank test did not show significant differences between GBA severe and GBA− patients ($\chi^2 = 0.868$, $p = 0.4$) (Fig. S1A).

A comparison of the off-medication axial score variation from the baseline to the three time points of follow-up after surgery found no significant difference between the two groups of patients at T1 (−5.15 ± 5.73 GBA severe versus −3.04 ± 4.05 GBA−, $p = 0.06$) and T3 (−2.64 ± 5.41 GBA severe versus −1.57 ± 4.58 GBA−, $p = 0.4$), while we detected a greater improvement of axial signs in GBA severe group at T5 (−6.43 ± 4.04 GBA severe versus −0.54 ± 4.43 GBA−, $p = 0.001$). However, comparing the Kaplan-Meier curves of axial worsening in the off-medication condition, the log-rank test did not show significant differences between GBA severe and GBA− patients ($\chi^2 = 0.220$, $p = 0.6$) (Fig. S1B).

Discussion

In this multicenter retrospective study, *GBA1* genotype did not influence the outcome of axial motor signs up to five years after STN-DBS in a cohort of 353 PD patients. To the best of our knowledge, this is the largest PD population with *GBA1* pathogenic variants in which axial signs have been specifically evaluated.

The prevalence of *GBA1* pathogenic variants in the study population (21%) is higher than the average prevalence of *GBA1* carriers within the Italian PD population[14], in line with other studies on patients with DBS[5,16]. In our cohort, at the time of DBS surgery, GBA+ patients were younger and had a shorter disease duration compared with the GBA− subjects. The two

Table 1 | Baseline demographic and clinical data of the two groups of patients

Variable	GBA + (*n* = 75)	GBA− (*n* = 278)	*p*-value
Sex (male/female)	47/28	189/89	0.4
Age at disease onset (years)	43.59 ± 7.9	45.7 ± 8.25	0.054
Age at surgery (years)	53.28 ± 7.87	57.41 ± 7.41	**<0.001**
Disease duration at surgery (years)	9.47 ± 3.83	10.72 ± 4.77	**0.049**
Motor phenotype (akinetic-rigid/tremor dominant/mixed)	47/15/13	142/82/54	0.2
Hoehn and Yahr stage	2.28 ± 0.67	2.13 ± 0.62	0.08
UPDRS III on-med	15.32 ± 7.55	14.6 ± 7.83	0.3
UPDRS III off-med	39.7 ± 13.74	36.39 ± 11.87	**0.037**
Levodopa responsiveness (%)[a]	60.07 ± 15.75	60.64 ± 15.83	0.8
UPDRS III axial subscore on-med	3.43 ± 2.08	3.12 ± 2.12	0.1
UPDRS III axial subscore off-med	8.96 ± 4.23	8.10 ± 3.83	0.2
MDRS	139.8 ± 4.46	139.26 ± 5.33	0.9
PDQ-8 SI	19.88 ± 18.84	18.32 ± 10.35	0.4
LEDD (mg)	1064.99 ± 377.62	1065.83 ± 423.62	0.9

UPDRS Unified Parkinson's Disease Rating Scale, *med* medication, *MDRS* Mattis Dementia Rating Scale, *PDQ-8 SI* Parkinson's Disease Questionnaire-8 Summary Index, *LEDD* levodopa equivalent daily dose, *mg* milligrams. Bold values indicate statistical significance with $p < 0.05$.
[a]Levodopa responsiveness is expressed as percentage reduction of UPDRS III.

