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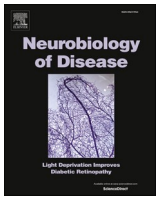

Association between plasma glucosylsphingosine levels and dyskinesia burden in *GBA1*-related Parkinson's disease

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ABSTRACT

Background: *GBA1* mutation is the most significant genetic risk factor for Parkinson's disease (PD). It encodes glucocerebrosidase (GCase), whose dysfunction – seen in Gaucher disease - leads to the accumulation of glucosylceramide and its derivate glucosylsphingosine (GlcSph). However, it remains unclear whether GCase and GlcSph are relevant in PD patients carrying no or monoallelic *GBA1* variants, and what their clinical impact might be.

Objective: Investigating the relationships between *GBA1* mutations, GCase, GlcSph, and clinical features in a large PD cohort.

Methods: We performed a cross-sectional study of PD patients screened for *GBA1* mutations, GCase activity, and GlcSph via dried blood spot tests. Patients were classified as heterozygous mutation carriers (*GBA1*-PD) or non-carriers (non*GBA1*-PD). Collected data included motor and non-motor parameters. Molecular and clinical differences were compared between *GBA1*-PD and non*GBA1*-PD. Distinctive clinical features were further investigated through multivariate models to test their correlations with biochemical data.

Results: The cohort included 611 subjects (225 *GBA1*-PD, 386 non*GBA1*-PD). *GBA1*-PD presented earlier onset, lower cognitive scores, higher incidence of mood disturbances and more advanced stage. Motor assessment revealed a higher frequency and severity of dyskinesias, independently from disease duration and LEDD. GlcSph levels showed an independent correlation with dyskinesia severity and time at onset in *GBA1*-PD patients, which was independent of sex, LEDD, UPDRS-III, disease duration and *GBA1* mutation class.

Conclusions: This study reveals an association between GlcSph and dyskinesias in *GBA1*-PD, that should prompt further investigation to assess the GlcSph role as a possible biomarker and target to tackle dyskinesias in *GBA1*-PD.

1. Introduction

Mutations of the *GBA1* gene are the major genetic risk factors for the development of Parkinson's disease (PD). *GBA1* encodes for glucocerebrosidase (GCase), a lysosomal enzyme, whose deficiency causes Gaucher Disease (GD), the most frequent lysosomal storage disorder (LSD) (Hertz et al., 2024; Riboldi and Di Fonzo, 2019). GCase deficiency causes the accumulation of glucosylceramide (GlcCer), which in turn is deacylated by the alpha acid ceramidase (AAC) enzyme to glucosylsphingosine (GlcSph) - the leading biomarker for diagnosing and monitoring GD (Hertz et al., 2024; Ferraz et al., 2016).

The interrelation between *GBA1* mutations, *GBA1* byproducts and the PD phenotype has been investigated in multiple studies (Petrucci et al., 2020; Toffoli et al., 2023; Oftedal et al., 2023; Alcalay et al., 2015). These provided a broad characterization of the *GBA1*-PD phenotype, which resulted in distinctive characteristics such as a more frequent akinetic-rigid phenotype and non-motor issues such as a higher burden of cognitive complaints, presence of behavioral abnormalities (e.g., anxiety, hallucinations), dysautonomia and sleep disturbances (i.e., REM sleep behavior disorder) (Petrucci et al., 2020; Toffoli et al., 2023; Menozzi and Schapira, 2021).

Previous large cohorts, also attempted a stratification of *GBA1*-PD phenotypes across mutation classes, identifying carriers of severe and risk mutations at a higher risk of developing cognitive complaints and hallucinations versus carriers of mild variants (Petrucci et al., 2020; Cilia et al., 2016). Noteworthy, *GBA1* gene mutation carriers were also at a higher risk of developing motor fluctuations and early dyskinesias as an additional and distinguishable clinical feature (Sosero et al., 2024; Thanprasertsuk et al., 2023).

Nevertheless, classifying *GBA1* mutations according to a "GD centered" model and consequently to the contribution of each mutation to the GCase enzymatic activity still fails to explain the *GBA1*-PD phenotype and progression heterogeneity, with inevitable drawbacks on interpretation and design of studies and clinical trials (Colucci et al., 2025).

GCase enzymatic and structural abnormality plays a role in accelerating the alpha-synuclein pathology (Hertz et al., 2024). Failure of GCase lysosomal activity led to the accumulation of lipid droplets - featured mainly by GlcCer and GlcSph - while GCase misfolding itself can affect both autophagic and mitochondrial pathways (Gegg et al., 2022; Leyns et al., 2023).

In a large study, we recently observed higher GlcSph levels in PD patients compared to controls, and in *GBA1*-PD patients compared to *GBA1* wild type patients (Marano et al., 2024). These findings, supporting the potential role of GlcSph as a disease biomarker, had also been reported by independent groups (Surface et al., 2022).

The study included consecutively enrolled PD patients at 20 Italian movement disorders centers who underwent dried blood spot testing for GD, retrieving data on *GBA1* genotype, GCase enzymatic activity, and GlcSph levels (Marano et al., 2024). GlcSph was measured in both *GBA1* mutation carriers and in *GBA1* wild type PD patients with reduced GCase activity ($\leq$3 nMol/h/ml).

Clinical data collected from the above-mentioned cohort have been analyzed herein, with our primary aim being the relationships between *GBA1* mutations, GCase activity, GlcSph levels, and the clinical phenotype of *GBA1*-PD. Given the relatively small number of non-mutated PD cases tested for GlcSph in the original cohort, we retrospectively expanded the sample by adding additional PD patients without *GBA1* mutations who had undergone complete dried-blood-spot assessments (GCase activity and GlcSph quantification) using the same analytical procedures outside the initial study.

2. Methods

A cross-sectional analysis was performed in a cohort of patients with idiopathic PD according to MDS criteria (Postuma et al., 2015)

undergoing a screening for *GBA1* gene mutations, GCase activity and GlcSph plasmatic levels in a real-world clinical setting. Genetic and biochemical data for most participants had previously been reported (Marano et al., 2024) where only carriers of GBA1 mutations and/or patients with reduced GCase activity (≤3 nMol/h/ml) were routinely screened for GlcSph levels, in accordance with standard clinical practice for GD (Marano et al., 2024). As only a minority of PD patients without *GBA1* mutations in the real-world cohort met the criteria for GlcSph testing, an enriched cohort was subsequently incorporated into the original sample for the present analysis. Herein, we included a total of 611 PD patients (225 GBA1-PD and 386 non-mutated PD, nonGBA1-PD). GCase activity analysis was available for 211 of 225 GBA1-PD (of whom 203 were also tested for GlcSph), and for 374 of 386 nonGBA1-PD (of whom 110 were also tested for GlcSph).

