Prodromal Clinical Markers of Parkinson disease in Gaucher Disease Individuals

Emilia M. Gatto a Jose Luis Etcheverry a Ana Sanguinetti a Martin Cesarini a Nicolas Fernandez Escobar b Guillermo Drelichman b

a Instituto de Neurociencias Buenos Aires, INEBA, and b Hospital de Niños Ricardo Gutierrez, CABA, Buenos Aires, Argentina

Abstract

Heterozygous mutations in the glucocerebrosidase (GBA) gene have been reported as a common risk factor for the development of Parkinson’s disease (PD) in Gaucher disease (GD) patients and in heterozygous GBA mutation positive carriers. In this study, we analyzed the occurrence of prodromal markers of PD in an Argentinean cohort with type 1 GD. After signed informed consent, we evaluated 26 patients with type 1 GD under enzymatic replacement therapy from a cohort of the Hospital Ricardo Gutierrez GD Study Group in Buenos Aires City, Argentina. We performed an extensive neurological examination, including cognitive assessment by Montreal Cognitive Assessment (MoCA) and a questionnaire performed ad hoc, to identify non-motor PD symptoms. Parasomnias were reported by 7 patients (26.92%), rapid eye movement behavior disorders in 2 (7.69%), constipation in 2 (7.69%), hyposmia in 1 (3.84%), tremor in 1 (3.84%), and depression in 3 cases (11.53%). MoCA assessment was abnormal in 44.44% of patients. No patient fulfilled PD diagnostic criteria (Queen Square Brain Bank criteria). The identification of prodromal markers of PD in type 1 GD suggests that this population represents a very interesting cohort for identifying potential biomarkers and neuroprotective therapies for PD.

Gaucher disease (GD) is a multisystemic lysosomal storage disorder that results from the accumulation of undegraded glucocerebrosidase due to deficiency of the enzyme glucocerebrosidase (GBA) caused by mutations in the GBA gene [1]. Heterozygotes for GBA develop GD while homozygotes for GBA do not develop GD but are an increased risk for Parkinson’s disease (PD) [2].

GBA mutations have been associated with different alpha-synucleinopathies, PD, Lewy Body Dementia and, recently, multiple system atrophy type C [3, 4].

Individuals with mutation in the GBA gene have a 21-fold increased lifetime risk for developing PD [3]. PD patients with GBA1 mutations cannot be discriminated from idiopathic PD (iPD) [4]. Moreover, fluorodopa PET or SPECT with dopamine demonstrates the same asymmetric pattern in both conditions [4]. Probably, a younger age at onset and a greater risk for earlier and more prevalent cognitive impairment could represent a clinical red flag for differentiating PD-GBA1 from iPD [4].

There is accumulating evidence that GBA1 mutant homozygote and heterozygote carriers without clinical evidence of PD exhibit potential markers of early neurodegeneration, including olfactory dysfunction, Montreal Cognitive Assessment (MoCA) impairment, significant deterioration in scores for depression, rapid eye movement (REM) sleep behavior disorder (RBD) and retinal abnormalities [2–6].

These data indicate that individuals with GBA1 mutations exhibit identical prodromal abnormalities like those with iPD [5, 6]. Taking into consideration the research priority given to the identification of biomarkers in PD, the exploration of the occurrence of prodromal PD symptoms in patients with GBA1 from different populations appears to be a very interesting challenge [3].

Here, we explore the neurological manifestations in type 1 GD patients from Argentina with a focus on prodromal PD signs and symptoms.

Patients and Methods

GD patients from the Hospital Ricardo Gutierrez GD Study Group in Buenos Aires City, Argentina were included after they gave their written informed consent. GD diagnosis was confirmed through the measurement of GBA activity (GCase). Enzyme activity was assayed in accordance with two previous procedures: fluorometrical enzymatic activity assays in blood spots that were dried onto filter paper (designated as 1 μmol of 4-methylumbelliferone released/l/h), and peripheral blood leuko-
Table 1. Ad hoc questionnaire to explore the presence of parasomnias, olfactory dysfunction and constipation

<table>
<thead>
<tr>
<th>Item</th>
<th>Question</th>
<th>Answer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBD</td>
<td>Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?</td>
<td>Yes, No</td>
<td>Postuma et al. [9], 2012</td>
</tr>
<tr>
<td>Olfactory</td>
<td>‘Are you experiencing problems with your sense of smell?’</td>
<td>Yes, No</td>
<td>Millar Vernetti et al. [10], 2012</td>
</tr>
<tr>
<td></td>
<td>Do you notice a change in ability to taste or smell?</td>
<td>Yes, No</td>
<td>Goetz et al. [11], 2008</td>
</tr>
<tr>
<td>Constipation</td>
<td>Over the past week have you had constipation troubles that cause you difficulty moving your bowels?</td>
<td>Yes, No</td>
<td>Goetz et al. [11], 2008</td>
</tr>
<tr>
<td>Parasomnia</td>
<td>Do you experience the following behaviors?</td>
<td></td>
<td>Fulda et al. [12], 2008</td>
</tr>
<tr>
<td></td>
<td>(a) Talking during sleep</td>
<td>Yes, No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) Frightening dreams and nightmares</td>
<td>Yes, No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(c) Sleepwalking</td>
<td>Yes, No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(d) Other unusual behaviors during the night</td>
<td>Yes, No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Describe please</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

cytes measured in the presence of taurocholate (T+) (designated as mU/mg protein/hour) [7, 8]. All patients were on enzymatic replacement therapy (ERT). Genetic testing was not available at the time of the study.

