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ORIGINAL ARTICLE

Levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson disease with genetic mutations

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Abstract

Background Levodopa-carbidopa intestinal gel infusion (LCIG) is a therapeutic option for advanced Parkinson disease (PD) patients with troublesome motor complications, unresponsive to conventional oral treatment. There is some evidence to suggest that the genetic background may influence the clinical presentation and rate of progression of PD. Whether the genetic background influences the outcome of device-assisted therapies is currently debated. Some studies have investigated the effectiveness of deep brain stimulation (DBS) in PD patients with different genetic background, while evidence is lacking regarding LCIG.

Methods A cohort of LCIG patients underwent genetic testing. The motor and neuropsychological outcomes of LCIG were retrospectively analyzed.

Results Fifty-six patients were analyzed, nine of them (15%) had at least one mutation/variant in a PD-associated gene: five GBA1, two SNCA, one LRRK2, one PRKN; 13 (23%) carried the BDNF Val66Met polymorphism. The mean duration of follow-up was 4.9 ± 2.6 years. There were no significant differences in motor or neuropsychological outcomes between patients with and without these gene mutations/variants. No cognitive worsening was observed at follow-up among GBA-PD patients, and they responded well to LCIG in terms of motor symptoms.

Conclusions Overall, we observed a significant benefit in terms of motor complications in our cohort, including patients carrying genetic mutations/variants. Due to the small sample and limited number of patients carrying genetic mutations/variants, no definitive conclusions can be drawn yet on the genotype impact on LCIG outcome. A careful selection of patients, regardless of the genetic background, is pivotal for an optimal outcome of LCIG.

Keywords Parkinson disease · Device-assisted therapies · Levodopa carbidopa intestinal gel infusion · Genetics · GBA · BDNF

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Introduction

Parkinson disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer disease, and it is characterized by several motor and non-motor symptoms [1]. Although oral therapy provides good control of motor symptoms during the initial stage of the disease, in some patients, the onset/worsening of levodopa-resistant symptoms, complications, and motor fluctuations in the advanced stage of the disease lead to increased disability and decreased quality of life, demanding the implementation of device-assisted therapies [1]. Device-assisted therapies, encompassing continuous levodopa/carbidopa intestinal gel (LCIG) infusion, deep brain stimulation (DBS), and apomorphine infusion, reduce some of the troublesome complications that are poorly managed with pharmacological therapy in advanced PD [2–4]. LCIG provides continuous levodopa infusion directly into the proximal jejunum by way of percutaneous endoscopic gastrostomy with a jejunal extension tube (PEG-J) connected to a portable infusion pump. The administration of a gel suspension of levodopa/carbidopa directly in the duodenum allows continuous uptake of the drug while bypassing the gastric emptying—a potential cause of suboptimal response to levodopa: this leads to less variability in plasma levels of levodopa with fewer motor fluctuations compared to oral levodopa [3]. Both clinical studies and real-life experience have demonstrated the efficacy of LCIG in relieving both motor and non-motor symptoms and improving activities of daily living and quality of life; however, complications related to both the device and to the therapy have been reported [5–9].

Even though the etiology of PD in most patients remains unknown, genetic mutations/variants are identified in approximately 5–10% of cases: they can be either high-penetrance (e.g., *SNCA*, *VPS35*, biallelic *PRKN/PINK1/DJ1*, rarer *LRRK2* variants), intermediate penetrance (e.g., *LRRK2* G2019S), low penetrance genetic risk factors (e.g., *GBA1* variants), and in other cases non-pathogenetic polymorphisms that have been linked with specific clinical features (e.g., *BDNF* variants) [1]. Among genetic mutations/variants, glucocerebrosidase (*GBA1*) is the most frequently found in idiopathic PD and is associated with clinical features, depending on the specific mutation/variant [10–13]. In the perspective of a tailored and personalized medicine for PD, whether the genetic status influences the outcome of device-assisted therapies is a question of great interest, also considering the importance of patients' selection for optimal outcome of these treatments. Several features must be considered: age, frailty, cognitive status, phenotype (motor and non-motor symptoms), response to levodopa, side effects or complication profile, the patient's comfort with invasive therapy options, and the caregiver's support [14, 15]. Some data is available regarding the effectiveness of DBS in patients with PD and different genetic background: although the efficacy of DBS was confirmed in all groups, differences among different genetic groups were found [16]. Indeed, a recent study suggested that the combined effects of *GBA1* mutations/variants and STN-DBS in PD negatively impact cognition [17]. To our knowledge, besides a meeting abstract reporting no difference between GBA-PD and other LCIG patients [18], genetic features and their relationship with clinical outcome and complications have not been extensively investigated in LCIG cohorts.