Clinical data were collected retrospectively through review of medical records and patient interviews at each of the 20 participating centers. Data on age, sex, disease duration, age at onset, Unified Parkinson's Disease Rating Scale (UPDRS) I, II, III (ON therapy) and IV (Martínez-Martín et al., 1994), time to dyskinesia onset [disease duration in years - years of dyskinesias], Montreal cognitive Assessment (MoCA) raw score, modified Hoehn and Yahr scale (ON therapy) and pharmacological therapy were gathered as key variables of interest. The levodopa equivalent daily dose (LEDD) was calculated for each patient (Jost et al., 2023).

Aggregated UPDRS subscores were calculated as grouping together specific sub-items of UPDRS II, III and IV as akinesia subscores (item 23, 24, 25 and 26 of UPDRS III), rigidity (item 22 at neck and limbs of UPDRS III), speech subscores (UPDRS II item 5 of UPDRS II and item 18 UPDRS III), postural instability and gait disorder subscore (item 13, 14 and 15 of UPDRS II, item 29 and 30 of UPDRS III), axial ADL subscore (item 5, 13, 14, 15 of UPDRS II), tremor subscore (items 20 and 21 UPDRS III and of item 16 of UPDRS II), dyskinesia subscore (item 32 and 33 of UPDRS IV-A), fluctuation subscore (items 36, 37, 38 and 39 of UPDRS IV-B). Each subscore was calculated as the mean value of its component items (i.e., the sum of the item scores divided by the number of items included).

Dyskinesia presence and severity were evaluated using the UPDRS Part IV dyskinesia subscore, supplemented by anamnestic reports. Dyskinesia was defined as present when the subscore was ≥1 or when dyskinesias were reported anamnestically, and as absent when the subscore was 0 and dyskinesias were no anamnestically reported. Severity was quantified using the UPDRS Part IV raw dyskinesia subscore, calculated as the mean of items 32 and 33 from UPDRS IV-A.

Other relevant information on motor and non-motor disease features and treatments including advanced therapies, use of dopamine agonists (DA), were also collected as dichotomous data (presence/absence of specific characteristics) and included as secondary variables of interest (supplementary materials).

GBA1 gene analysis, GCase (nMol/h/ml) and GlcSph (ng/ml) were obtained according to methods previously described (Marano et al., 2024). We adopted the classification of *GBA1* variants used in GD, in which based on the impact on the enzymatic activity "severe" variants are associated with neuronopathic forms and "mild" variants with non-neuronopathic forms. Complex alleles are classified as severe variants. The E326K, the T369M, the E388K and other variants that are not considered pathogenic for GD, but are actually associated with PD, have been classified as "risk" variants. Variants of uncertain significance (VUS) were classified as "unknown" (Parlar et al., 2023; Rossi et al., 2025).

2.1. Statistics

Data are described as mean ± standard deviation or frequencies (%). Data distribution was investigated through the Shapiro-Wilks test. Differences across groups were tested through *t*-test. Differences across multiple groups were tested through one-way ANOVA, with post-hoc t-test corrected for multiple comparisons through the False Discovery Rate (FDR) method. The chi-squared test has been used to compare groups for categorical variables. The association between continuous variables has been investigated through the Pearson test, according to data distribution. Variables with $p < 0.05$ in Shapiro-Wilk test were considered non-normally distributed; for these, Spearman correlation was used in addition to Pearson correlation, yielding consistent results. The strength of associations and the effect of multiple variables on the dependent variable have been tested through uni- and multivariate linear or logistic regressions. Time-to-event analyses (survival analysis) were performed using retrospectively collected data and the Kaplan-Meier method, with comparisons conducted using log-rank tests. Disease onset was defined as time zero, and dyskinesia onset as the event of interest. Patients without dyskinesias at last follow-up were censored accordingly. Statistics and graphs have been generated through the JMP 18.0 software (SAS Inc.). A *p*-value <0.05 was adopted for statistical significance.

Missing data were quantified for each variable, with absolute numbers and percentages reported in supplementary materials. To explore potential missingness mechanisms, we tested associations between missingness indicators and other observed covariates using chi-squared tests for categorical variables and Welch's *t*-tests for continuous variables. Variables showing significant associations ($p < 0.05$) were treated as plausibly Missing At Random (MAR), while those without such associations – or with no missing observations - were considered consistent with Missing Completely At Random (MCAR). For MAR variables, multiple imputation by chained equations (MICE) was applied in regression models where they were included as essential predictors or covariates. Variables missing by design (e.g., GlcSph not measured in part of the nonGBA1-PD group) were not imputed. Missing data analysis is reported in supplementary materials.

The present study has been approved by the ethical committee of the Fondazione Policlinico Universitario Campus Bio-Medico (RetroGBA; PAR 37.23 OSS) and has been conducted in accordance with the declaration of Helsinki. All participants have signed a regular informed consent. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The study has been reported according to the Strengthening the reporting of observational studies in epidemiology (STROBE) guideline (supplementary materials).

3. Results

In this study we included a total of 611 PD patients, 225 GBA1-PD (141, 62.7% Male; 84, 37.3% Female) and 386 nonGBA1-PD (252, 65.3% M; 134, 34.7% F). Data on GCase activity was available for 211 of 225 (97.7%) *GBA1*-PD (of whom 203 were also tested for GlcSph), and for 374 of 386 (96.9%) nonGBA1-PD (of whom 110 were also tested for GlcSph). Of the 225 *GBA1*-PD patients, 87 (38.6%) were carriers of a severe mutation, 69 (30.6%) of a risk variant, 52 (23.1%) of a mild variant and 17 (7.5%) of a VUS (Fig. 1A and B).

The following analyses, on molecular and clinical findings, have been carried out comparing the two main groups of patients (*GBA1*-PD vs nonGBA1-PD), and after stratifying *GBA1*-PD patients according to their mutation class (severe, mild, risk). Secondary clinical findings, based on anamnestic data on prodromal, motor and non-motor patient features and therapies are reported in supplementary materials.

