Gaucher's disease

is an uncommon hereditary lysosomal storage disease characterized by the accumulation of glucocerebroside in the lysosomes of macrophages of the reticuloendothelial system.

Mutations in the glucocerebrosidase (GBA) gene are divided into mild and severe (mGBA, sGBA) based on their contribution to the phenotype of Gaucher disease (GD) among homozygotes.

Biomarker

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. [1)].

Classification

Gaucher's disease (GD) has four common clinical subtypes.

These subtypes have come under some criticism for not taking account of the full spectrum of observable symptoms (the phenotypes). Also, compound heterozygous variations occur which considerably increase the complexity of predicting disease course.

Gaucher disease type 1.

Spleen enlargement and bone marrow replacement cause anemia, thrombocytopenia, and leukopenia. The brain and nervous system are not affected pathologically, but lung and, rarely, kidney impairment may occur. Patients in this group usually bruise easily (due to low levels of platelets) and experience fatigue due to low numbers of red blood cells. Depending on disease onset and severity, type I patients may live well into adulthood. The range and severity of symptoms can vary dramatically between patients.

GD type II (acute infantile neuropathic) typically begins within 6 months of birth and has an incidence rate around one 1 in 100,000 live births. Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow. Affected children usually die by age two.

GD type III (chronic neuropathic) can begin at any time in childhood or even in adulthood, and occurs in about one in 100,000 live births. It is characterized by slowly progressive, but milder neurologic symptoms compared to the acute or type II version. Major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, skeletal irregularities, eye movement disorders, blood disorders including anemia, and respiratory problems. Patients often live into their early teen years and adulthood.

Etiology

Biallelic GBA gene mutations cause Gaucher disease (GD), and heterozygous carriers are at risk for synucleinopathies. No founder GBA mutations in French-Canadians are known. GBA was fully sequenced using targeted next generation and Sanger sequencing in French-Canadian Parkinson's disease (PD) patients (n=436), REM-sleep behavior disorder (RBD) patients (n=189) and controls (n=891). Haplotype, identity by descent (IBD) and principal component analyses (PCA) were performed using SNP-chip data. Data on GD patients from Toronto and Montreal were collected from patients' files. A GBA p.Trp378Gly mutation was identified in two RBD and four PD patients (1% of all patients combined), and not in controls. The two RBD patients had converted to DLB within 3 years of their diagnosis. Haplotype, IBD and PCA analysis demonstrated that this mutation is from a single founder. Out of 167 GD patients screened, 15 (9.0%) carried the p.Trp378Gly mutation, all in trans with p.Asn370Ser. Three (20%) of the GD patients with the p.Trp378Gly mutation had developed Parkinsonism, and 11 patients had family history of PD. The p.Trp378Gly mutation is the first French-Canadian founder GBA mutation to be described, which leads to synucleinopathies and to GD type 1 when in compound heterozygosity with p.Asn370Ser [2)].

Clinical

The disorder is characterized by bruising, fatigue, anemia, low blood platelet count and enlargement of the liver and spleen.

Skeletal manifestations are variable in severity and typically involve the long bones. Vertebral involvement is less well characterized, particularly in children and adolescents.

Case series

Kocher and Hall, report on the surgical management of spinal involvement in four children and adolescents with Gaucher's disease; two for kyphotic deformity and two for kyphotic deformity associated with neurologic compromise. They recommend anterior spinal release with fusion and posterior spinal fusion with segmental instrumentation in cases of kyphotic deformity. In cases of spinal cord compromise at the apex of the kyphotic deformity with retropulsion of involved bone, anterior decompression also should be performed. Routine surveillance for spinal deformity in patients with Gaucher's disease is necessary to allow early intervention before the development of

severe deformity and neurologic compromise [3].

Case reports

Mitrovic et al., report a treatment-naïve patient with Gaucher disease (GD) who experienced repeated bleeding after three neurosurgeries for a brain tumour, identified as an oligoastrocytoma. The patient had normal values on basic haemostatic tests: prothrombin time, 75-105%; activated partial thromboplastin time, 30.3-34 s; and mild thrombocytopaenia, 96-115 × 10(9)cells/l. However, additional tests showed mild von Willebrand factor (vWF) deficiency (vWF antigen, 56%; vWF ristocetin cofactor, 49%; factor VIII [FVIII], 54%) and abnormal collagen-mediated platelet aggregation (0.45-0.55). Bleeding control was achieved after vWF/FVIII concentrate and platelet transfusions. This case raises questions about the safe platelet count and basic haemostatic tests for assessing bleeding risk in patients with GD prior to surgery. In patients with GD, a minimum haemostatic evaluation should include platelet count and basic haemostatic tests such as fibrinogen, prothrombin time, activated partial thromboplastin time as well as platelet function tests and assessing vWF and FVIII levels. Specific coagulation factors or platelet function deficiencies should be corrected with factor concentrates or platelet transfusions [4].

A 3-year-old male with type 3 Gaucher's disease, whose genotype for the beta-glucosidase gene was D409H/unknown mutation, is presented. After the onset of visceral and neurologic signs during infancy, a radiologic investigation at 3 years of age revealed communicating hydrocephalus, an unusual complication of Gaucher's disease. A ventriculoperitoneal shunt operation led to clinical and radiologic improvement. The possibility of this complication should be considered in the treatment of patients with Gaucher's disease [5].

An individual with Type I nonneuronopathic Gaucher's disease who experienced the rare complication of spinal cord compression secondary to a sclerotic vertebral fracture. He successfully underwent anterolateral spinal cord decompression and spinal fusion despite the severity of his generalized skeletal disease [6].

1)
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