The aim of this study was to evaluate motor and cognitive outcomes in a series of LCIG patients with genetic mutations/variants.

Methods

Patients

All patients underwent LCIG and were followed up at our institution between 2008 and 2018. They underwent a cross-sectional neurological and neuropsychological evaluation, and blood sample collection between 2017 and 2019. Patients who underwent neurological follow-up within 2 ± 1 years after the LCIG start were included in the analysis. All baseline data were retrospectively extracted from the data system of the Movement Disorders Centre of the University of Turin, Italy. Follow-up assessment was performed during clinical outpatient visits. Inclusion criteria were as follows: diagnosis of idiopathic PD [19], fulfilment of inclusion criteria for the LCIG therapy (including clinical evaluation with levodopa and/or naso-intestinal tube infused levodopa challenge, neuropsychological tests, psychological assessment, motivational assessment, caregiver consultation, absence of comorbidities), and the treatment with LCIG delivered by PEG-J, as previously described [20]. All patients gave their informed consent for genetic testing and participation in the study. The study was performed in agreement with the principles of the Declaration of Helsinki and in compliance with Italian legislation on retrospective studies and was approved by the local ethics committee.

Outcome measures

All the available demographic and clinical variables at the time of LCIG start (baseline) were collected and analyzed: gender, age, disease duration, duration of motor fluctuations, levodopa equivalent daily dose (LEDD) [21], stage of PD as per the Hoehn and Yahr score, Unified Parkinson's Disease Rating Scale (UPDRS) parts I–IV or Movement Disorder

Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I–V [22], Schwab and England score (SE) [23]. A validated formula was used to convert MDS-UPDRS II and III into UPDRS II and III scores, when needed [24]. Part III at baseline was assessed in two dopaminergic treatment conditions: "OFF" (after ≥ 12 h withdrawal from antiparkinsonian medication) and "ON" (45 min after the administration of levodopa); at follow-up, patients were assessed while in "ON" condition with their habitual therapy ("daily ON").

In patients with UPDRS III at baseline, four composite motor scores from UPDRS-III were calculated: (1) akinesia (sum of the face item 19; hands items 23, 24, 25; feet item 26; and global akinesia item 31, range 0–40), (2) rigidity (items 22, range 0–20), (3) tremor (items 20, 21, range 0–28), and (4) axial (speech item 18; arising from a chair item 27; posture item 28; gait item 29; and postural stability item 30, range 0–20) as previously described [25].

Cognitive and behavioral assessments were performed in the best clinical "ON" condition at baseline and at a follow-up visit. Patients were submitted to an extensive neuropsychological battery assessing reasoning, memory, frontal executive functions, and phonemic and category verbal fluency tasks as previously described [26]; mild cognitive impairment (MCI) was defined as moderate or severe impairment on at least two neuropsychological tests, when cognitive deficits are not sufficient to interfere significantly with functional independence, in accordance with the Level-I of MDS criteria for MCI [27]. PD-Dementia (PD-D) was defined according to the MDS criteria [28].

The following behavioral measures were also collected [26]: depression, assessed by means of the Beck Depression Inventory (BDI); apathy, assessed by means of the Apathy Scale (AS). Quality of life (QoL) was assessed through the Parkinson's Disease Questionnaire (PDQ-39).

In addition, all patients were evaluated at baseline and follow-up for peripheral neuropathy (PNP), defined as the symmetric alteration of action potential amplitudes or velocities in at least two motor or sensory nerves at the nerve conduction studies (NCS), either clinical or subclinical, as previously described [29].