3.1. Molecular findings

GBA1-PD patients exhibited lower GCase (4.34 ± 2.01 vs 5.54 ± 2.57; $p < 0.001$) and higher GlcSph levels (6.03 ± 2.07 vs 5.5 ± 1.59; $p = 0.010$) compared to nonGBA1-PD patients, confirming our previous observation (Table 1, Fig. 1C-D). GCase activity was influenced by the mutation class ($F_{2,208} = 8.4$, $p < 0.001$), with higher enzymatic activity detected in subjects carrying risk (5.21 ± 2.57) compared to severe (3.85 ± 1.45, $p < 0.001$) and mild (3.89 ± 1.34, $p = 0.002$) variants

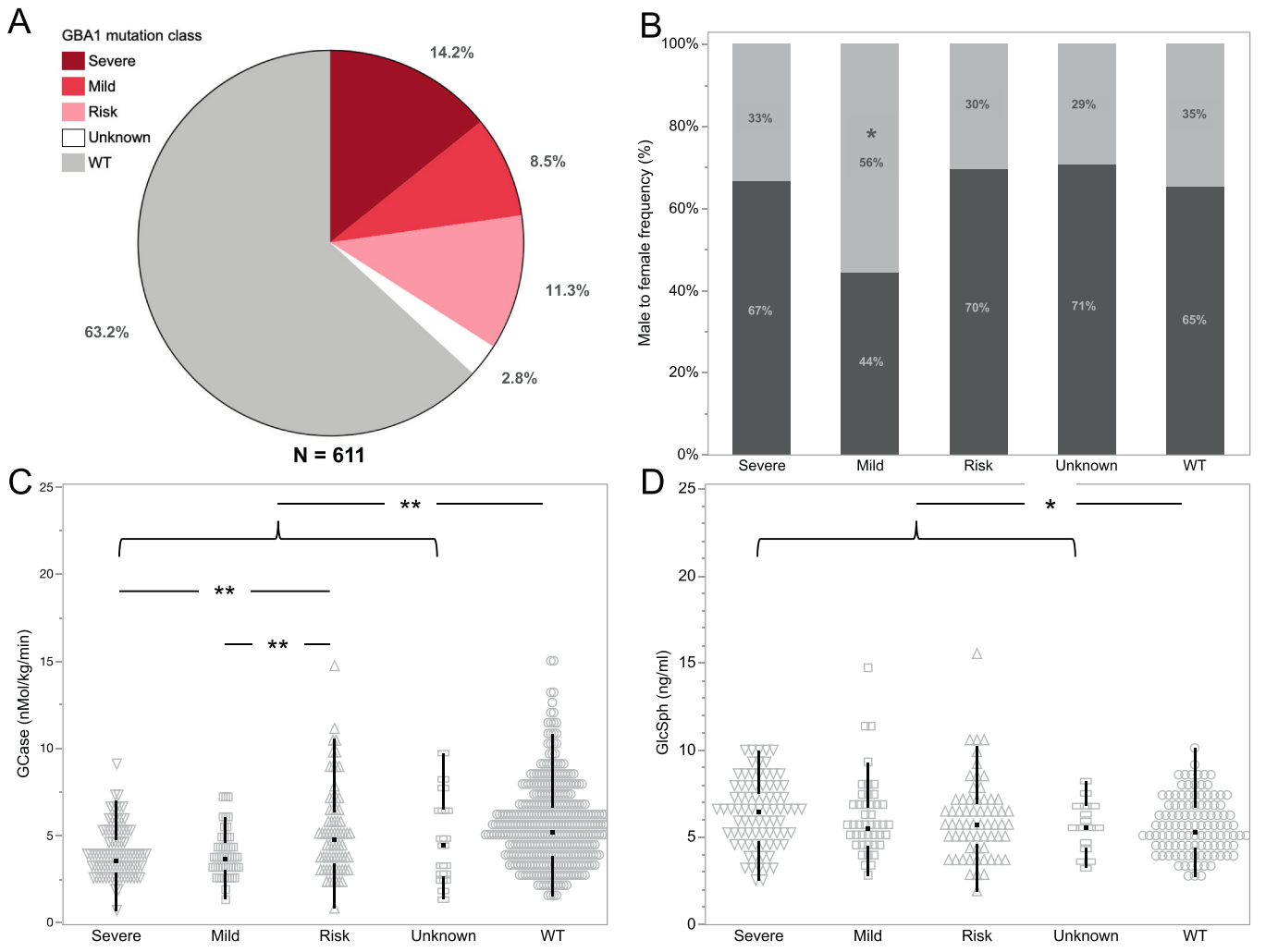

Fig. 1. A) *GBA1*-PD mutation class distribution; B) Sex distribution across mutation classes; C) GCase activity and D) GlcSph differences across all PD groups. $^{**}p < 0.01$, $^{*}p < 0.05$; *WT, nonGBA1-PD; Reverse triangles, severe mutation; squares, mild mutations; triangles, risk mutations; rectangles, unknown mutations; rounds, non-GBA1-PD.*

(supplementary table 3, Fig. 1C). No differences in GCase activity were observed between mild and severe mutation groups ($p = 0.674$). GlcSph levels did not significantly differ in patients carrying severe ($n = 80$, 6.22 ± 1.93), mild ($n = 44$, 6.95 ± 2.27) and risk ($n = 63$, 5.97 ± 2.2) variants ($F_{2,190} = 0.33$, $p = 0.713$), although levels were numerically higher in carriers of severe/mild mutations (Supplementary Table 3, Fig. 1D). Interestingly, the increased GlcSph levels were not associated with a reduction of the GCase activity, in either *GBA1*-PD or nonGBA1-PD (Supplementary Fig. 1).

3.2. Clinical findings: demographic data distribution

The disease duration was similar in *GBA1*-PD and nonGBA1-PD groups (7.5 ± 5 vs 7.35 ± 6, $p = 0.725$), while age at examination (61.2 ± 9.9 vs 64.3 ± 10.2, $p < 0.001$) and age at onset (53.8 ± 10.5 vs 57 ± 10.5, $p < 0.001$) were lower in *GBA1*-PD. Among *GBA1*-PD patients, carriers of severe variants showed significantly lower age at examination and age at onset than those with mild and risk mutations (supplementary table 3). Importantly, even if the sex distribution was similar between *GBA1*-PD and nonGBA1-PD, the M:F ratio observed in carriers of a mild mutation showed a significantly higher prevalence of women (M:F, 0.79:1) than the one observed in carriers of severe (2.03:1) and risk mutations (2.33:1) and in nonGBA1-PD (1.86:1) ($p = 0.023$, Fig. 1B and supplementary table 3).

3.3. Clinical findings: motor and non-motor rating scales, and aggregated subscores

The analysis of UPDRS subscores showed that part I and IV significantly differed between groups ($p = 0.026$ and $p = 0.012$, respectively), while part II and III did not (Table 1). These changes were furtherly explored through the analysis of UPDRS I and II subitems, and of UPDRS aggregated subscores. *GBA1*-PD had significantly higher scores at UPDRS I intellectual impairment and depression subitems, while showed significantly higher scores at UPDRS II sensory complaints, falling (unrelated to freezing), salivation and turning in bed subitems (supplementary table 4). Also, the modified Hoehn and Yahr score and the MoCA differed between groups, with *GBA1*-PD reporting a higher frequency of patients with a modified Hoehn and Yahr scale >2.5 ($p = 0.022$) and lower MoCA score ($p = 0.008$) than nonGBA1-PD (Table 1). The LEDD was similar across the two groups (Table 1).