Demographic and epidemiological data were collected. An extensive neurologic examination was conducted by a neurologist specializing in movement disorders. Ancillary tests included Montreal Cognitive assessment (MoCA, cut-off for dementia <24), Beck’s Depression Inventory (BDI) score (cut-off for depression BDI >13), UPDRS part III and an ad hoc questionnaire to explore the presence of parasomnias, RBD, olfactory dysfunction and constipation (table 1) [9–13].

Results

The sample was composed by 26 type 1 GD patients (11 men and 15 women), mean age 22.38 ± 13.18 (range 6–52 years), with a mean age at disease onset of 7.88 (range 1–29 years). European ancestry was reported in all patients but one with Amerindian ancestry. Spleen and liver involvement was present in 26 and 25 patients, respectively. Hematologic and bone involvement occurred in 11 and 19 individuals, respectively.

Median GCase activity assayed by fluorometric enzymatic activity was 0.505 µmol of 4-methylumbelliferone released/l/h, with a range of 0.12–2.1 (normal range >3; cut-off ≤2.5), while median GCase activity in peripheral blood leukocytes measured in the presence of T+ was 2.05 mU/mg protein/h, with a range of 0.1–4.1 (normal range >5.0 mU/mg protein/h).

We identified parasomnias in 7 patients (somniloquy) (26.92%), bilateral action tremor of upper limbs in 1 (3.84%), hyposmia in 1 (3.84%), RBD in 2 (7.69%), constipation in 2 (7.69%) and depression in 3 cases (11.53%), with a BDI mean value of 33.5 ± 14.85. In addition, eye movement abnormalities with limitation of horizontal saccades were present in 2 (7.69%) patients. No patient fulfilled the Queen Square Brain Bank diagnostic criteria for PD, and UPDRS III (motor score) was 0 in all but one previously mentioned patient with bilateral action tremor of upper limbs (total UPDRS III score 4) [11, 13]. Eighteen patients completed a cognitive evaluation using the MoCA test, and cognitive impairment was identified in 8 of them (44.44%), with a mean value of 24.78 ± 3.98. Seven of these 8 patients showed MoCA <24 (mean value 21.85 ± 3.67). Interestingly, patients with RBD showed an MoCA score <24 in 1 case and depression (BDI = 23) in another case. While in one patient constipation occurred associated with a MoCA score of <24, in another patient it was associated with a BDI score of 44.

Discussion

We identified in this Argentinean GD type 1 cohort, several prodromal PD clinical markers. These results agree with previous data reported by Beavan et al. [6]. As in our patients, the authors found a deteriorating trend in RBD, olfactory function, cognitive tests (MoCA and MMSE), BDI score, and autonomic dysfunction in patients with GD and GBA carriers.

International efforts were conducted to best characterize the phenotypes of this rare disease and to analyze demographic and ethnic factors that may influence phenotypes of GD types 1 and 3, despite the fact that data collection was not standardized [14]. In this regard, the Collaborative Gaucher Group (ICGG) Gaucher registry has provided relevant information from different countries around the world [14]. Nevertheless, data from Argentina were not included. To the best of our knowledge, this is the first preliminary study to report neurological signs and symptoms in type 1 GD from our country.

These findings could contribute to the identification of type 1 GD populations at risk of developing PD. However, the validation of these findings remains under discussion [14, 15].

The present study has several limitations. All patients were on ETR, no validated test was used to assess olfactory and autonomic dysfunction, and genetic testing was not available for the identification of specific genotypes. Although we cannot exclude ERT-induced prodromal PD symptoms, no previous data have been reported in the literature.

On the other hand, this study possesses much strength. To the best of our knowl-
edge, this is the first study conducted in an Argentinean cohort to identify neurological and prodromal PD signs and symptoms in type 1 GD patients. Moreover, as mentioned by the ICGG statement, new data from other populations not already included in this Registry provide an unprecedented opportunity to characterize new phenotypes.

Interestingly, our cohort shows a cognitive dysfunction that agrees with recent reports that support a high correlation of cognitive impairment in type 1 GD-associated parkinsonism [16].

In summary, we agree with Beavan et al. [6] that GD and GBA mutation carrier individuals are a very interesting population for the exploration of different biomarkers and for testing potential neuroprotective therapies in PD. Similarly, McNeill et al. [17] recently demonstrated that ambroxol, a potential neuroprotective agent, increased GBA activity and decreased oxidative stress in fibroblasts from GBA carriers with and without PD and decreased alpha-synuclein levels in the over-expression of neuroblastoma cells.

Although this study has limitations, we believe that the analysis of prodromal symptoms of PD in different populations contributes to the increase in international efforts to find more sensitive and specific biomarkers and to identify particular phenotypes and environmental factors involved in the increased risk for PD. Extensive studies are warranted.

Acknowledgments
The authors would like to thank all patients and families for their contribution to this study.

References

Disclosure Statement
E.M.G. and J.L.E. do not have any potential conflicts of interest involving the work under consideration. N.F.E. and G.D. received honoraria by Genzyme.

Financial Activities
E.M.G. received honoraria for consultations and payment for lectures from Glaxo Smith Kline, Tuteur, Boehringer Ingelheim, Bagó, UCB. From May 2016 on, E.M.G. and J.L.E. have received honoraria from Genzyme. J.L.E. received honoraria for consultancies and payment for lectures from Teva, Tuteur, Bagó, Merck. N.F.E. received honoraria for consultancies and payment for lectures from Genzyme, Biotoscana, Drellichman received honoraria for consultations and payment for lectures from Genzyme, Biotoscana and Novartis.