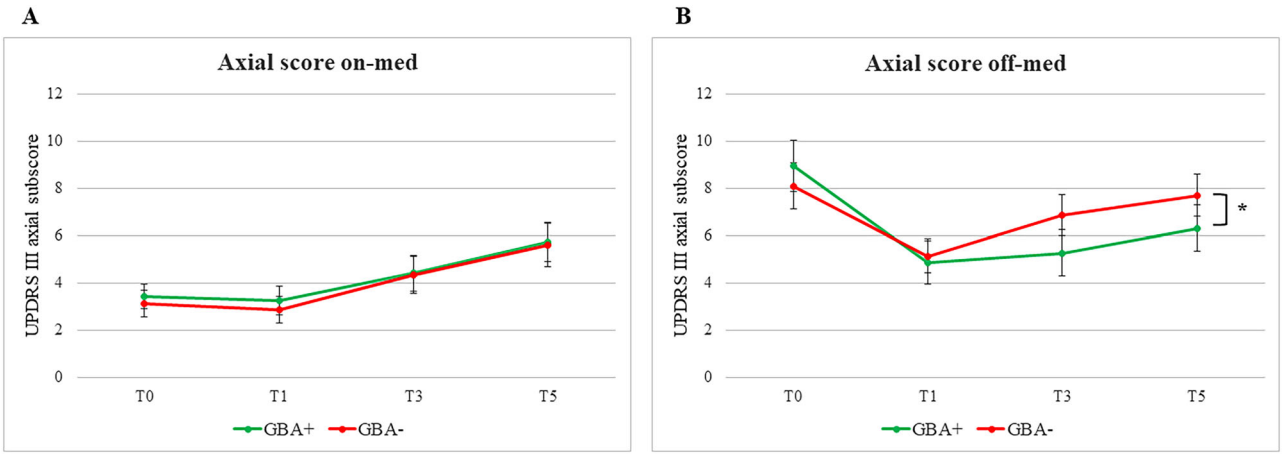

Fig. 1 | Outcome of the UPDRS III axial subscore after STN-DBS. UPDRS III axial subscore before (T0) and after surgery (T1 = 1 year, T3 = 3 years, T5 = 5 years) in on-medication (**A**) and off-medication condition (**B**) in the two groups of PD patients carriers (GBA+ versus GBA−). * $p < 0.05$.

Table 2 | UPDRS III axial subscore in both on-medication and off-medication conditions before and after DBS surgery in the two groups of GBA+ and GBA− patients

Group	Baseline	1 year	3 years	5 years	Friedman test *p*-value	Wilcoxon Signed-Rank test *p*-value		
						T0 vs T1	T0 vs T3	T0 vs T5
				On-med				
GBA+	3.43 ± 2.08	3.26 ± 2.35	4.42 ± 2.93	5.74 ± 3.22	**<0.001**	0.9	**0.006**	**<0.001**
GBA−	3.12 ± 2.12	2.85 ± 2.19	4.34 ± 2.97	5.59 ± 3.53	**<0.001**	0.1	**<0.001**	**<0.001**
				Off-med				
GBA+	8.95 ± 4.23	4.87 ± 3.48	5.28 ± 3.78	6.32 ± 3.81	**<0.001**	**<0.001**	**0.02**	**<0.001**
GBA−	8.10 ± 3.83	5.14 ± 2.82	6.87 ± 3.4	7.7 ± 3.44	**<0.001**	**<0.001**	**<0.001**	0.2

Bold values indicate statistical significance with p < 0.05.

groups of patients were matched for cognitive and motor scores, including the severity of axial signs, except for the UPDRS III total score in off-medication condition, which was higher in GBA+ patients. These differences between the groups may be explained by the contribution of *GBA1* pathogenic variants to anticipate and accelerate the neurodegenerative process, resulting in earlier disease onset and faster progression of motor symptoms, which would lead patients being referred for DBS surgery earlier in the disease course[6,17].

Assessing axial motor signs through specific items of UPDRS or MDS-UPDRS part III, we found a similar course of the scores in the on-stimulation/on-medication condition for GBA+ and GBA− patients up to the 5-year follow-up after DBS surgery. In both groups, we observed a deterioration of axial signs at three- and 5-year follow-ups, likely due to disease progression, as previously reported in long-term observational studies[12,18]. While in the on-medication condition the motor effects of DBS are masked by dopaminergic drugs, in the on-stimulation/off-medication condition both groups of patients presented a significant improvement of axial motor signs at 1-year and 3-year follow-up. It is well-known that STN-DBS improves levodopa-responsive axial signs in the short/medium-term follow-up, but this response tends to wane over time[12]. In our study, the response of axial motor signs declined in both groups during the follow-up. Nevertheless, the improvement of axial signs in the off-medication condition remained significant at the 5-year follow-up only in the GBA+ group. This discrepancy may be explained by the higher off-medication UPDRS III score at baseline in the GBA+ group compared to the GBA− cohort. In fact, higher scores of UPDRS III in the off-medication condition at baseline predict a better long-term motor response to stimulation[19]. Supporting this interpretation, the multivariable Cox regression models, in our cohort, identified the lower UPDRS III score in the off-medication condition as predictor of axial motor signs worsening after STN-DBS. Although the mechanism underlying this association is not fully understood, it is hypothesized that patients with more severe baseline motor symptoms may derived greater benefit from DBS, owing to a larger margin for improvement (i.e., the more significant the underlying dysfunction, the more noticeable the impact of DBS can be)[1]. As expected, the reduced levodopa responsiveness also emerged as a significant predictor of axial motor signs decline[20], whereas the *GBA1* status was not identified as a risk factor.