GBA1-PD patients included in this study showed differences in dyskinesia prevalence, severity, and time to onset compared with nonGBA1-PD patients.

Dyskinesia prevalence was 41.7% (58/139) in the *GBA1*-PD group and 30.9% (82/265) in the nonGBA1-PD group ($p = 0.031$; OR 1.59, 95% CI 1.04–2.44; Fig. 2A), although there was no difference across GBA1 mutation classes (Fig. 2B), and dyskinesia severity was higher in *GBA1*-PD than in nonGBA1-PD (UPDRS Part IV dyskinesia subscore 0.72

Table 1
Demographic and clinical description of the study cohorts between groups.

	GBA1-PD ($n = 255$)	non*GBA1*-PD ($n = 386$)	
	Mean ± sd / n (%)	Mean ± sd / n (%)	*p*-value
GCase (nMol/h/ml)	4.34 ± 2	5.5 ± 2.5	***<0.001***
GlcSph (ng/ml)	6 ± 2	5.5 ± 1.5	*0.019*
Age	61.1 ± 9.9	64.2 ± 10.2	***<0.001***
Sex (F)	84 (37.3%)	134 (34.7%)	0.515
Disease duration (y)	7.5 ± 5	7.35 ± 6	0.720
Age at onset (y)	53.8 ± 10.5	57 ± 10.5	***<0.001***
Mod. Hoehn and Yahr	2.2 ± 0.9	2 ± 0.8	0.055
>2.5	58 (28.7%)	69 (20%)	*0.022*
MoCA	23.7 ± 5.1	25.4 ± 3.8	***0.001***
LEDD	702.8 ± 477.2	655.1 ± 459.8	0.3248
UPDRS I	3.5 ± 2.8	2.7 ± 2.5	*0.021*
UPDRS II	11.3 ± 7.8	10 ± 7.1	0.173
UPDRS III	25.2 ± 15.2	23.3 ± 13.5	0.156
UPDRS IV	3.9 ± 4.3	2.5 ± 3.2	*0.012*
UPDRS subscores			
Axial ADL	0.8 ± 0.8 (N missing = 123, 54.7%)	0.7 ± 0.6 (N missing = 182, 47.2%)	0.218
PIGD	1 ± 0.8 (N missing = 123, 54.7%)	0.86 ± 0.64 (N missing = 185, 47.9%)	0.145
Rigidity	1 ± 0.77 (N missing = 63, 28%)	1 ± 0.65 (N missing = 121, 31.3%)	0.854
Akinesia	1.12 ± 0.74 (N missing = 64, 28.4%)	1.12 ± 0.67 (N missing = 121, 31.3%)	0.075
Tremor	0.32 ± 0.36 (N missing = 64, 28.4%)	0.41 ± 0.42 (N missing = 122, 31.6%)	*0.017*
Speech	1 ± 0.88 (N missing = 126, 56%)	0.92 ± 0.73 (N missing = 192, 49.7%)	0.289
Fluctuation	0.41 ± 0.47 (N missing = 144, 64%)	0.29 ± 0.41 (N missing = 220, 57%)	0.057
Dyskinesia	0.72 ± 1.04 (N missing = 86, 38.2%)	0.45 ± 0.79 (N missing = 121, 31.3%)	***0.003***
Dyskinesia onset time	6 ± 3.1 (N missing = 4, 6.9%) *	6.3 ± 4 (N missing = 2, 2.5%) *	0.592
Advanced therapies			
LCIG	7 (4.79%)	24 (10.48%)	0.051
CSAI	3 (2.05%)	0	0.058
DBS	35 (17.95%)	17 (6.12%)	***<0.001***

$p < 0.05$ in *Italic*; $p < 0.01$ in *Italic* Bold. Missing data are reported in supplementary materials; *missing data for dyskinesia onset time are calculated on patients reporting dyskinesias (GBA1-PD = 58, nonGBA1-PD = 82); LCIG, levodopa Carbidopa Intestinal Gel; DBS, Deep Brain Stimulation; CSAI, continous apomorphine infusion.

± 0.07 vs 0.45 ± 0.79; $p < 0.001$; Fig. 3A), as expected. Moreover, after stratifying *GBA1*-PD patients by *GBA1* mutation type and adjusting for disease duration (Fig. 3B, upper panel) and total LEDD (Fig. 3B, lower panel), dyskinesia scores were higher in *GBA1*-PD in carriers of mild and severe mutations. Stratification by sex showed that increased dyskinesia severity in *GBA1*-PD patients was particularly pronounced in females, especially among carriers of mild mutations (Fig. 3B). This sex difference persisted after adjustment for disease duration and LEDD.

Time to dyskinesia onset was shorter in *GBA1*-PD than in nonGBA1-PD patients (9, 6–11; vs 11, 6–15; years from diagnosis; $p = 0.051$), although this difference did not reach statistical significance. This trend was not influenced by mutation class (Fig. 3C-D, supplementary materials).

Among the other UPDRS subscores, tremor score was higher in *nonGBA1-PD* and fluctuation score was slightly increased in *GBA1*-PD (Table 1, Fig. 3A).

3.4. Clinical-biochemical correlations

A multivariable correlation analysis was performed to examine the relationships between GCase, GlcSph, global clinical measures of PD (modified Hoehn and Yahr stage, MoCA, LEDD, UPDRS I–IV) and UPDRS subscores in *GBA1*-PD and nonGBA1-PD, while controlling for disease duration, when appropriate.

In GBA1-PD patients, GlcSph levels were significantly higher in those with dyskinesias than in those without dyskinesias (6.5 ± 2.3 vs 5.5 ± 1.7, $p = 0.013$; OR = 1.27; 95% CI 1.05–1.53; Fig. 4A). This association was not evident in nonGBA1-PD patients (Fig. 4B).

To minimize floor effects, analyses were restricted to patients with dyskinesias. Within this subgroup, GlcSph levels correlated positively with dyskinesia severity (UPDRS IV dyskinesia subscore) ($r = 0.457$, $p < 0.001$; Fig. 4C), and negatively with time to dyskinesia onset in *GBA1*-PD patients ($r = -0.267$, $p < 0.001$; Fig. 4D). No significant associations between GlcSph levels, dyskinesia severity, or time to onset were detected in the nonGBA1-PD group ($r = 0.004$, $p = 0.966$ and $r = -0.138$, $p = 0.227$, respectively) (Fig. 4C-D). No other significant correlation between molecular findings and clinical parameters adjusted for disease duration was observed in *GBA1*-PD and nonGBA1-PD (supplementary materials).