Genetic testing

Patients were tested for nine PD-related genes using a next-generation sequencing (NGS) approach (see Supplementary Table 1 for the complete list of genes included in the panel). A custom panel was designed with the HaloPlex online design tool (SureDesign, Agilent Technologies) and sequenced on the MiSeq platform (Illumina, Inc., San Diego, CA, USA). Exon dosage changes were investigated by ligation-dependent probe amplification method (MLPA) using a P051 kit (MRC Holland, Amsterdam, the Netherlands) (GBA1 was not included in the MLPA analysis). Samples were additionally genotyped for *GBA1* variants by Sanger sequencing, and *BDNF* polymorphisms were assessed, among other variants, using the Neurochip, as described elsewhere [30].

Statistical analysis

Descriptive statistics (mean, standard deviation, and range) were used for continuous variables and frequency for categorical data. Shapiro-Wilk test was used to test normality. Independent sample *t*-test (continuous variables with normal distribution), the Mann-Whitney *U* test (continuous variables without normal distribution), or Fisher's exact test (categorical variables) was used to compare demographic and clinical data between the groups of LCIG patients: patients with mutations/variants vs all other patients, *GBA1* variants vs all other patients, *BDNF* Val66Met vs all other patients. Wilcoxon signed-rank test was used to compare outcomes at different time points within the same group. ANOVA repeated measures were used to compare the evolution of clinical measures between the different groups (patients with mutations/variants vs all other patients, *GBA1* mutations/variants vs all other patients, *BDNF* Val66Met vs all other patients); the analyses were covaried for age, duration of PD, and length of follow-up, and Bonferroni correction was applied. All *p*-values reported are two-tailed, and a $p < 0.05$ was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 26 for Windows, Chicago, IL).

Results

Patients

Data from 56 consecutive PD patients who underwent LCIG were analyzed. The mean age of patients at the onset of PD symptoms was 54.3 ± 7.9 years, disease duration was 12.6 ± 4.1 years, and LCIG treatment duration at the last follow-up was 4.9 ± 2.6 years (Table 1). Nine patients (15%) had at least one variant in any PD-associated gene, and 13 (23%) had *BDNF* Val66Met polymorphism. There was no significant difference in the time of follow-up between the groups, except for the *SNCA* group (which had a shorter follow-up, Table 1). There was a significant difference in age at LCIG between patients with no mutations/variants and patients with *BDNF* Val66Met polymorphism (*BDNF* Val66Met = 71.5 ± 4 years old, no-mutation patients = 66.9 ± 7.5 years old, $p < 0.005$) (Table 1); there was no significant difference in other variables within these groups. Demographic and clinical features of all the patients are detailed in Tables 1

Table 1 Baseline vs follow-up clinical features of patients with and without genetic mutations

Genetics	Age at onset	Age LCIG	PD Duration t0	Years after LCIG (t1)	LEDD T0 (mg/day)	LEDD T1 (mg/day)	SE T0	SE t1	HY t0	HY t1	UPDRS II t0	UPDRS II t1	UPDRS III OFF t0	UPDRS III ON t0	UPDRS III ON t1	UPDRS IV t0	UPDRS IV t1
All (56)	54.3± 7.9	66.9±7.5	12.6±4.1	4.9±2.6	1164.56± 438.1	1542± 425.2*	64.8±13	50.9±11*	2.6±0.6	3.3±1.2*	12.6±5.4	26.3±9.5*	46.9±9.8	23.6.9±9.6	37.1±14.4*	9.4±2.9	5.1±3*
No mutations/ variants (34)	51.5± 4.8	65.3±7.8	12.7±3.2y	5.1±2.8	1226± 392.5	1565.41±418.2	65.2±12	51.7±20*	2.5±0.6	3.2±1.2 *	13.1±6.4	28.1±8.4	46.4±9.3	23.7±9.8	39.7±13.7	9.5±2.9	5.3±2.6*
BDNF Val-66Met (13)	57.8± 6.6	71.5±4§	13.7±5.8	5.3±2.2	955.4± 387.5	1516.6± 488.8	63.6±14	48.3±21	2.9±0.6	3.4±1.3	14.8±2.9	24.9±11.9	45.6±10.1	23.8±10.8	36.3±15.3	10±3.1	5.8±3.7*
GBA1 (5)	58.2±3	72.0±5.3	11.2±3y	5.1±1.6	1102.8± 311.9	1513.7 ±189.1	53.3±5.8	40.0±20	2.6±0.9	4±0	10.3±3	25.8±10.1	47.4±13.2	23.3±10.5	34.5±10.5	8.3±2.1	3.2±2.9
SNCA (2)	49± 14.1	56±14.8	6.5±2.1	2.0±0.3	712.5±10	1790±551.5	75±21.2	60.0±42	2.25±0.3	3±1.4	11	18.5±12.3	51.3±18.8	17.8±0.2	17.1±1	7.5±0.7	3±2.8
PRKN (1)	45	68	19	5.5	1400	1600	60	60	2	3	1	26	48.5	17	30	8	5
LRRK2 (1)	60	75	11	4.8	1200	1300	50	20	2	3	#	35	51	37	56	16	7

