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Quantitative evaluation of white matter hyperintensities in the central nervous system in infantile Pompe disease

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Pompe disease is a lysosomal storage disorder caused by deficiency of acid-alpha glucosidase. There are limited data on central nervous system (CNS) involvement in survivors of infantile Pompe disease (IPD). The objective of this cross-sectional study is to implement the Fazekas scale, a visual MRI rating scale, to quantify white matter hyperintensities (WMH) on T2-weighted-Fluid Attenuated Inversion Recovery (T2-FLAIR) brain MRI images and to determine the extent of white matter (WM) involvement in the CNS of patients with IPD. Twelve patients (aged 6.1-18.1 years, 7 males, 5 females) with IPD and on long-term enzyme replacement therapy were included in the study. We assessed WM involvement in ten anatomical areas of the brain- juxtacortical U-fibers, subcortical WM, periventricular WM in the centrum semiovale and in the frontal and parietal lobes at the level of corona radiata, corpus callosum, anterior and posterior limb of the internal capsule, external capsule, corticospinal tracts at cerebral peduncles, midbrain, and pons and the medullary decussation of corticospinal tracts. Based on the severity of WMH, each area was graded on the Fazekas scale from zero (absent) to 3 (severe) and a total score (range 0-30) was obtained. Ten patients (ages 6.6-18.1 years) had WMH on brain MRI (range of scores: 2-23) using the Fazekas scale. Five of the 10 patients (ages 6.7-18.1 years) had scores greater than 15 (range 16-23) indicating severe WMH and 2/10 patients (aged 6.1 years and 7.3 years) had no WM involvement with a score of zero. Our results provide a means to quantify WM involvement in the CNS of patients with IPD. Fazekas scale could serve as a biomarker for longitudinal follow up of WM abnormalities in patients with IPD and to better understand the extent of CNS involvement in IPD. [A portion of this study was funded by Genzyme Sanofi]

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Evaluating the content validity of the Diary of Irritable Bowel Syndrome Symptoms - Mixed (DIBSS-M) to assess gastrointestinal symptoms associated with Fabry disease

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This study sought to identify the most important and relevant gastrointestinal (GI) symptoms experienced by patients with Fabry disease (FD) and the best way to measure GI symptoms in clinical trials of new treatments for FD. A targeted literature review on GI symptoms relevant in FD for measurement was completed. Qualitative interviews with open-ended concept elicitation and cognitive debriefing were conducted in individuals with FD to explore the relevance of GI symptoms from the patient perspective and to evaluate the content validity of the Diary of Irritable Bowel Syndrome Symptoms—Mixed (DIBSS-M) in the FD population. In the literature review, a high degree of variability of GI symptoms was reported abdominal pain and altered bowel function were most common. Diarrhea was more common in males constipation in females. Additionally, discomfort, bloating and early satiety were frequently noted. Except for early satiety, all these symptoms are addressed in the DIBSS-M. Interviews were conducted in 17 patients diagnosed with FD (13 male, 4 female) ≥ 16 years old mean age of 40.9 years (15.0) in the United States. The most commonly reported symptoms were diarrhea (94% n=16), abdominal pain (64% n=11), bloating (47.1% n=8), and vomiting (41.2% n=7). While nausea is not included on the DIBSS-M, 47.1% of patients found it relevant to their FD. In contrast to the literature, interviewees infrequently noted constipation (5.9% n=1). Patients reported substantial limitation of social and work activities. Patients found the DIBSS-Measy to understand and answer, with an appropriate recall period and distinct options for each question. 88% of patients found the items measured on DIBSS-M to be relevant, especially those about stool frequency, stool consistency, urgency, and abdominal pain. Results support use of the DIBSS-M in clinical studies for FD with a focus on improvements in abdominal pain and altered bowel functioning.

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Identification of MPS clusters in Latin America: An opportunity for targeted health care programs

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The mucopolysaccharidoses (MPS) include 11 rare disorders caused by deficiency of specific lysosomal enzymes resulting in the accumulation of undegraded glycosaminoglycans (GAGs) and several clinical consequences. The combined incidence for all MPS subtypes is approximately 1:25,000 live births. Clusters of these diseases have been identified in areas with high consanguinity and/or founder effect associated to endogamy. The MPS Brazil Network, associated to the Brazilian Institute of Population Medical Genetics, identified several MPS clusters in Latin America. Three clusters were confirmed in Brazil, of MPS IIIC (state of Paraíba), MPS IVA (state of Paraíba) and MPS VI (state of Bahia). Two clusters were identified in Ecuador: MPS IIIB (state of Manabi) and MPS IVA (state of Pastaza). A cluster of MPS VI was also identified in the Dominican Republic. Other clusters are being investigated in Haiti (MPS VI), Panamá (MPS IVA), and Brazil (MPS IIIB, Minas Gerais state). Haplotype analyses are underway to better characterize mutation profiles, and results already available for the clusters of MPS IVA and MPS VI in Brazil indicate founder effects with common ancestors. As one example of the benefits of cluster identification, a newborn screening program