Univariate and multivariate regression analysis were performed to further investigate the association between GlcSph and dyskinesias in *GBA1*-PD, adjusting for other potential associated factors including mutation types (severe, mild, risk, unknown), motor performances (UPDRS III), disease duration, total LEDD, age and sex. Age at onset was not directly included in the model, as it is derived from the relationship between age and disease duration. The multivariate model ($F_{9,102} = 12.66$, $p < 0.001$) detected the presence of an independent relationship between GlcSph and the UPDRS dyskinesia subscore only in *GBA1*-PD patients ($p < 0.001$) (Table 2, Fig. 4C). Disease duration, sex, and LEDD independently correlated with dyskinesias in GBA1-PD and nonGBA1-PD groups (supplementary materials). None of these factors substantially modified the association between GlcSph and dyskinesia. Moreover, since advanced therapies - particularly DBS - substantially reduce dyskinesia scores, we performed sensitivity analyses excluding these patients to assess the robustness of GlcSph-dyskinesia associations. Likewise, a sensitivity analysis was performed to investigate the effect of DA use on the same model. Results of both analyses were consistent with findings from the original data set (supplementary materials). In addition, analyses using multiply imputed data for variables exhibiting a MAR pattern yielded coherent results with complete-case analyses (supplementary materials), supporting the robustness of the observed associations.

4. Discussion

While *GBA1* variants are related to clinical features, disease penetrance and progression in heterozygous carriers (Cilia et al., 2016; Gan-Or et al., 2008), the impact of GCase activity and GlcSph levels on PD is still unclear (Omer et al., 2022; Lerche et al., 2024). To fill this gap of knowledge we explored the interplay between PD clinical aspects, type of *GBA1* variant, GCase activity and GlcSph levels in a multicentric study enrolling consecutive PD patients.

The phenotypic profile of *GBA1*-PD in our cohort is consistent with previous reports from international studies (Petrucci et al., 2020; Menozzi and Schapira, 2021), being characterized by earlier onset, greater non-motor symptom burden - particularly mood disturbances - and poorer cognitive performance compared with non-carriers. While no significant differences were observed in several motor domains (e.g., rigidity, PIGD), patients with *GBA1*-PD exhibited lower tremor scores and higher dyskinesia scores, further supporting an akinetic-rigid predominance coupled with an increased susceptibility to dopaminergic

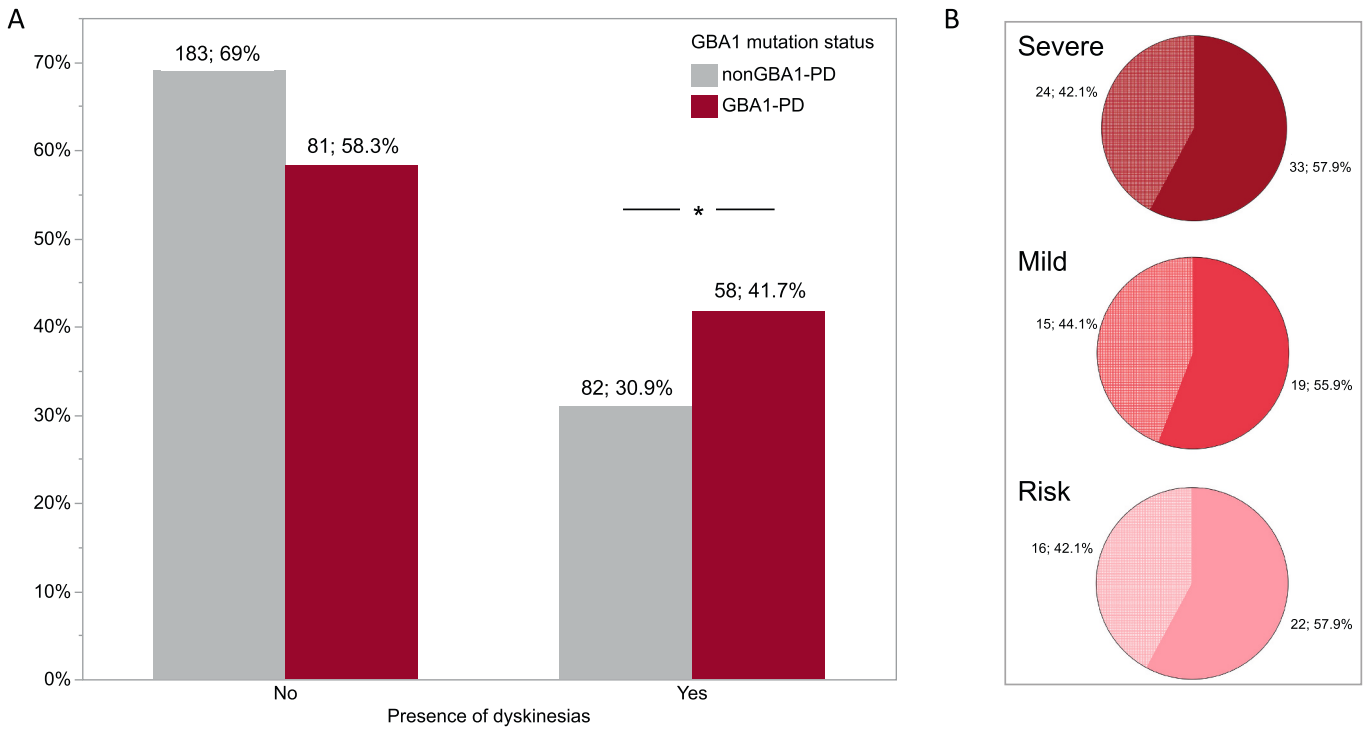

Fig. 2. A) Prevalence of dyskinesias in GBA1-PD and nonGBA1-PD patients; B) Prevalence of dyskinesias across *GBA1* mutation classes. *$p < 0.01$.

complications - particularly in light of recent evidence highlighting a higher rate of dopaminergic denervation in *GBA1*-PD patients, which collectively makes them more prone to motor fluctuations (Filippi et al., 2022; Grisanti et al., 2023; Avenali et al., 2024).

The finding of a higher prevalence of dyskinesias in *GBA1*-PD is in line with observations highlighted on large patient cohorts (Sosero et al., 2024). Although the sex distribution in *GBA1*-PD may vary across different variants and cohorts (Ortega et al., 2022), in this study, the female sex was strongly associated with a higher burden of dyskinesias in *GBA1*-PD, particularly among carriers of mild mutations. This is likely due to the greater dopaminergic denervation observed in female *GBA1*-PD patients, as documented by studies on longitudinal cohorts (Caminiti et al., 2025; Pellecchia et al., 2025; Hong et al., 2014) and in patients with different *GBA1* mutation type (Cilia et al., 2016). Future studies assessing in vivo dopaminergic imaging and GlcSph levels are warranted to better clarify the role of GlcSph as a biomarker of neurodegeneration and motor complications.

