Letter to the Editor

Parkinson’s disease and the heterozygous state for glucocerebrosidase mutations among Brazilians

We have read with interest the publication by Spitz et al. [1] regarding their results on the association study of glucocerebrosidase mutations and Parkinson’s disease (PD) among Brazilian patients. Before them, several publications confirmed the association between PD and the heterozygote state for glucocerebrosidase (GAB) mutations in patients from Israel, USA, Canada, Norway, Venezuela, Taiwan (for a review see Refs. [1,2]), and now São Paulo, Brazil. Table 1 summarizes these results.

We also investigated the association between PD and GBA mutations in Brazilians by recruiting patients with PD in Porto Alegre, in the south of Brazil. PD was diagnosed according to the clinical criteria proposed by Gelb et al. [3]. Patients participated in the study, which was approved by the local and national ethics committees, after giving informed consent. A single neurologist (MS) examined all cases and performed a full neurological examination and applied the Hoehn and Yahr (HY) modified scale as well as the Unified PD rating scale (UPDRS). The study patients were unrelated. All patients had their GBA activity measured in their peripheral leukocytes using the standard 4-methylumbelliferyl-β-D-glycopyranoside assay. Activities below 10 nmol/h/mg were considered to be associated with an increased risk for the carrier state if they were confirmed in a second blood specimen. Common GBA mutations L444P, N370S, and IVS2+1 were analyzed by PCR-RFLP using NciI, XhoI and HphI, respectively; while 84GG was analyzed by ARMS-PCR.

The clinical data of the 62 (37 male) study patients are shown in Table 2. Mean ± SD age at examination was 50.14 ± 10 yr.; mean ± SD age at onset was 41.4 ± 10 yr. Patients were of Brazilian origin with mixed ethnic backgrounds, including Portuguese, Spanish, Italian, German, Amerindian and African ancestry. There were two (3.5%) heterozygotes for GD as follows: one carrying the N370S mutation and the other carrying the L444P mutation. Five patients, that is, the L444P carrier plus four additional patients without common mutations, had a leukocyte GBA activity below 10 nmol/h/mg of protein.

The two GBA heterozygotes seemed to have an earlier age at onset than the other PD patients (37 ± 4 versus 41.4 ± 10.8 yr.), although the difference was not significant; however, these differences almost reached significance when ages at onset of PD were compared between patients with normal levels of GBA activity (41.4 ± 10 yr.) and patients with low levels of GBA activity (37.5 ± 2.7 yr., p = 0.052), as shown in Table 2. Other disease characteristics, namely, MMSE, HY, UPDRS, ADL-on and ADL-off scores, as well as consanguinity, recurrence in the family, years of schooling, and patterns of daily levodopa intake, showed no differences between groups.

Our results are quite comparable to those previously described and confirm the rate of 3% of the heterozygote state among Brazilian PD patients. Although the attributable risk was not too high, it was repeatedly found in several ethnic backgrounds, with one exception, i.e., the Norwegian study. In other words, being a PD patient is related to a 3–9 times increased risk of being a GBA mutation carrier (Table 1). We also observed that PD patients with either GBA mutations or low GBA activity had a younger onset of symptoms; this finding was described as early as the first reports on this association and has been recently reconfirmed by Clark (revised in Ref. [2]).

All these recent observations suggest a connection between Gaucher disease and/or the GBA heterozygote state and the synucleinopathies. Not only has the screening of patients with parkinsonism identified a greater than expected frequency of GBA mutations, but an increased incidence of synucleinopathies has also been found in Gaucher probands and their relatives. Moreover, in four individuals with Gaucher disease and parkinsonism, Lewy bodies were observed in the substantia nigra (SN), as well as SN neural depletion, SN gliosis, and involvement of hippocampal CA2-4 layers [4]. Several hypotheses have been raised to explain these findings. Mutations in GBA might cause lysosomal dysfunction or interfere with receptor binding of alpha-synuclein at the lysosomal membrane, resulting in reduced alpha-synuclein degradation and cell toxicity. Or perhaps GBA mutations that result in misfolded protein might overwhelm the ubiquitin–proteasome ability to degrade other abnormally accumulated proteins, including alpha-synuclein. A third mechanism proposed was...
that abnormal lipids, present in neurons with low GBA activities, would promote alpha-synuclein aggregation and toxicity through the formation of protofibrils (for a review see Ref. [5]). In any case, the underlying mechanism does not depend on the GBA substrate storage in neurons; it would neither be necessary nor sufficient for the appearance of PD, since the majority of Gaucher disease patients do not develop parkinsonian features. However, we are certain that studying the pathophysiology underlying this association will help understand both Parkinson’s and Gaucher’s diseases, perhaps resulting in a better management of these conditions.

References


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