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Cause of death in patients with attenuated acid sphingomyelinase deficiency: Comprehensive literature review and report of new cases

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Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disorder that comprises a clinical spectrum ranging from acute, neuronopathic Niemann-Pick disease type A (NPD A) to chronic neuronopathic (intermediate phenotype) and chronic non-neuronopathic (NPD B) forms. In patients with ASMD, sphingomyelin accumulates predominantly in macrophages of the reticuloendothelial system (liver, spleen, lung, and bone marrow), hepatocytes, and the CNS (type A and intermediate phenotype only) resulting in a progressive multisystemic disease. While NPD A is a uniformly fatal neurodegenerative disease with death by age 3, the ages and causes of death in patients with attenuated disease (intermediate and NPD B) is less understood and limited to a single-center series (N = 18) and several case reports. In order to better understand the disease course leading to death in patients with attenuated ASMD, we performed a comprehensive literature review of published data and report on over 50 published and between 20 and 25 additional, previously unpublished, cases collected as part of a retrospective multi-center, global study. The two leading causes of death, hepatic and respiratory disease, were more prominent in patients who experienced onset of ASMD-related symptoms prior to the age of 18 years. Other causes of death included bleeding, cancer, multiple organ failure, cardiac, and neurologic disease. Associated morbidities in deceased patients include hepatosplenomegaly, pulmonary disease, liver dysfunction, thrombocytopenia, anemia, ophthalmologic, cardiac, and neurologic disease (in patients with intermediate ASMD). The disease course of patients who died of liver failure or respiratory disease will be discussed in greater detail. These data support the life-threatening nature of the attenuated form of ASMD, and the need for an effective treatment. The study was supported by Genzyme, a Sanofi company.

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Bone marrow transplantation treatment for a 4 year old asymptomatic patient with metachromatic leukodystrophy (MLD)

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Metachromatic leukodystrophy (MLD) is an inherited neurodegenerative lysosomal disorder caused by the deficiency of arylsulfatase A (ASA), resulting in progressive coordination and speech problems, seizures, behavioral disturbances and eventually deterioration to death. Treatment options are limited. Allogeneic bone marrow transplantation (BMT) is considered a treatment option in adult onset and juvenile onset patients and has been reported to halt disease progression. However, reports of BMT outcomes in the medical literature are relatively few and conclusions are mixed. We report a 5 year old girl followed by our team, whom we previously described. She presented at 3 years of age with history of intermittent abdominal pain and underwent cholecystectomy. The pathology finding revealed gallbladder polyposis. A diagnosis of MLD was confirmed with low ASA in leukocytes (6 nmol/h/mg; reference 21-72 nmol/h/mg) and significantly elevated urine sulfatides at 3001 ug/L (normal <170). Genetic testing confirmed she is a compound heterozygote for two ARSA variants, c.190G > A (missense, ACMG category 3) and c.871C > T (nonsense, ACMG category 2). The patient was monitored closely. She did not present any neurological or abdominal symptoms. Repeated brain MRI studies and nerve conduction testing were normal. Neuropsychological assessment confirmed age appropriate intellectual status. She recently underwent ovarian cryopreservation surgery followed by uneventful allogeneic BMT from unrelated donor and had developed full donor chimerism. ASA in leukocytes performed approximately a month after the transplant revealed normal enzyme activity (60 nmol/h/mg; reference 21-72 nmol/h/mg). Allogeneic BMT is not commonly performed in young children. In this rare case, the child was neurologically intact and was diagnosed with MLD based on pathological findings of gallbladder polyposis. Hence, a potential diagnosis would include juvenile or adult type MLD. As MLD might progress for a substantial period before implanted cells populate the central nervous system, close monitoring is warranted.

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Autophagy lysosome pathway and mitochondrial crosstalk in Gaucher disease

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The major cellular clearance pathway for organelle turnover and unwanted proteins is the autophagy-lysosome pathway (ALP). Lysosomes not only house proteolytic enzymes, but also traffic organelles, sense nutrients, and repair mitochondria. Mitophagy is initiated by the damaged mitochondria, which is ultimately degraded by the autophagic pathway to compensate for ATP loss. Gaucher disease (GD), a lysosomal disease, is caused by glucocerebroside accumulation in the lysosomes. Autophagic abnormalities have been reported in cultured GD cells. However, in vivo ALP and mitochondrial function have not been studied, and the effect of enzyme replacement therapy (ERT) is unknown. We studied cellular energy homeostasis, ALP abnormalities, and effects of ERT in peripheral blood mononuclear cells (PBMC) from GD patients using Cyto-ID autophagy, ToxGlo™ assays, LysoTracker dye, and Western blots. PBMCs were collected pre- and post-ERT infusion from GD types 1 and 3 patients. An autophagy inducer Rapamycin (mTOR inhibitor), autophagy inhibitor (3-MA), and endosomal acidification inhibitor (CQ) were used to study autophagy. Result: autophagic vacuoles number was decreased with increasing cytoplasmic localization of LC3A/B, accompanied by the accumulation of the lysosomes and normal ATP level between GD and control samples. CQ increased the number of autophagic vacuoles in cells, while Rapamycin did not activate autophagosome formation and led to ATP inhibition in GD samples. ERT stressed the energy balance in PBMCs and did not impact autophagosome vesicle levels. However, LC3-II accumulation and decreased LC3-I/LC3-II ratios were