We confirmed previous observations showing significantly reduced GCase activity (Oftedal et al., 2023; Alcalay et al., 2015; Huh et al., 2020) and elevated GlcSph levels in *GBA1*-PD patients compared with nonGBA1-PD (Surface et al., 2022; Marano et al., 2024).

As a novel, and most notable finding, we observed an association between GlcSph and the time at onset and severity of dyskinesias in *GBA1*-PD. Moreover, the association between GlcSph and dyskinesias was not modified by adjusting the model for major clinical determinants of dyskinesias such as disease duration, LEDD, UPDRS III and the sex (Pellecchia et al., 2025; Warren Olanow et al., 2013), and even by the exclusion of DBS patients by the analysis. The inclusion of patients treated with advanced therapies, particularly deep brain stimulation (17.9% of *GBA1*-PD patients), represents a potential confounder, as these interventions substantially reduce UPDRS Part IV dyskinesia scores (Avenali et al., 2025). While sensitivity analyses excluding these patients yielded consistent results, this limitation should be considered when interpreting the strength of the GlcSph-dyskinesia association.

However, the mechanisms underlying such correlation remain to be elucidated. Interestingly, GlcSph levels had only a mild trend of increasing related to the type of *GBA1* mutation class and did not correlate with GCase activity reduction. This suggests that beyond the measurable CGase activity, GlcSph may be influenced by additional hits which may include impairment in other sphingolipid pathways, altered lipid turnover, or compensatory responses to lysosomal and mitochondrial stress (Straniero et al., 2022; Robak et al., 2017; Serebryany-Piavsky et al., 2025).

In this study, genetic screening was limited to the GBA1 gene. Mutations in other lysosomal enzyme genes that may be associated with PD (Robak et al., 2017) were not systematically evaluated, which could affect the specificity of our findings. Moreover, we measured GlcSph but not GlcCer or other related lipid subspecies, in accordance with our study methods. The investigation of metabolic pathways related to *GBA1* mutation in PD patients has the potential to shed light on this observation, as previous works reported an association between serum and CSF glycosphingolipids and dyskinesias in patients with PD (Santos-Lobato et al., 2022).

Our findings raise the possibility that GlcSph is not just biomarker of lysosomal dysfunction but may play an active role in modulating treatment-related motor complications, other than in disease pathology.

In line with this hypothesis, studies on fibroblasts of *GBA1*-PD patients reported a characteristic enrichment in sphingolipids in membranes, correlated with the extent of enzymatic loss, with shorter-chain species capable of promoting α-synuclein aggregation in vitro (Galvagnion et al., 2022). Membrane glycosphingolipids are also essential for proper 5-HT$_1$A ligand binding and surface expression, while cholesterol and sphingolipids together shape D1 receptor and G-protein membrane organization. In addition, direct modulation by GlcSph has been demonstrated for 5-HT2A/2B receptors (Mystek et al., 2016; Singh et al., 2012; Sanjel et al., 2022; Afzal and Shim, 2022). Elevated GlcSph levels have further been shown to promote neuroinflammation and maladaptive plasticity in response to dopaminergic therapy, thereby contributing to the development of dyskinesias (Santos-Lobato et al., 2022; Servillo et al., 2024).

Notably, the levels of GlcSph in PD carrying heterozygous *GBA1* variants are lower than those observed in GD, where biallelic *GBA1* mutations cause a marked loss of GCase activity leading to the accumulation of GlcCer, and consequently of GlcSph, a pattern not detected

