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Short communication

Glucocerebrosidase mutations and phenoconversion of REM sleep behavior disorder to parkinsonism and dementia

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ABSTRACT

Background: Mutations in the glucocerebrosidase (*GBA*) gene are strongly associated with REM sleep behavior disorder (RBD). It is unclear whether *GBA* mutations might affect clinical phenotype or rate of phenoconversion to parkinsonism or dementia.
Methods: We sequenced *GBA* in polysomnographic-proven idiopathic RBD (iRBD) patients. The effect of *GBA* mutations on clinical neurodegenerative markers and phenoconversion rate was assessed.
Results: Of 102 patients sequenced, 13 (13%) had *GBA* mutations and 89 did not. Aside from lower self-reported age of RBD onset in subjects with *GBA* mutations, no significant differences were observed in any clinical marker between patients with and without mutations. However, *GBA* mutations were associated with 3.2-fold higher phenoconversion rate from RBD to parkinsonism and/or dementia (95% CI = 1.4–7.3, p = 0.006).
Conclusion: Although *GBA* mutations do not appear to affect clinical neurodegenerative markers (and thus are not differentiable as an independent subtype of iRBD), they may accelerate the conversion of RBD to defined neurodegenerative synucleinopathy.

1. Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by a loss of muscle atonia and dream enactment behavior. It has emerged as the most powerful clinical predictor of neurodegenerative synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Recently, it has been discovered that 3–20% of patients with PD from different populations have a mutation of the glucocerebrosidase (*GBA,* sometimes referred to as *GBA1*) gene. Odds ratios (OR) for developing PD range from 2.2 for mild mutations to > 10 for severe mutations [1], and mutation carriers have an earlier age of onset. *GBA* mutations are common in patients of French-Canadian descent [2]. Moreover, they are commonly observed in patients with idiopathic/isolated RBD; studies have found that 10.2% of European RBD patients had a known pathogenic *GBA* mutation, corresponding to an OR = 6.2. When the PD risk variants p.E326K and T369M are included, the proportion of *GBA* pathogenic variants in RBD rises to 14% [3].

In this study, we investigated the role of the *GBA* gene in determining phenoconversion of RBD to parkinsonism and dementia, and whether patients with *GBA* mutations are identifiable as an independent subtype of RBD.

2. Methods

2.1. Patients

Patients with polysomnographic-proven RBD were recruited from the Centre for Advanced Research in Sleep Medicine of the *Hôpital du Sacré-Coeur de Montréal* (Montreal, QC, Canada) from 2004 to 2017, as

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previously described [4]. Ethics approval was obtained from the research ethics board of the hospital and all patients gave informed consent to participate according to the Declaration of Helsinki. All patients had idiopathic RBD as defined by the standard International Classification of Sleep Disorders-II criteria and were free of parkinsonism or dementia at baseline. The large majority of patients were of French-Canadian descent. Thirteen patients (13%) reported a family history of PD and 9 (9%) reported a family history of dementia.

2.2. Procedures

Patients had a comprehensive neurological/neuropsychological examination as it has been extensively described elsewhere [4]. Neurodegenerative markers included motor measures (the Unified Parkinson Disease Rating Scale 2 and 3, Purdue Peg Board, Timed Up and Go, alternate tap test, cognition (the Montreal Cognitive Assessment), autonomic manifestations (systolic blood pressure drop, symptoms of urinary, erectile, constipation, and orthostatic dysfunction from the 1–4 point MSA rating scale), olfaction (the 12-item cross-cultural version of the University of Pennsylvania Smell Identification Test), color vision (the Farnsworth-Munsell 100 Hue test), and the Beck Anxiety and Depression scales. This visit was then repeated annually. At each follow-up visit, neurological examination was conducted for parkinsonism and dementia, diagnosed according to standard criteria as previously described [4].

2.3. GBA analysis

Genetic analysis of *GBA* was performed as previously described [5], and the full protocol is available upon request. In brief, molecular inversion probes (MIPs) were used for targeted capturing of the coding sequences of *GBA,* followed by sequencing using the Illumina HiSeq 2500 platform at the McGill University and Genome Quebec Innovation Centre. Since exons 10 and 11 were not properly aligned due to the high similarity to the pseudo-*GBA* gene, they were also sequenced using Sanger sequencing in all samples. *GBA* mutations were also confirmed using Sanger sequencing. Full protocols are available upon request.

2.4. Statistical analysis

All statistical analyses were performed in Statistical Package for the Social Sciences version 24 statistical software (SPSS, Chicago, IL, USA). Differences in clinical markers between RBD patients with or without mutations in the *GBA* gene were determined using independent sample t-tests. The influence of the *GBA* gene on rate of conversion of RBD patients to parkinsonism or dementia was determined using Cox regression analysis, adjusting for baseline age and sex. A p-value < 0.05 was considered significant. No correction for multiple testing was performed, therefore results should be considered exploratory in nature.

