Glucosylsphingosine (lyso-Gb1) plays a central role in the diagnosis and proper assessment of disease severity in Gaucher patients

Introduction: Gaucher disease (GD) is an autosomal recessive, rare genetic disorder characterized by the deposition of glucocerebrosides in cells of the macrophage-monocyte system. Materials and methods: We have developed and systematically validated a high-throughput workflow for the simple testing of GD patients: beta-glucocerebrosidase enzymatic activity, glycosylsphingosine (lyso-Gb1) quantification in DBS followed by GBA gene sequencing from the sample blood sample. We report data from over 940 Gaucher individuals. Determination of lyso-Gb1 using LC/MRM-MS was investigated in three GBA cohorts comprising of: (A) 247 homozygotes GBA cases; (B) 308 compound heterozygotes GBA patients and (C) 305 Gaucher carriers. Lyso-Gb1 has a sensitivity and specificity of 100% for the primary diagnosis of GD. The clinical severity of the mutations and their location could be 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.318C>A with extremely high lyso-Gb1 values (> 600 ng/mL). The most common GBA mutations are c.1226A>G (34 %) and c.1448T>C (25.5 %). c.1448T>C is a severe mutation correlating to a massive increase of lyso-Gb1 up to 2,850 ng/mL. Lyso-Gb1 for c.1226A>G can vary from very mild to moderate. Summary: Lyso-Gb1 concentrations in blood can be used for the easy, early and highly specific diagnosis of GD patients.

Figure 1: Symptoms of GD

N Gaucher individuals = 940
N Gaucher affected = 603
N Gaucher carriers = 337

Figure 2: Characterization of GD Cohort: A – Geographical distribution; B – Age distribution

• 1,671 pathogenic alleles /copies
• 940 independent GD cases
• 150 GBA unique variants

Figure 3: Genetic characterization of the GD cohort; most frequent GBA pathogenic variants

Figure 4: Lyso-Gb1 levels in GD: A- Lyso-Gb1 in affected GD patients vs controls; B- Lyso-Gb1 levels in GD patients of different ages

Figure 4: Lyso-Gb1 levels in correlated with different GBA pathogenic variants

References
1. Rolfs et al, 2013, PloS

Disclosure of conflict of interest: This study was sustained in part by Centogene AG, Rostock. Author of the presentation, CC & AR are employees of Centogene AG, Rostock, Germany.