GBA1-associated parkinsonism

GBA1 mutations, which result in the lysosomal disorder Gaucher disease, are the most common known genetic risk factor for Parkinson's disease and Dementia with Lewy Bodies (DLB). The pathogenesis of this association is not fully understood, but further elucidation of this link could lead to new therapeutic options.

The natural history of PD may follow a more benign motor-predominant course in some patients, while in others the disabling non-motor features predominate. The underlying basis of the clinical heterogeneity is poorly understood, but it is becoming clear that this is, at least in part, due to genetic factors [1) 2) 3)]. One of these genetic risk factors is mutation in the GBA1 gene, which has emerged numerically as the most important genetic abnormality associated with PD [4) 5)], being found in about 5% of patients with the so-called sporadic PD

Biallelic mutations in the GBA1 gene encoding glucocerebrosidase cause Gaucher's disease, whereas heterozygous carriers are at risk for Parkinson's disease (PD). Glucosylsphingosine is a clinically meaningful biomarker of Gaucher's disease but could not be assayed previously in heterozygous GBA1 carriers.

The aim of a study was to assess plasma glucosylsphingosine levels in GBA1 N370S carriers with and without PD.

Methods: Glucosylsphingosine, glucosylceramide, and four other lipids were quantified in plasma from N370S heterozygotes with (n = 20) or without (n = 20) PD, healthy controls (n = 20), idiopathic PD (n = 20), and four N370S homozygotes (positive controls; Gaucher's/PD) using quantitative ultra-performance liquid chromatography tandem mass spectrometry.

Results: Plasma glucosylsphingosine was significantly higher in N370S heterozygotes compared with noncarriers, independent of disease status. As expected, Gaucher's/PD cases showed increases in both glucocerebrosidase substrates, glucosylsphingosine and glucosylceramide.

Plasma glucosylsphingosine accumulation in N370S heterozygotes shown in this study opens up its future assessment as a clinically meaningful biomarker of GBA1-PD. [6)].

Treatment

As our understanding of GBA1-associated Parkinson's disease increases, new treatment opportunities emerge. MicroRNA profiles are providing examples of both up-regulated and down-regulated proteins related to GBA1 and may provide new therapeutic targets. Chaperone therapy, directed at either misfolded glucocerebrosidase or α-synuclein aggregation, is currently under development and there are several early clinical trials ongoing. Substrate reduction therapy, aimed at lowering the accumulation of metabolic by-products, especially glucosylsphingosine, is also being explored. Basic science insights from the rare disorder Gaucher disease are serving to catapult drug discovery for parkinsonism [7)]

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