T0, baseline; *t1*, follow-up; *LEDD*, levodopa equivalent daily dose; *SE*, Schwab and England score; *HY*, Hoen and Yahr stage in ON; *ADLs*, activities of daily living (MDS UPDRS II), motor score (MDS UPDRS III) in ON and OFF conditions, motor complications (MDS UPDRS IV) of patients with and without genetic mutations. *, significant difference between t0 and t1 in the same group; §, significant difference between patients in the BDNF Met66Val group and no mutations group

Table 2 Motor UPDRS-subscores at baseline and levodopa response in a subgroup of patients with and without genetic mutations

Genetics	Akinesia OFF	Akinesia ON	Rigidity OFF	Rigidity ON	Axial OFF	Axial ON	Tremor OFF	Tremor ON
No mutations/ variants (33)	20.3±5.8	12.2±5.7	7.7±2.6	3.6±2.3	11.2±3.8	6.9±3.4	2.8±2.9	0.7±1.2
BDNF Val66Met (13)	21.6±5.2	12.4±7.1	7.3±3.1	3.5±2.6	11.8±4.2	6.8±2.9	2±2.2.8	0.2±0.4
GBA1 (5)	25.5±5.5	12.5±3.1	9.1±2.8	2.1±2	14±1.2	8.6±4.2	2.8±2.1	0.5±0.6
SNCA (1)	20	7.5	6	3.5	10	4	1	0
PRKN (1)	25	9	11	5	10	3	2	0
LRRK2 (1)	17	9	12	5	8	2	6	0

Composite motor scores from Unified Parkinson's Disease Rating Scale (UPDRS) part III: (1) akinesia (sum of the face item 19; hands items 23, 24, 25; feet item 26; and global akinesia item 31, range 0–40); (2) rigidity (items 22, range 0–20); (3) tremor (items 20, 21, range 0–28); and (4) axial (speech item 18; arising from a chair item 27; posture item 28; gait item 29; and postural stability item 30, range 0–20)

and 2. Information on each patient, including the specific mutation/variant, is summarized in Table 3.

Motor outcome

Compared to baseline, the whole groups showed a significant worsening in SE, HY, UPDRS II and III, and LEDD and a significant reduction in motor complications (UPDRS IV) at follow-up (Table 1). Compared with the baseline, there was a significant reduction of UPDRS IV in the *BDNF* Val66Met subgroup at follow-up (Table 1). Changes in motor outcome during follow-up did not reach significance in other subgroups (Table 1).

At baseline and follow-up, there was no significant difference in motor assessment between patients with vs patients without mutations/variants and between patients with *GBA1* mutations/variants vs all other patients (Table 1). ANOVA repeated measures did not show any significant difference in the change of motor symptoms during the follow-up between different groups.

Neuropsychological outcome

The baseline neuropsychological assessment, performed on 49 patients, showed the following cognitive profiles: normal cognitive profile in 22 patients, MCI in 24 patients, and dementia in three patients; these latter cases received LCIG therapy due to the severe motor picture and high reliability of their caregivers. Thirty-two patients underwent neuropsychological follow-up after 1.9 ± 1 year; in this subgroup, 25 had no mutations, four carried *GBA1* variants, two carried *SNCA* mutations, one carried *PRKN* mutations, and nine carried the Val66Met *BDNF* variant. There were no significant differences in the time of follow-up between the groups (Table 4, supplementary table 2 and 3). ANOVA repeated measures did not show any significant difference in the change of neuropsychological assessments during the follow-up between different groups.