We excluded a relevant confounding effect from stimulation parameters or dopaminergic medication, as these did not differ substantially between GBA+ and GBA− patients over time.

Furthermore, we analyzed the outcome of axial motor signs after STN-DBS in the group of 28 patients with severe/complex variants of *GBA1* and compared them with non-carriers of *GBA1* pathogenic variants. The same results of the global cohort of *GBA1* patients were detected for this subgroup, indicating that even the presence of severe/complex variants of *GBA1* did not influence the outcome of axial motor signs after STN-DBS.

Globally, our findings provide useful insights for the pre-operative selection phase of patients with PD and *GBA1* pathogenic variants, excluding a detrimental role of *GBA1* genotype on the outcome of axial motor signs after STN-DBS. The DBS literature pays considerable attention to axial signs, which are less responsive to stimulation than appendicular motor signs and, in some cases, may be also worsened by DBS itself[21], particularly by subthalamic stimulation[22]. Our results suggest that STN-DBS may be considered in this specific population and do not provide worse outcomes in terms of axial motor signs compared to non-carriers. Although axial signs have a higher prevalence in the *GBA1* population[14], the careful patients' selection prior to DBS allows the exclusion of patients with levodopa-resistant axial signs or cognitive decline[23], resulting in a cohort of *GBA1* carriers with motor outcomes comparable to the general PD population. Future prospective studies on DBS outcomes in PD should incorporate genetic profiling to better elucidate whether the observed inter-individual variability in DBS response can be attributed to specific genetic variants, ultimately guiding more personalized and effective treatment strategies.

This study is subject to certain limitations inherent to its retrospective design. A first limitation of the study is the availability of motor scores in the off-medication condition for a lower number of patients respect to motor

Table 3 | Predictors of axial motor signs worsening in on-medication and off-medication conditions after STN-DBS

Variable	Hazard ratio	95% CI (lower-upper)	*p*-value
On-med			
UPDRS III off-med	0.98	0.97–0.99	**0.009**
Levodopa responsiveness	1.01	0.99–1.02	0.2
GBA1 status (+ or -)	1.07	0.73–1.56	0.7
Off-med			
UPDRS III off-med	0.93	0.90–0.96	**<0.001**
Levodopa responsiveness	0.98	0.96–0.99	**0.02**
GBA1 status (+ or -)	0.86	0.39–1.86	0.7

UPDRS Unified Parkinson's Disease Rating Scale.
Bold values indicate statistical significance with $p < 0.05$.