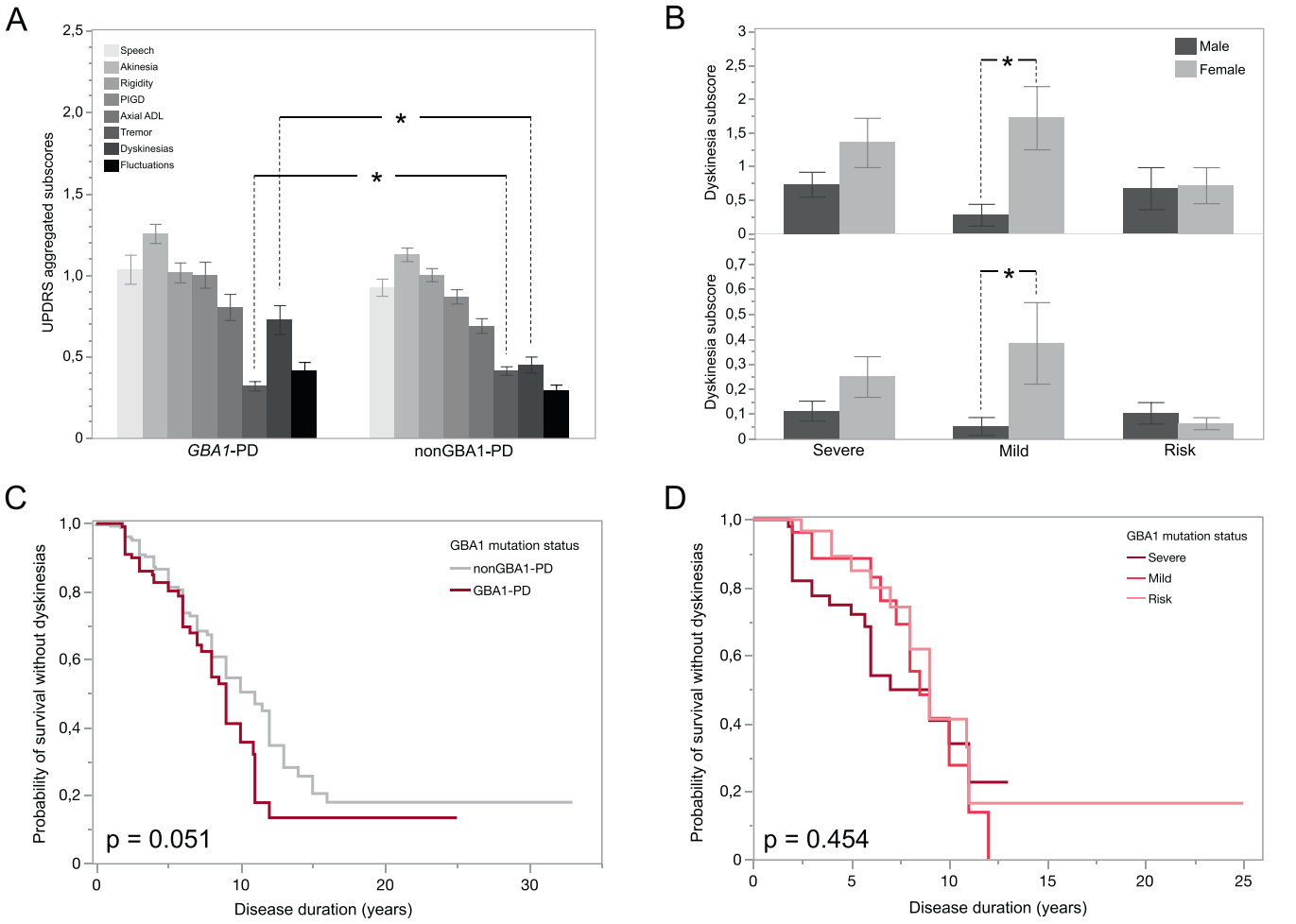

Fig. 3. A) Comparison of UPDRS aggregated subscores between patients with *GBA1*-PD ($n = 139$) and nonGBA1-PD ($n = 265$); B) Dyskinesia subscores stratified by *GBA1* mutation class and sex, adjusted for disease duration (upper panel) and for disease duration and LEDD (lower panel); C) Time to event analysis on the probability of developing dyskinesias in *GBA1*-PD vs nonGBA1-PD and D) across *GBA1* mutation classes; $^*p < 0.05$.

in monoallelic mutation carriers (Hertz et al., 2024; Riboldi and Di Fonzo, 2019; Ferraz et al., 2016). Further studies are warranted to assess how elevated GlcSph levels in GD patients who develop PD influence dyskinesia onset and severity.

The cross-sectional correlation between GlcSph levels and both dyskinesia severity and time at dyskinesia onset highlights the importance of further investigation on GlcSph as a potential biomarker of dyskinesia burden in *GBA1*-PD. Longitudinal studies are required to determine whether baseline GlcSph levels predicts future dyskinesia development, which would establish its value as a prognostic factor. If validated, GlcSph measurement could inform early risk stratification and guide personalized therapeutic strategies aimed at minimizing treatment-related complications of *GBA1*-PD. The absence of a similar association in nonGBA1-PD needs to be investigated in larger cohorts.

The main limitations of this study stem from its retrospective, cross-sectional design, which precludes causal inference and, although time-to-event analyses were anchored at disease onset and patients without dyskinesias were appropriately censored at last follow-up, residual immortal time bias cannot be entirely excluded. Moreover, GlcSph measurements were available in a non-uniform subset of nonGBA1-PD patients and, due to the study design, dosages of other relevant lipids such as GlcCer were not available. Classification of mutation severity, although based on widely accepted criteria, may not capture the full range of in vivo functional effects. Finally, the absence of longitudinal follow-up and detailed pharmacological history limits our ability to assess the predictive value of GlcSph for disease progression.

In conclusion, our study shows that PD patients carrying *GBA1* mutations exhibit higher GlcSph levels, and a clinical phenotype marked by higher dyskinesia burden. The novel, genotype-specific association between GlcSph and dyskinesias should prompt further investigation to assess its role as a possible biomarker of this specific treatment-related complication in *GBA1*-PD. Finally, our observations suggest that GlcSph may serve as potential biomarker of dyskinesia burden, with potential prognostic value awaiting validation in longitudinal studies, and highlight GlcSph as a candidate target for therapeutic interventions aimed at reducing motor complications in *GBA1*-PD.

CRediT authorship contribution statement

Massimo Marano: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carmela Zizzo:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis. **Francesco Cavallieri:** Writing – review & editing, Investigation, Data curation. **Micol Avenali:** Writing – review & editing, Investigation, Data curation. **Tommaso Schirinzi:** Writing – review & editing, Investigation, Data curation. **Edoardo Monfrini:** Writing – review & editing, Investigation, Data curation. **Francesca Spagnolo:** Writing – review & editing, Investigation, Data curation. **Rosa De Micco:** Writing – review & editing, Investigation, Data curation. **Silvia Ramat:** Writing – review & editing, Investigation, Data curation. **Maria Chiara Malaguti:** Writing – review & editing,