Treatment-related adverse events

At baseline, neuropathy was observed in five patients in the no-mutations/variants group, three in the *BDNF* Val66Met group, one in the *GBA1* group, one in the *SNCA* group, zero in the *PRKN* group, and one in the *LRRK2* group. At follow-up, six patients in the no-mutations/variants group, six in the *BDNF* Val66Met group, two in the *GBA1* group, one in the *SNCA* group, one in the *PRKN* group, and one in the *LRRK2* had polyneuropathy. Ten patients in total underwent removal of the LCIG device due to complications: six patients in the no-mutations/variants group, after a mean of 1.14 years (two due to abdominal pain, one due to neuropathy, two due to lack of benefit, one due to excessive dyskinesias); one in the *BDNF* Val66Met group (after 2 years due to neuropathy in a concomitant hematological disease); two patients in the *GBA1* group (one patient immediately after the LCIG start due to delirium and one patient after 8 years due to global worsening); one patient in the *PRKN* group (after 6 years due to bumper syndrome).

Discussion

Besides improving our understanding of the pathophysiological mechanisms of PD, the increasing knowledge of the genetics of the disease offers the possibility of improving treatments, not only by designing new target-directed drugs, but also through a better classification of PD populations.

The identification of specific clinical feature associated with genetic markers and the characterization of response to treatment can be a fundamental tool to implement a personalized approach in the treatment of PD; this is particularly relevant in the field of device-assisted therapies, as these are directed to patients with a more complex clinical picture, are more invasive than standard pharmacological therapy, and require a greater commitment of the patients and their caregivers. The selection of patients is the cornerstone of success in device-assisted therapies, and the identification of genetic

Table 3 Clinical characteristics of mutation carriers

Gene	Mutation	Sex	Age at onset	Age at LCIG	Family history	UPDRS III T0	UPDRS III T1	UPDRS IV t0	UPDRS IV t1	Clinical features
GBA1	c.1093G>A, p.Glu365Lys (E365K) (Het)	F	62	76	No family history of GD, PD nor other neurodegenerative diseases	OFF=60 ON=36	ON=29	10	4	LCIG was removed after 7 years due to general worsening and managing difficulties
	c.236A>G, p.Tyr79Cys (Y79C) (Het)	F	56	71	Parent affected by dementia and tremor (onset: 80 YO), no diagnosis of PD	OFF=54 ON=24	ON=26	7	4	Anxiety and depression. ICD (gambling) during pramipexol therapy. Postural instability
	c.1226A>G, p.Asn409Ser (N409S) (Het)	M	56	65	No family history of GD, PD nor other neurodegenerative diseases	OFF=30 ON=7	ON=32	10	2	Hallucinations and psychosis treated with clozapine
	c.721G>A, p.Gly241Arg G241R (Het)	F	61	70	No family history of GD, PD nor other neurodegenerative diseases	OFF=45 ON=25	ON=50	6	0	Autonomic dysfunction (moderate orthostatic hypotension). Memory deficit. Hallucinations treated with quetiapine
	[c.882T>G; c.1342G>C], p[His294Gln;. Asp448His] + c.1226A>G, p.Asn409Ser; (Comp Het)	M	55	65	Offspring affected by a not specified neuropsychiatric developmental disorder. No family history of GD, PD nor other neurodegenerative diseases	OFF=46 ON=25	NA	10	NA	Affected by bipolar disorder. LCIG was removed immediately due to severe delirium
SNCA	EX1-6 Duplication (Het)	M	39	44	Parent diagnosed with PD at 58 YO. Siblings of affected parent diagnosed with PD at 53 and 48 YO	OFF=65 ON=17	ON=27	7	5	Mild ICD, persistence of motor fluctuations. Depression. 6 kg weight loss after the start of LCIG
	c.89C>G, p.Ala30Gly (A30G) (Het)	M	59	67	Parent affected by Alzheimer's disease	OFF=38 ON=18	ON=11	8	2	ICD (hypersexuality). 10 kg weight loss after the start of LCIG
LRKK2	c.6055G>A,p. Gly2019Ser (G2019S) (Het)	M	60	71	Parent diagnosed with PD at 65 YO. Affected parent's sibling diagnosed with PD at 60 YO	OFF=51 ON=36	ON=56	16	7	Severe bladder detrusor hyperactivity
PRKN	EX2-3 Deletion (Homo)	M	45	64	2 siblings diagnosed with PD at 40 YO	OFF=48 ON=17	ON=30	8	5	LCIG was removed after 6 years due to bumper syndrome and infective complications. Severe postural instability