3. Results

3.1. Baseline results

This study included 102 patients who were seen at baseline and still actively followed as of 2009 (when genetic testing commenced). Since recruitment, six patients were lost to follow-up, and three patients died; all were still included in analysis. Additionally, due to the ongoing recruitment into this study, at this time 5 patients have been seen only once without prospective follow-up. At baseline, 37 patients were taking clonazepam, 16 melatonin, and 30 had received antidepressants. Mean follow up duration was 5.1 ± 3.2 years. Of 102 patients who were genotyped, 13 (13%) had an identified *GBA* mutation. Of these 13 patients, 9 had mild mutations/risk variants (E326K = 4, T369M = 4, N370S = 1) and 4 had severe mutations (H225Q = 1, W291X = 1, W378G = 2). Age at baseline, sex, and RBD duration were not significantly different between the RBD subjects with and without *GBA* mutations (Table 1). Similarly, no difference was observed in any motor feature, autonomic manifestation, or measure of cognition, olfaction, color vision, anxiety, or depression. The only difference between groups was the self-reported age of RBD onset, which was lower among *GBA* mutation carriers (50.2 ± 15.3) than non-carriers (57.7 ± 12.1, p = 0.047).

Table 1
Clinical characteristics of neurodegeneration in GBA mutation carriers and non-carriers at baseline.

	Non-Carriers (n = 89)	GBA Mutation Carriers (n = 13)	p value
Age at Baseline (years)	66.0 ± 8.0	63.9 ± 5.9	0.36
Sex (% Male)	66/89 (74.2)	10/13 (76.9)	0.83
Age Self-Reported RBD Onset (years)	57.7 ± 12.1	50.2 ± 15.3	0.047
PSG-Diagnosed RBD Duration (years)	8.1 ± 7.8	13.7 ± 13.6	0.17
Systolic Drop (mm Hg)	9.9 ± 13.0	16.3 ± 16.0	0.11
Urinary dysfunction	0.43 ± 0.59	0.38 ± 0.65	0.79
Erectile dysfunction	1.7 ± 1.5 (n = 64)	1.3 ± 1.3 (n = 10)	0.44
Endorses Erectile Dysfunction (%)	52% (n = 64)	30% (n = 10)	0.40
Constipation	0.64 ± 0.82	0.54 ± 0.78	0.68
Constipated (%)	18%	15%	0.79
Orthostatic symptoms	0.33 ± 0.56	0.15 ± 0.38	0.15
UPSIT (% Normal)	77.4 ± 27.1	65.0 ± 25.9	0.13
Farnsworth-Munsell test (% normal)	48%	42%	0.70
UPDRS 2	1.6 ± 1.8	1.9 ± 2.0	0.65
UPDRS 3	3.9 ± 3.4	4.7 ± 5.5	0.47
Purdue Peg Board (no. pegs)	11.4 ± 1.7	11.2 ± 2.5	0.64
Timed Up and Go (seconds)	6.3 ± 1.0	6.6 ± 1.2	0.42
Alternate Tap Test (HR per 10 taps)	185.7 ± 27.7	174.5 ± 32.2	0.19
MoCA	25.3 ± 2.8 (n = 80)	26.7 ± 2.0 (n = 12)	0.12
Beck Anxiety Inventory	8.6 ± 7.2 (n = 68)	8.5 ± 7.0 (n = 10)	0.96
Beck Depression Inventory	10.2 ± 7.2 (n = 67)	7.7 ± 5.2 (n = 11)	0.27
UPDRS Depression	0.50 ± 0.86 (n = 46)	0.44 ± 0.73 (n = 9)	0.86
Depression Diagnosed (% yes)	39% (n = 46)	25% (n = 8)	0.45

3.2. Disease conversion

Despite having no baseline differences in any clinical marker, patients carrying *GBA* mutations had a higher rate of phenoconversion of RBD to defined neurodegenerative disease (Fig. 1). Overall, the HR for phenoconversion with a *GBA* mutation was 3.2 (95% CI = 1.4–7.3, p = 0.006, unadjusted HR = 2.5 [1.1–5.4]). HR for mild mutations was 2.3 (95% CI = 0.8–6.3) and for severe mutations was 5.5 (95% CI = 1.7–17.0).

