



Clinical short communication

Impulse control behavior in GBA-mutated parkinsonian patients

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ABSTRACT

Objective: To assess the prevalence and phenomenology of Impulse control behavior (ICB) in Parkinson's disease (PD) patients carrying mutations in the β -glucocerebrosidase (GBA) gene.

Background: GBA mutations are a common genetic factor predisposing to PD. ICB is among the most disabling non-motor complications of PD. The occurrence of ICB in PD patients carrying GBA gene mutations (GBA-PD) has not been yet established.

Methods: Forty-six patients with clinically definite PD (23 GBA-PD and 23 non-mutated patients, NM-PD) were screened for ICB. Diagnosis was clinically and rating based on a specific questionnaire (QUIP-RS). Other demographic and clinical variables did not differ between groups.

Results: ICB occurred more frequently in GBA-PD patients (52.2%) compared to NM-PD (13%) and the total QUIP-RS score was higher in the GBA-PD group. Hypersexuality and compulsive shopping were the most prevalent ICB types occurring in GBA patients. ICB occurred only in one GBA-PD patient on levodopa monotherapy and in 11 patients taking dopamine agonists, either monotherapy or combined with levodopa (the corresponding figures in NM-PD patients were 0 and 3). Most GBA-PD patients were heterozygous for two common genetic variants, without appreciable difference in their ICB profile.

Conclusion: ICB is more common in GBA-PD patients compared to NM-PD. Dopamine agonist therapy may be synergic to GBA carrier status for ICB occurrence.

1. Introduction

Mutations of the gene encoding the lysosomal enzyme β -glucocerebrosidase (GBA) are the most common genetic factor predisposing to Parkinson's disease (PD) [1]. The clinical phenotype of GBA-mutated PD (GBA-PD) differs from that of non-mutated PD (NM-PD), particularly regarding a higher prevalence of non-motor features. Compared to NM-PD, GBA-PD patients frequently develop cognitive dysfunction, autonomic impairment and behavioral disturbances [2].

Impulse control behavior (ICB) is among the most disabling non-motor complications of PD including gambling, hypersexuality, compulsive shopping, compulsive eating, hobbyism/punding and compulsive medication use [3]. ICB is associated with the use of

dopaminergic medications, in particular dopamine agonists [4]. Earlier observations on ICB occurrence in GBA-related PD are inconsistent, with some series reporting increased prevalence [5,6] and other no difference [7,8]. The question arises whether the prevalence of ICB is higher in GBA-PD patients.

We studied the prevalence and phenomenology of ICB in a group of GBA-PD patients compared to a matched group of NM-PD patients.

2. Materials and methods

From the genetic parkinsonian registry of Humanitas Research Hospital, including patients with a diagnosis of clinically established PD [9] who had genetic testing, we identified patients with mutations in the

Abbreviations: GBA, glucocerebrosidase gene; GBA-PD, GBA mutation carrier PD; ICB, Impulse control behavior; LEDD, levodopa-equivalent daily dose; NM-PD, nonmutated PD; PD, Parkinson's disease; QUIP-RS, Questionnaire for impulse control disorders in Parkinson's disease – rating scale; UPDRS-III, Unified Parkinson's disease Rating Scale motor score..

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GBA gene. GBA carriers with mutations in other genes were excluded, as well as patients with dementia (adjusted total score ≤ 71.25 at PD cognitive rating scale; [10]), hallucinations or delusions. From the same registry, a group of clinically established NM-PD patients matched for gender, age at disease onset and at time of study, and disease duration was selected. All the study participants had a reliable caregiver who agreed to participate. The study protocol was approved by the institutional review board; all patients and caregivers provided an informed consent for study participation.

All patients in the registry underwent genetic screening as follows. The total genomic DNA was extracted from peripheral blood of the patients. DNA has been analyzed with a customized gene panel (Nextera Rapid Capture Custom Enrichment) containing 23 genes associated with parkinsonian syndromes, including: ATP13A2, DNAJC13, DNAJC6, EIF4G1, FBX07, GBA, GCH1, GYG2F2, GRN, HTRA2, LRRK2, MAPT, PRKN, DJ1, PINK1, PLA2G6, SNCA, VPS35, SYNJ1, UCHL1, TMEM230, RAB39B. The panel was designed with Illumina Design Studio tool, according to a previously described methodology [11]. Sanger sequencing was used to confirm the mutation in the patient. Possible duplications or deletions were confirmed by MLPA analysis according to instructions (SALSA MLPA P051 e P052, MRC-Holland).