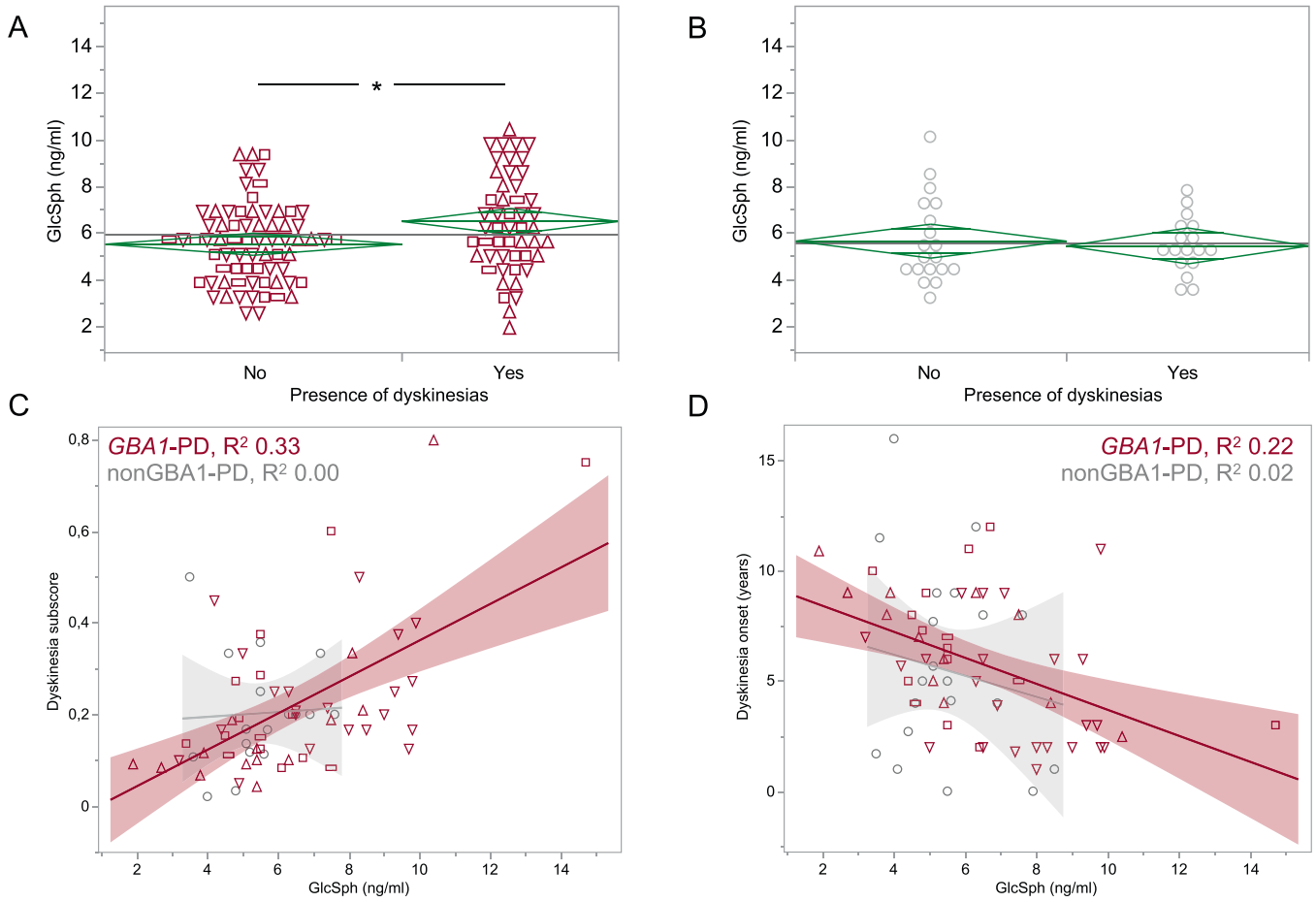

Fig. 4. A) GlcSph levels of patients with ($n = 51$) and without dyskinesias ($n = 70$) of the *GBA1*-PD group B) A) GlcSph levels of patients with ($n = 17$) and without dyskinesias ($n = 19$) of the nonGBA1-PD group; C) Correlation between GlcSph levels and UPDRS dyskinesia subscore corrected for disease duration in *GBA1*-PD (n = 51) and nonGBA1-PD (n = 17) patients. D) Correlation between GlcSph levels and time of dyskinesia onset in *GBA1*-PD ($n = 47$) and nonGBA1-PD ($n = 16$) patients. Reverse triangles, severe mutation; squares, mild mutations; triangles, risk mutations; rectangles, unknown mutations; rounds, nonGBA1-PD.

Investigation, Data curation. **Federico Reali:** Writing – review & editing, Supervision, Formal analysis. **Roberto Cilia:** Writing – review & editing, Investigation, Data curation. **Miryam Carecchio:** Writing – review & editing, Investigation, Data curation. **Andrea Pilotto:** Writing – review & editing, Investigation, Data curation. **Roberto Erro:** Writing – review & editing, Investigation, Data curation. **Ilaria Antonella di Vico:** Writing – review & editing, Investigation, Data curation. **Mario Meloni:** Writing – review & editing, Investigation, Data curation. **Giulia Di Lazzaro:** Writing – review & editing, Investigation, Data curation. **Sara Pietracupa:** Writing – review & editing, Investigation, Data curation. **Claudia Ledda:** Writing – review & editing, Investigation, Data curation. **Giovanni Mostile:** Writing – review & editing, Investigation, Data curation. **Marcello Mario Mascia:** Writing – review & editing, Investigation, Data curation. **Valentina Fioravanti:** Writing – review & editing, Investigation, Data curation. **Giulia di Rauso:** Writing – review & editing, Investigation, Data curation. **Roberta Bovenzi:** Writing – review & editing, Investigation, Data curation. **Simone Aloisio:** Writing – review & editing, Investigation, Data curation. **Marco Liccari:** Writing – review & editing, Investigation, Data curation. **Ruggero Bacchin:** Writing – review & editing, Investigation, Data curation. **Fabiana Colucci:** Writing – review & editing, Investigation, Data curation. **Giulia Bonato:** Writing – review & editing, Investigation, Data curation. **Alessandro Lupini:** Writing – review & editing, Investigation, Data curation. **Alessandro Magliozzi:** Writing – review & editing, Investigation, Data curation. **Cristiano Sorrentino:** Writing – review & editing, Investigation, Data curation. **Francesca Leo:** Writing – review & editing, Investigation, Data curation. **Giulia Franco:** Writing – review & editing, Investigation, Data curation. **Nicola Modugno:** Writing – review & editing, Investigation, Data curation. **Maurizio Zibetti:** Writing – review & editing, Investigation, Data curation. **Gennarina Arabia:** Writing – review & editing, Investigation, Data curation. **Anna Rita Bentivoglio:** Writing – review & editing, Investigation, Data curation. **Elena Caputo:** Writing – review & editing, Investigation, Data curation. **Filippo Tamma:** Writing – review & editing, Investigation, Data curation. **Alessandro Padovani:** Writing – review & editing. **Mario Zappia:** Writing – review & editing. **Roberto Eleopra:** Writing – review & editing. **Michele Tinazzi:** Writing – review & editing. **Giovanni Fabbrini:** Writing – review & editing. **Alessandro Tessitore:** Writing – review & editing, Project administration. **Vincenzo Di Lazzaro:** Writing – review & editing. **Enza Maria Valente:** Writing – review & editing, Resources, Investigation. **Giovanni Duro:** Writing – review & editing, Resources, Methodology. **Alessio Di Fonzo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Table 2
Univariate analysis and multivariate model on the correlation between clinical parameters, laboratory findings and dyskinesias.

Univariate analysis (dependent variable: dyskinesias subscore)				
Variable [Continuous]	B	SE	T	p-value
Age	−0.008	0.018	−0.48	0.631
Sex [F]	0.592	0.173	3.41	***<0.001***
Disease duration	0.196	0.031	6.16	***<0.001***
UPDRS III	0.000	0.011	−0.08	0.934
LEDD	0.001	0.000	4.65	***<0.001***
GlcSph (ng/ml)	0.310	0.090	3.42	***<0.001***
Variable [Categorical]	**N**	**SE**	**F**	**p-value**
Mutation class	3	24.38	1.90	0.131
Multivariate (dependent variable: dyskinesia subscore)				
R2	**Adjusted R2**	**N**	**F**	**Model p-value**
0.527	0.486	111	12.664	*<0.001*
Variable	**B**	**SE**	**T**	**p-value**
Age	−0.002	0.005	−0.34	0.731
Sex [F]	0.239	0.078	3.07	***0.002***
Disease duration	0.105	0.017	6.04	***<0.001***
UPDRS III	−0.010	0.004	−2.14	*0.034*
LEDD	0.000	0.000	3.22	***0.001***
Mutation class				
Severe	0.034	0.120	0.28	0.777
Mild	0.100	0.147	0.68	0.495
Risk	−0.050	0.134	−0.38	0.707
GlcSph (ng/ml)	0.167	0.037	4.53	***<0.001***

$p < 0.05$ in *Italic*; $p < 0.01$ in *Italic* Bold.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2026.107271.

Data availability

Data will be made available on request.

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