T0, baseline; *t1*, follow-up; *PD*, Parkinson disease; *GD*, Gaucher disease; *YO*, years old; *ICD*, impulse control disorder. For cDNA numbering, +1 corresponds to the A of the first ATG translation initiation codon; *Het*, heterozygous mutations; *Homo*, homozygous mutations

Table 4 Neuropsychological tests at baseline and follow-up

Genetics	*N* t0	*N* t1	Years FU (t1)	MMSE t0	MMSE t1	Cognitive status t0	Cognitive status t1	BDI t0	BDI t1	TOT PDQ t0	TOT PDQ t1	PDQ SI t0	PDQ Si t1	Apathy t0	Apathy t1
No mutations/variants	34	17	2.04±1.1	27.6±1.8	26.7±3.2	sMCI=6 mMCI=8	sMCI=4 mMCI=1 d=5	14.1±6.7	17.3±7.7	279.1±117.5	300.4±112.5	43.7±43.5	37.5±14.1	12.8±6.6	12.9±6.8
BDNF Val-66Met	13	9	2.09±1.3	26.9±3.2	25±4.1	sMCI=3 mMCI=3 d=2	sMCI=2 mMCI=1 d=4	17.5±9.6	16±10.5	373.1±107.7	320.1±142.9	46.6±13.5	40±17.9	12.9±6.3	12.9±7.4
GBA1	5	4	1.96±1.1	26.8±2.1	25.5±0.5	mMCI=2	mMCI=1	18.3±6.6	23±10.4	352.8±195	431.3±190	44.1±24.4	53.9±23.7	16.8±3.6	16.7±3.5
SNCA	2	2	1.88±1.3	27.5±0.7	26±2.8	d=1	d=1	7.0±8.5	3	191.1±226	69.7	23.9±28.3	8.4	6.5±4.9	6.5
PRKN	1	1	1.13	28.0	27	sMCI=1	sMCI=1	6.0	21	183.7	264	23.0	33	13.0	13
LRKK2	1	0	NA	23.0	NA	mMCI=1	NA	26.0	NA	256.2	NA	32.0	NA	14.0	NA

T0, baseline; *t1*, follow-up; *MMSE*, Mini-Mental State Examination; *sMCI*, single domain mild cognitive impairment; *mMCI*, multiple domain MCI; *d*, dementia; *BDI*, Beck's depression inventory; *PDQ*, Parkinson disease quality of life questionnaire; *PDQ SI*, Parkinson disease quality of life questionnaire Social Impairment; *Apathy*, Marin apathy scale; *NA*, not available

criteria might add important information to this process. Hence, we aimed to analyze our LCIG cohort to determine if specific genotypes are associated with different outcomes.

Currently, together with subcutaneous apomorphine infusion and DBS, LCIG represents a therapeutic option for patients with fluctuating symptoms, unresponsive to optimal oral treatment. Current evidence suggests that genetic background may influence the clinical picture, the natural progression of the disease, and the individual responsiveness to treatments in PD [9]. Some genetic mutations/variants have been associated with some specific features in PD; for example, *GBA1* variants have been associated with earlier onset, more rapid motor deterioration, and a higher risk of cognitive impairment (for a review, see [10]); while the *BDNF* polymorphism Val66Met has been associated with milder motor symptoms, a slower rate of progression, and a higher risk of levodopa-induced complications, cognitive impairment, and psychiatric symptoms [31]. However, it is still unclear how genetic factors influence the outcome of device-assisted therapies for PD.