The following clinical data were collected: gender, age, years of education, age at disease onset, disease duration, Unified Parkinson's disease Rating Scale motor score (UPDRS-III), levodopa-equivalent daily dose (LEDD) for levodopa and dopamine agonists [12] and the duration of dopamine agonists exposure (years). Executive functions were assessed using a dedicated battery including tests for working memory (digit span backward test, [13]), suppression of automatic responses (Stroop test, [14]), attentional shifting (trial making test, [15]) and set activation and maintenance (phonological fluency test, [16]). A composite executive function score (executive score) was calculated for each patient by averaging the Z scores of the neuropsychological tests [17]. Psychiatric symptoms were assessed using the Beck depression inventory [18] and the State trait anxiety inventory [19]. ICB occurrence and phenomenology were assessed by detailed interviews of patient and a close caregiver [3]. In addition, each patient compiled the Questionnaire for impulsive-compulsive disorders in PD – rating scale (QUIP-RS) to measure ICB [20].

Between-group comparisons were performed non-parametrically, using the Fisher exact test for categorical variables, and the Mann-Whitney test for continuous variables. Statistical level was set at $p < .05$. Statistics were performed with the SPSS 25 software package.

3. Results

A total of 23 GBA carriers and 23 NM-PD fulfilling inclusion criteria were included in the study: 21 GBA-PD patients had monoallelic and two had biallelic mutations; 19 patients carried the common genetic variants p.Leu483Pro and p.Asn409Ser (Table 1). All the recruited patients presented with classical parkinsonian motor features and sustained response to dopamine replacement medications. In the GBA-PD group there were no appreciable extra neurological features, such as hepatosplenomegaly, anemia, thrombocytopenia, or skeletal defects. The demographic characteristics of the two groups are listed in Table 2, as

Table 1

Frequencies of mutations in the GBA-PD cohort. Aminoacidic (and nucleotidic) changes are shown for each allele.

	Allele 1	Allele 2
Patients	GBA gene mutations	
10	p.Leu483Pro (c.1448 T > C)	
9	p.Asn409Ser (c.1226A > G)	
1	p.Lys480Asn (c.1438G > C)	
1	p.Ser310Gly (c.928A > G)	
1	p.His294Gln (c.882 T > G)	p.Asp448His (c.1342G > C)
1	p.His294Gln (c.882 T > G)	p.Thr408Met (c.1223C > T)

Table 2

Demographic, clinical, cognitive and psychiatric characteristics of two PD populations differentiated based on the occurrence of mutations in the GBA gene or no PD-related mutation.

	GBA-PD (23)	NM-PD (23)	p- value
Demographic			
Gender (f/m)	11/12	7/16	NS
Age (years)	52.7 (± 7)	52.1 (± 6.6)	NS
Education (years)	11.6 (± 3.4)	12.3 (± 3.2)	NS
Clinical			
Age at disease onset (years)	46.5 (± 7)	47.2 (± 7)	NS
Disease duration (years)	6.2 (± 3.1)	4.9 (± 2.4)	NS
UPDRS–motor part	16.7 (± 7.7)	15.6 (± 5.4)	NS
Dopamine replacement medications			
Patients on levodopa (number)	17	21	NS
Patients on levodopa monotherapy (number)	7	5	NS
Patients on dopamine agonists (number)	16	18	NS
Patients on dopamine agonist monotherapy (number)	6	2	NS
Patients on levodopa and dopamine agonist treatment (number)	9	16	NS
Levodopa LEDD (mg equivalents)	388.7 (± 335.2)	403.6 (± 281.2)	NS
Dopamine agonist LEDD (mg equivalents)	168.8 (± 161.8)	195.7 (± 213.5)	NS
Total LEDD (mg equivalents)	575.5 (± 273.1)	599.2 (390.6)	NS
Dopamine agonist treatment (years)	4.8 (± 2.9)	3.4 (± 2.7)	NS
Cognitive			
Span backward	4.7 (± 0.9)	4.6 (± 0.9)	NS
Stroop (time)	19.9 (± 7.8)	18.8 (± 6)	NS
Stroop (errors)	0.4 (± 0.8)	0.9 (± 1)	NS
TMT (time)	96.4 (± 65.6)	72 (± 34.5)	NS
Phonological fluency (words)	38.8 (± 10.7)	40.7 (± 11.1)	NS
Executive domain (z-score)	−0.56 (± 3.2)	0.57 (± 2.5)	NS
Psychiatric			
BDI (raw score)	13 (± 9.2)	9 (± 7.2)	NS
STAY (raw score)	45 (± 10.9)	39.9 (± 10.3)	NS

Categorical variables are expressed as number and continuous variables are expressed as mean ($\pm$ SD). Comparisons were made by Fisher exact test and Mann-Whitney test, as appropriate. Significant differences ($p < .05$) are expressed in bold.

Abbreviations: BDI, Beck depression inventory; LEDD, Levodopa equivalent daily dose; STAY, State trait anxiety inventory; TMT, Trial making test; UPDRS, Unified Parkinson's disease rating scale; NS, Not-significant.

well as the levodopa and dopamine agonist treatments, cognitive and psychiatric features.