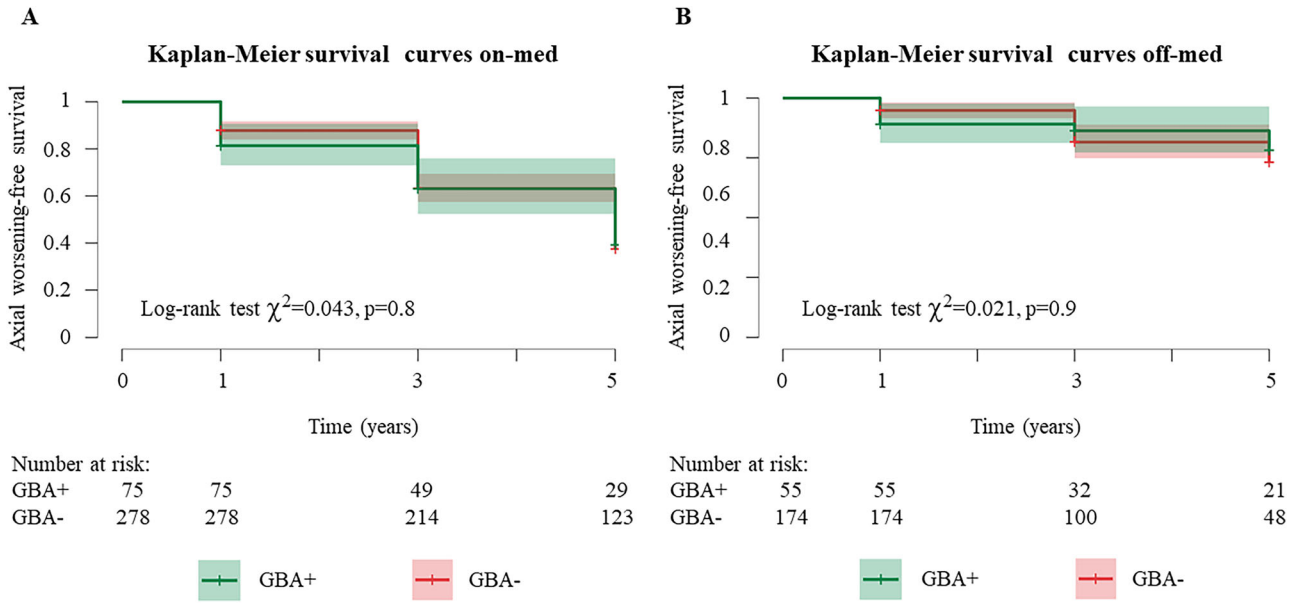

Fig. 2 | Axial worsening-free survival curves. Kaplan-Meier curves of axial worsening-free survival (reported with 95% upper and lower confidence interval) of GBA+ and GBA− in on-medication (**A**) and off-medication conditions (**B**). The "axial worsening-free survival" reflects axial impairment progression intended as the achievement of a ≥ 2-point higher UPDRS III axial subscore during the follow-up compared to the baseline score. Cross marks indicate censored data.

scores in the on-medication condition, which were available for all patients. The limited availability of motor scores in the off-medication condition at later follow-ups (T3 and T5) is primarily due to the retrospective and multicenter nature of the study. In routine clinical practice, long-term follow-up visits are typically conducted in the on-medication state, as this better reflects patients' functional status in daily life. In addition, a full washout of dopaminergic medication is often not feasible several years after surgery due to disease progression, increased frailty, or logistical difficulties in reaching the clinic while off-medication. These factors have contributed to the reduced number of complete off-medication assessments at long-term timepoints. A second limitation is the imperfect matching of the two groups of patients with regard to UPDRS-III score in the off-medication condition, age and disease duration at surgery. A third limitation is the lack of information about leads' localization and volume of tissue activated (VTA), due to the retrospective nature of the study. The localization of active electrodes is a potential modifier of axial motor signs outcome and should be considered in future prospective studies. Another limitation comes from the presence of 14 patients of the GBA+ group with variants that were classified as "unknown", with uncertain pathogenic impact. However, statistical analysis was performed both including and excluding these patients, with similar results. Finally, we did not perform a comparative analysis among subgroups of patients classified according to the severity of *GBA1* variants, due to the limited number of patients for each subgroup.

In conclusion, pathogenic variants of the *GBA1* gene did not impact the outcome of axial motor signs up to five years after STN-DBS in a large cohort of Italian PD patients. This finding contributes to the body of knowledge regarding the motor outcomes of patients carriers of *GBA1* pathogenic variants following STN-DBS, improving the pre-operative counseling and decision-making process for surgery. In this population, with a proper pre-operative selection, STN-DBS may be considered as a valid therapeutic option.

Methods

Study design and population

This retrospective cohort study involved 9 Italian tertiary level Movement Disorder Centres as part of the Italian PARKNET project (see Supplementary Information). From this cohort, we retrospectively selected PD subjects who underwent bilateral STN-DBS. All patients received a diagnosis of Parkinson's disease according to the United Kingdom Parkinson's Disease Brain Bank criteria[24], and fulfilled the inclusion and exclusion criteria proposed by the core assessment program for surgical interventional therapies in Parkinson's disease panel[25]. Patients with previous neurosurgical interventions for PD or implantation of DBS electrodes in other deep brain nuclei were excluded from the study, as well as subjects with pathogenic or likely pathogenic variants in PD-related genes other than *GBA1*.