Of the 33 phenoconvertors, 19 converted to parkinsonism first without dementia in the first year (PD with mild cognitive impairment [MCI] = 9, PD without MCI = 8, MSA = 2), and 14 to dementia first (8 with associated parkinsonism at diagnosis, 4 with one cardinal parkinsonian sign, and 2 with no parkinsonian signs). Among the patients with *GBA* mutations who phenoconverted, 5/9 (56%) of *GBA* mutation carriers developed parkinsonism as the first manifestation similar to 14/24 (58%) of mutation non-carriers. All dementia convertors met 2017 consensus criteria for DLB [6]. Mean follow up time was 3.4 ± 2.7 years for patients who converted to DLB and 4.0 ± 3.1

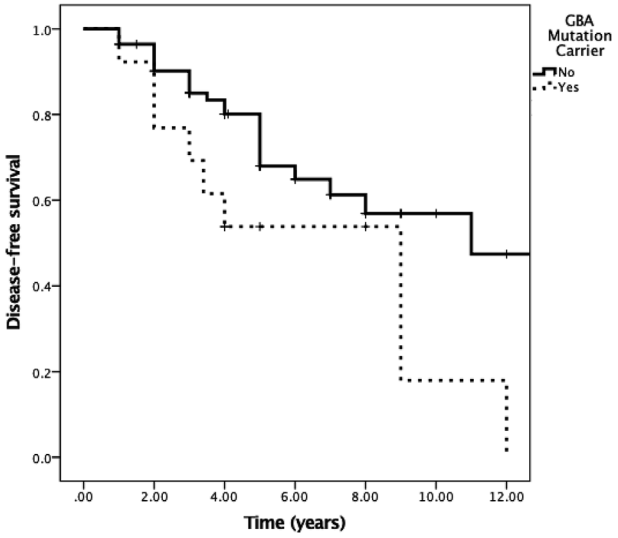

Fig. 1. Phenoconversion rate in RBD patients with and without *GBA* mutations. Ticks indicate censoring events.

years for patients who converted to PD. Among phenoconvertors at the time of phenoconversion, we again saw no differences in any neurodegenerative marker between patients with and without *GBA* mutations (Supplemental Table 1).

4. Discussion

The findings of this study suggest that RBD patients who carry mutations in the *GBA* gene, despite having a similar profile of neurodegenerative markers at baseline, have an accelerated phenoconversion from idiopathic RBD to defined neurodegenerative disease.

There has been one study previously assessing *GBA* and phenoconversion in RBD. This study found no increased risk among *GBA* mutation carriers and non-carriers [7]. It is not clear why we found different results; of note, our sample size was larger (13 carriers in our study vs. 8 in Gamez-Valero, which included two novel variants of uncertain pathophysiologic significance), suggesting the possibility that simple random variation may be responsible for the difference. We also found that the reported age of RBD onset was significantly lower in patients who carry the *GBA* gene. This (along with the faster phenoconversion rate) is consistent with previous findings that PD patients with *GBA* mutations have an age of disease onset approximately 5 years earlier than controls [8]. Interestingly, while the p.E326K variant is not associated with Gaucher's disease, it is a risk factor for PD associated with cognitive decline [9], suggesting that the pathophysiology of *GBA* mutation sin PD are not identical to that of Gaucher's.

It is notable that despite a significantly higher phenoconversion rate, there were no differences between *GBA* mutation carriers and non-carriers in any of the other clinical markers we investigated either at baseline or at phenoconversion. This suggests that within idiopathic RBD patients, those with *GBA* mutations are not clinical differentiable from those without, and therefore do not delineate a distinct subtype. This is contrast to findings in PD overall, in which subjects with *GBA* mutations have faster motor progression and are more likely to develop dementia [9]. Notably, the presence of RBD in PD also marks a similar severe subtype of PD characterized by increased risk of dementia, more autonomic dysfunction, and worse overall prognosis [10]. This suggests that RBD and *GBA* largely mark a similar subtype of PD. If clinical subtype is similar, there may be important pathophysiologic overlaps between RBD and *GBA*. There is some evidence for this; for example, *GBA* mutations may increase PD risk via specific bidirectional feed-forward interaction with synuclein [11], and within autopsy studies of PD and DLB, RBD is associated with increased deposition of synuclein (i.e. marking a 'synuclein-driven' pathophysiology) [12].

The main limitation of this study is the relatively small sample size. This is particularly important for the comparison of patients at phenoconversion (n = 9 vs n = 24); this analysis should be considered preliminary, and it is possible that some clinical differences will emerge in larger studies. One of the positive findings of this study (lower age of RBD onset in subjects with *GBA* mutations) is limited by the age of onset being self-reported, and so uncertain in its reliability.

In conclusion, we see no difference in clinical subtype between RBD patients with and without *GBA* mutations, but a clear increase in phenoconversion rate with mutations. That may suggest *GBA* mutations function primarily as an accelerant of a similar pathophysiologic mechanism as which occurs in the RBD subtype of PD/DLB.

Disclosure

The authors have no financial disclosures in relationship to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.04.016.

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Abbreviations

DLB: Dementia with Lewy Bodies
GBA: Glucocerbrosidase
MCI: Mild Cognitive Impairment
MoCA: Montreal Cognitive Assessment
MSA: Multiple System Atrophy
PD: Parkinson's Disease
PSG: Polysomnogram
(i)RBD: (idiopathic) Rapid eye movement Sleep Behavior Disorder
UPDRS: Unified Parkinson Disease Rating Scale
UPSIT: University of Pennsylvania Smell Identification Test