In our LCIG cohort, we observed a prevalence of 15% of PD-related mutations/variants, five *GBA1* (8.7%), two *SNCA* (3.5%), one *LRRK2* (1.7%), and one *PRKN* (1.7%); 13 (23%) carried the *BDNF* Val66Met polymorphism. We did not find any significant differences in motor and cognitive outcome among patients with and without mutations/variants. Patients carrying mutations/variants showed a satisfactory response to LCIG and did not report more adverse events than patients without mutations/variants, except for one patient carrying complex GBA1 mutations/variants and with psychiatric comorbidities who developed infectious complications and delirium after initiation of LCIG, leading to its withdrawal. As in other PD cohorts, *GBA1* variants were the most frequent (8.7% of patients). The percentage of patients with genetic variants in our cohort reflects that reported in general unselected PD populations, in contrast to data on DBS cohorts in which genetic mutations/variants are overrepresented, probably due to the selection of younger patients with good prognostic factors for DBS (i.e., absence of cognitive impairment and comorbidities) [32]. In DBS cohorts, some differences have been noted in GBA-PD patients: they tend to undergo DBS earlier than other patients [32], possibly because of a more aggressive disease course, and—despite motor improvement—they tend to show more complications, specifically cognitive impairment [16]. Indeed, GBA-PD is associated with a greater risk of dementia depending on the variants/mutations [12], and STN-DBS seems to increase this risk: GBA-PD patients show more cognitive impairment after DBS than PD patients without GBA1 mutations/variants who underwent DBS, and they also show a worse cognitive outcome after STN-DBS compared with GBA-PD patients who did not undergo DBS—also when stratified according to the mutation/variant

type. Accordingly, with what was observed in non-DBS cohorts, cognitive decline after STN-DBS is faster in subjects carrying neuronopathic mutations/variants [17]. In our cohort, we have not observed significant differences between GBA-PD patients and other groups in terms of motor and non-motor symptoms and complications of LCIG; it must be considered that the small size of the sample might account for these results.

Several studies have linked the *BDNF* Val66Met with the susceptibility, incidence, and clinical features of several neurodegenerative disorders, including PD [31]. In our cohort, there was no difference in motor or neuropsychological outcome between patients carrying this polymorphism and others. Patients with the *BDNF* Val66Met polymorphism tended to undergo LCIG at an older age than patients without mutations, possibly a reflection of a slighter older age at onset than the other groups (this difference did not reach statistical significance).

The follow-up of our cohort as a whole showed a significant increase in SE, HY, UPDRS II and III, and LEDD reflecting the progression of the disease, but a significant reduction in motor complications (UPDRS IV), as a confirmation of the effectiveness of LCIG therapy on motor complications. Although the trend was similar in subgroups, these differences did not always reach significance, likely due to the smaller sample size.

Overall, we observed no cognitive worsening at follow-up among four *GBA1* patients, with a concomitant significant benefit in terms of motor symptoms. However, due to the small sample and limited number of patients carrying genetic mutations/variants, statistical analyses were underpowered: this is a limitation of this study; hence, no definitive conclusions can be drawn yet on the genotype impact on LCIG outcome.

Although it has been suggested by some authors that LCIG should be the preferred advanced therapy in severe GBA1 phenotypes, [33] due to the scarcity of data available in GBA-PD who underwent LCIG, it is our opinion that patients carrying such variants/mutations should be assessed independently following the indications for patients' selection in LCIG. The final decision on the most appropriate device-assisted therapy for PD (such as DBS, LCIG, or apomorphine infusion) should be based on clinical evaluation, assessment of patients' needs, and the potential risk and benefits that are associated with each procedure. Moreover, the role of the caregiver is particularly important when addressing patients for LCIG. We have previously reported that cognitive impairment is the main determinant of mortality in LCIG patients: considering the greater risk of cognitive impairment in GBA-PD, these patients might be identified as more vulnerable after LCIG [20]. This study has several limitations that hinder the possibility of drawing definitive conclusions, such as the small sample size, the crossover design, and the limited number of genes included in our panel (which does not include other genes that have been associated with atypical forms of Parkinson's disease, e.g., PLA2G6, ATP13A2, FBXO7, DNAJC6, SYNJ1, VPS13C, RAB39B). Prospective, long-term studies on infrequent genotypes should be performed by multinational collaboration in order to reliably decipher genotype-related differences in device-assisted therapy outcome and offer new insights to customize the treatment of PD; moreover, a prospective study design would provide more reliable and controlled data. While waiting for more data on the influence of the genetic background on LCIG outcome, we further stress the importance of a careful selection of patients, and we recommend a cautious use of LCIG in patients with cognitive alterations regardless of the genetic background, given the impact of cognitive deficits on device management and survival [20].

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