All patients had detailed clinical data, including the score of the Unified Parkinson's Disease Rating Scale (UPDRS)[26] or MDS-UPDRS[27] part three, within six months (mean 2.3 ± 2.1 months) before surgery (T0) and at least 1-year after surgery (T1). When available, 3-year (T3) and 5-year (T5) follow-up data were also recorded.

Genetic testing for *GBA1* and major PD-related genes had already been performed at time of recruitment in all subjects. However, it is worth noting that most patients underwent genetic testing recently (as part of the PARKNET project), and therefore after they received DBS implant. Analysis of the *GBA1* gene was performed mostly by a novel NGS-based method, which relies on the selective amplification of the whole GBA gene in one long PCR fragment (6 kb) followed by Nextera sequencing and a customized bioinformatics pipeline aimed at masking the *GBAP1* pseudogene[28]. In a minority of patients, the *GBA1* gene was tested by conventional Sanger sequencing upon PCR-based amplification of the gene in three overlapping fragments[29]. Identified variants were all validated by conventional Sanger sequencing. Pathogenic variants in 15 PD-related genes associated with autosomal dominant (*SNCA*, *LRRK2*, *VPS35*, *GBA1*), X-linked (*RAB39B*), and autosomal recessive PD (*PRKN*, *PINK1*, *PARK7*, *ATP13A2*, *PLA2G6*, *DNAJC6*, *SYNJ1*, *FBXO7*, *VPS13C*, *PTRHD1*) were searched for by means of NGS-based sequencing of a PD gene panel (which varies from center to center, but always includes this minimal set of genes) as well as MLPA analysis (SALSA Kit P51-P52, MRC Holland), as previously reported[30].

Ethics approval was obtained by the local ethics committees of Bologna (ID 22033), Fondazione Policlinico Universitario A. Gemelli IRCCS (ID 5323), IRCCS Besta Neurological Institute, Lombardia 5 (ID 844/22), Padova, Pavia (ID 20200055587), Regione Liguria, Torino and Trento. All patients gave written informed consent.

Outcomes and measures

The primary objectives of the study were to assess the course of axial motor signs after STN-DBS in PD patients carriers of *GBA1* pathogenic variants (GBA +) and those non-carriers (GBA−), to compare the outcome of axial signs between the two groups, and to evaluate the potential role of *GBA1* pathogenic variants as a predictor of worsening of axial signs after STN-DBS.

The assessment of axial motor signs was conducted in both on- and off-medication conditions through the axial score (ranging from 0 to 20), composed by the sum of the items 27 or 3.9 (arising from chair), 28 or 3.13 (posture), 29 or 3.10 (gait), 30 or 3.12 (postural stability), 31 or 3.14 (body bradykinesia)[15] of the UPDRS or MDS-UPDRS III.

As secondary endpoints, we investigated the predictors of worsening of axial signs after STN-DBS in our cohort, to identify, among the clinical variables at baseline, potential confounders influencing the course of axial signs in the two groups of patients. We also compared stimulation parameters and dopaminergic therapy between GBA+ and GBA− patients at the three time points after surgery (T1, T3, T5). These assessments were done to rule out a different management of pharmacological or stimulation therapy between the two groups that could have affected the outcome of axial signs. Finally, we investigated the course of axial signs after STN-DBS in the group of patients carriers of severe/complex *GBA1* variants (GBA severe), comparing them with the group of GBA− patients.

