P41

GBA mutations and Parkinson's disease. What happens in Southern Italy?

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Objectives: GBA1 mutations represent the most common genetic risk factor for developing Parkinson's disease (PD) [1]. However, many aspects of this association need to be clarified, especially to identify specific clinical or biological markers capable to distinguish parkinsonian carriers of GBA1 mutations. Glucosylsphingosine (Lyso-GB1), a deacylated form of glucosylceramide, is degraded by the ß-glucocerebrosidase enzyme. Lyso-Gb1 was proved to be a highly sensitive and specific biomarker for diagnosis and monitoring of patients with GD [2]. This is the first study reporting the possible role of Lyso-GB1 for detecting the state of GBA1-heterozygosity in a relatively large cohort of subjects suffering from PD.

Materials and Methods: Sixty consecutive PD-subjects attending our Movement Disorders Unit were included in this study. Dried blood spots were collected on filter cards (CentoCard®) and ß-glucocerebrosidase activity, Lyso-GB1 analysis and GBA1 gene sequencing were carried out in Centogene, Rostock, Germany [2]. Subjects with PD were further divided in two groups, according to the presence (PD-GBA+) or absence (PD-GBA-) of GBA1 mutations. Difference in clinic-demographic characteristics between GBA1- carriers *vs* non-carriers were further analyzed.

Results: Thirteen PD-subjects resulted GBA1-carriers (21%), disclosing a surprisingly high prevalence of GBA1 mutations in the PD-population of this geographic area. GBA1 mutations were, namely, Asn409Ser (7 subjects), Leu483Pro (4 subjects), Glu365Lys (1 subject), Val414Ala (1 subject). There was no statistically significant difference in age, gender, disease duration, Hoehn & Yahr Stage, positive familial history for PD and Total Levodopa Equivalent Daily Dose between PD-GBA+ and PD-GBA-. Tremor-dominant PD was significantly more common in the PD-GBA- than in PD-GBA+ group (51% *vs*23%; *p=0.04*). Moreover, the two groups significantly differed in the use of device-aided therapies, showing an higher utilization in the PD-GBA+ group (5/13 subjects, 38%; namely 4 Deep Brain Stimulations-DBS, 1 Levodopa-carbidopa intestinal gel-LCIG) than in the PD-GBA- group (4/47 subjects, 8.5%; 4 DBS; *p=0.007*). A significant difference was also observed in ß-glucocerebrosidase activity and Lyso-GB1 levels between the two groups, with PD-GBA+ subjects showing a lower enzymatic activity and higher Lyso-GB1 concentrations (ß-glucocerebrosidase: 2.8 ± 0.6 *vs* 3.2 ± 0.6, *p=0.04*; Lyso-GB1 5.8 ± 1.8*vs*4.7 ± 1.4, *p=0.03*, respectively for PD-GBA+ and PD-GBA-groups).

Discussion: GBA1 mutations in PD-populations are probably underreported and an analysis of their impact in different geographical areas should be performed. In our study PD-GBA1 carriers showed a lower ß-glucocerebrosidase activity associated with higher Lyso-GB1 substrate accumulation. These data further support the "loss-of-function" hypothesis of GBA1 mutation carriers, leading to lysosomal substrate accumulation, disruption of autophagic-lysosomal function, and induction of alpha-synuclein pathology responsible for PD. Interestingly PD-GBA1 subjects seem to require more frequently complex, device-aided therapies. This should be keep in mind examining long-term follow-up data about DBS and LCIG efficacy.

Conclusions: The association between GBA1 gene mutations and Parkinson's disease has provided critical clues into PD-etiology and will hopefully change the therapeutic approach of several neurodegenerative conditions in the near future.

References

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