The prevalence of ICB and their severity were higher in the GBA-PD group compared to NM-PD (Table 3). Twelve GBA-PD patients had ≥ 1 ICB type (compared to three patients in the NM-PD group, $p = .011$); eight GBA-PD patients had ≥ 2 ICB types (compared to one patient in the NM-PD group, $p = .022$). Hypersexuality and compulsive shopping were more common in GBA-PD patients than in NM-PD ($p = .049$ and $p = .047$, respectively; Table 3). The total QUIP-RS score was higher in GBA-PD patients compared to NM-PD ($p = .015$).

In the GBA-PD group only one patient on levodopa monotherapy had ICB, compared to 11 patients on dopamine agonists, either monotherapy or combined with levodopa (the corresponding figures in NM-PD patients were 0 and 3). Ten patients were heterozygous for the p.Leu483Pro mutation and 9 for the p.Asn409Ser mutation. Comparison of these subgroups revealed no differences in ICB profile.

4. Discussion

ICB is a collection of potentially hazardous behavioral symptoms

Table 3

Characteristics of ICB observed in two PD populations differentiated based on the occurrence of mutations in the GBA gene or no PD-related mutation.

	GBA-PD (23)	NM-PD (23)	p- value
Impulse control behavior			
• Gambling (patients)	1	0	NS
• Hypersexuality (patients)	5	0	0.049
• Compulsive shopping (patients)	7	1	0.047
• Compulsive eating (patients)	6	1	NS
• Hobbyism/punding (patients)	7	2	NS
• Compulsive medication use (patients)	1	0	NS
Patients with ICB (number)	12	3	0.011
ICB subtypes (number of ICB types per patient)	1.17 (±1.5)	0.2 (±0.5)	0.003
QUIP-RS (total score)	13.2 (±14.4)	5.3 (±8.6)	0.015

Categorical variables are expressed as number and continuous variables are expressed as mean (±SD). Comparisons were made by Fisher exact test and Mann-Whitney test, as appropriate. Significant differences ($p < .05$) are expressed in bold.

Abbreviations: ICB, Impulse control behavior; QUIP-RS, Questionnaire for impulsive-compulsive disorders in PD – rating scale.

observed in PD, associated with decreased quality of life and familiar, financial and legal issues. We assessed the prevalence and phenomenology of ICB in GBA mutation carriers, compared to a matched group of PD patients without mutations in PD-associated genes. We observed that the GBA-PD group had a more pronounced ICB phenotype: they had an increased prevalence and on average showed more than one ICB subtypes. The prevalent ICB profile included hypersexuality and compulsive shopping, which are frequently associated with dopamine agonist use [21]. In keeping we observed that GBA-PD patients on dopamine agonist treatment were more prone to develop ICB, suggesting a possible synergic effect of GBA carrier status and medication use.

There were previous hints on a possible increase of ICB in GBA-PD. A PD progression markers initiative study on different genetic populations observed a 40.3% prevalence of ICB in the GBA-PD population, compared to 20.2% in NM-PD [5]. An Italian cohort study reported a 34.7% prevalence of ICB in the GBA-PD population, compared to 24.3% in NM-PD: these two groups received comparable doses of dopamine agonists [6]. This study expands these earlier observations by reporting an even greater disproportion (52.2% vs. 13%) in two highly matched groups. By contrast, no differences in ICB prevalence was found in two earlier studies on GBA-PD [7,8]. These studies did not report information regarding dopamine agonists medications and ICB assessment method. Some studies reported that patient self-report may underestimated ICB occurrence [22,23]; in the present study, ICB has been specifically addressed by extending the assessment also to caregivers.

ICB has been described in other monogenic PD populations, such as patients carrying PINK1 or PRKN mutations [24,25]. No case-control data are available for PINK1 mutation carriers, and no increased ICB occurrence has been observed for PRKN PD patients [26], raising the question whether GBA mutations have different behavioral influences compared to monogenic PD genes. GBA mutations are by far the most common genetic risk factor for PD. Current evidence suggests that from 2 to 9% of patients with PD carry a GBA gene mutations [27]; this figure further increases when the analysis is not limited to the most common mutations, but the entire exome is sequenced [28,29].

The observed higher prevalence of ICB in GBA-PD patients rise the question on a possible synergic effect of dopamine agonist prescription to a genetic GBA-related predisposition to ICB onset. Clinically, our data suggest special caution when managing GBA-mutated patients treated with dopamine agonists medications.

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Ethics approval

The Ethics Committee of Humanitas Research Hospital approved the study that was performed in accordance with the ethical standards of Declaration of Helsinki and its later amendments.

Consent to participate

All participants provided an informed consent for genetic analysis and for study participation.

Declaration of Competing Interest

Dr. Paolo Amami reports no disclosure; Dr. Barbara Garavaglia reports no disclosures; Dr. Federica Invernizzi reports no disclosures; Dr. Tiziana De Santis reports no disclosures; Prof. Alberto Albanese reports speaker's honoraria from Ipsen Pharma, Merz Pharma.

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