The following variables were collected at T0: age at surgery, disease duration at surgery, age at disease onset, sex, motor phenotype (akinetic-rigid/tremor dominant/mixed)[31], Hoehn and Yahr stage, total score and axial subscore of the UPDRS or MDS-UPDRS part III in on- and off-medication conditions, levodopa responsiveness (measured by percentage reduction of UPDRS III from off- to on-medication condition), levodopa equivalent daily doses (LEDD)[32], Mini-Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA), Parkinson's Disease Questionnaire-8 (PDQ-8), reported as Summary Index (PDQ-8 SI) ranging from 0 (no impairment) to 100 (maximum impairment). The total score of MDS-UPDRS part III was regressed to the corresponding UPDRS scores using the available conversion formulas[33] (see online Supplementary Table S5 for further details). MMSE and MoCA scores were both converted to Mattis Dementia Rating Scale (MDRS) scores following a validated method[34]. After surgery (at T1, T3 and T5), the following variables were collected: total score and axial subscore of the UPDRS or MDS-UPDRS part III in on-stimulation/on-medication and on-stimulation/off-medication conditions, LEDD, MMSE or MoCA, PDQ-8, stimulation parameters (amplitude, pulse width and frequency of both hemispheres).

GBA1 variants were classified into five classes (mild, risk, severe, complex and unknown) in accordance with the literature[35]. Severe and complex variants were merged in the group of GBA severe for statistical analysis[6].

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are reported as absolute numbers. For each time point, between-group comparisons (GBA+ versus GBA− and GBA severe versus GBA−) were performed with Mann-Whitney U test for continuous variables and χ^2 test for categorical variables. Friedman test was used for intra-group comparisons among the different time points, followed by post-

hoc Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons. Between-group comparisons of the axial score variation between two time points (Δ axial score = baseline value – follow-up value) were carried out with the Mann-Whitney U test.

Survival analysis and multivariate Cox regression models were performed to evaluate preoperative predictive factors of worsening of axial signs in both on- and off-medication conditions. For each patient, we considered as "event" the achievement of a ≥ 2-point higher UPDRS III axial subscore during the follow-up compared to the baseline score. We chose a 2-point threshold considering that a 1-point change may fall within the rater variability inherent in the UPDRS, not reflecting a clinically meaningful deterioration. Survival analysis statistics were calculated from baseline to outcome achievement or censored data at the last available follow-up, up to five years after surgery. All preoperative demographic and clinical variables were selected as independent factors for multivariate Cox regression models, except for UPDRS subscales, which were excluded due to collinearity with the total scale. We used a stepwise selection process to build the final regression models with the significant variables and the variable "GBA status" (i.e., presence or absence of *GBA1* pathogenic variants). To rule out collinearity or absence of independence, the variance inflation factor (VIF) was checked among the significant continuous variables. Adjusted hazard ratio (HR) with 95% confidence interval (CI) was calculated for each variable in the regression models. Bonferroni correction for multiple comparisons was applied in the final regression models. Kaplan-Meier method was used to illustrate "axial worsening-free survival" curves of GBA+ versus GBA− groups and GBA severe versus GBA− groups. The log-rank test was performed to test curves' differences.

All statistical computations were two-tailed, and a p-value < 0.05 was considered significant. The statistical analyses were performed with SPSS version 26 for MAC.

Data availability

The data supporting the findings of this study are available from the corresponding author upon request.

Received: 7 June 2025; Accepted: 31 August 2025;
Published online: 17 October 2025

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Acknowledgements

This study received no funding.

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F.B., A.R.B. and C.P. contributed to the conception and design of the study; D.G., A.D.B., Al.A., An.A., C.A.A., L.A., M.A., L.B., G.C.B., I.C., N.C., R.C., A.C., Fa.C., F.D.B., V.D., R.E., G.G., N.G.A., A.G., G.I., A.I., C.L., M.L., L.L., M.C.M., R.M., P.M., L.M.R., E.M.V. and R.Z. contributed to the acquisition of data; F.B., Fr.C., V.F., P.C. and F.V., A.R.B. and C.P. contributed to the analysis and interpretation of data; F.B. and D.G. contributed to drafting the text and preparing figures; E.M.V., P.C., A.R.B. and C.P. revised the manuscript for important intellectual content.

Competing interests

A.A. has received a grant from Medtronic. F.B. has received reimbursement of travel expenses to attend scientific meetings from Boston Scientific. L.L. has received speaker honoraria from Medtronic. N.G.A. and C.P. have received reimbursement of travel expenses to attend scientific meetings by Boston Scientific and Medtronic. There are no other conflicts of interest specifically related to this manuscript.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41531-025-01140-7.

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