Blood glucosylsphingosine concentration in Gaucher patients reflects the severity of GBA mutations – data from a large global cohort

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Introduction: Gaucher disease (GD) is an autosomal recessive, rare genetic disorder characterized by the deposition of glucocerebroside in cells of the macrophage-monoocyte system. Still, the rate of proper early diagnosis of GD patients is low. Standardized, simple and highly reproducible workflows for the diagnosis are crucial, especially since more than 15 years a highly effective treatment is available.

Materials and methods: We have developed and systematically validated a high-throughput workflow for the simple testing of GD patients: beta-glucocerebrosidase enzymatic activity, glucosylsphingosine (lyso-Gb1) quantification in DBS followed by GBA gene sequencing from the same DBS sample. Here, we report data from a study that compassed 4.5 years a screening of over 2,800 individuals that led to the identification of 643 affected Gaucher patients and 354 carriers. Determination of lyso-Gb1 is performed by LC/MS. The GD patients’ phenotype was divided according to lyso-Gb1 levels in: very mild (12ng/mL - 25.0 ng/mL), mild (25.1 - 50 ng/mL), moderate (50.1 - 200 ng/mL) and severe (>200 ng/mL). Lyso-Gb1 was proven to have a sensitivity of 100% and a specificity of 99.9%. We sequenced 2,616 alleles and identified 153 different pathogenic GBA variants. From the 153 variants, 34% were not reported in the literature. The clinical severity of the mutations and their location was correlated with the lyso-Gb1 in the homozygous cases, e.g. c.1295G>T is correlated with mild lyso-Gb1 values while c.1060G>A and c.518C>A with extremely high lyso-Gb1 values ( > 600 ng/mL). The most common mutations were c.1268A>G (30.1%) and c.1448T>C (24.7 %), Lyso-Gb1 for c.1226A>G varies from very mild to moderate; whereas c.1448T>C is a severe mutation correlating to a massive increase of lyso-Gb1 up to 1,250 ng/mL. Most of the GD cases were linked to clinical information such as: organomegaly (32.4%), hematological symptoms (27.9%, from which 42.3% thrombocytopenia), skeletal symptoms (13%) and neurological symptoms (8.2%). The earliest and only manifestation was in 84.5% just thrombocytopenia which seems to be actually not properly understood for the early GD diagnosis.

Summary: LysoGb1 concentrations in blood is an excellent parameter for the easy and early diagnosis of GD patients and for treatment monitoring.

References

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