subjects with high speed Internet capability in their home. Before initiating virtual visits, the study team determined which activities could be completed remotely. An encrypted virtual video platform provided confidentiality and privacy. Before the virtual research visit, a test visit was completed to familiarize subjects with remote research processes. Instructions on using the virtual visit platform were sent ahead of time, including a study team contact telephone number in case problems arose during connecting. Test visit activities included assessment of audio/video quality and evaluation of the home study site. A quiet space, free of distractions and interruptions in the subject's home was selected with sufficient lighting and appropriate space and positioning for assessment. Seating position was optimized to enhance the examiner's view of the subject's face and body, as body language could be missed over video. For the research visit, eConsent was obtained utilizing REDCap, a secure website which allowed for synchronous consent review and sign off. Study team members were scheduled to join at certain times or kept in a virtual "waiting room" until they were needed to reduce visit disruptions. Some subjects opted to complete portions of the visit at different times of the day. In the 6 months since the beginning of pandemic restriction, we completed 19 virtual study visits across two separate research protocols. Virtual visit activities have included neurologic exam, neuropsychological assessment, and administration of a disease-specific rating scale. Future goals include use of wearable devices and biometric assessments in the home environment. Virtual visits are a feasible way to continue to engage subjects when travel is impossible.

doi:10.1016/j.ymgme.2020.12.267

262

Neuro-networks investigating the neurological impairment of mucopolysaccharidoses using a system biology approach

Gerda Cristal Villalba Silva, Ursula Matte, *Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*

Mucopolysaccharidoses (MPS) are lysosomal diseases characterized by defects in the activity of lysosomal hydrolases involved in glycosaminoglycan degradation, with progressive multisystemic involvement. Neurological damage is present in MPS I; MPS II; MPS IIIB, and MPS VII. Using biological networks for searching for genes with functional relevance give us clues about pathophysiological mechanisms of neurological diseases. The aims of this work was to identify potential biomarkers for neurological impairment in different types of MPS using public available transcriptomic data. The most relevant proteins in the networks and ontology terms related to neurological damage in MPS were identified and compared among diseases. We performed the clustering analysis for GSE111906 (MPSI), GSE95224 (MPSII), GSE23075 (MPSIIIB), GSE15758 (MPSIIIB), and GSE76283 (MPSVII). Regarding biomarker discovery analysis, the top 10 genes were ranked according to the maximal clique centrality. Different ontologies were present in the different types of MPS. For instance, for MPS I, the related ontologies were clathrin derived vesicle budding and clathrin-mediated endocytosis. MPS II top genes were related to brain renin-angiotensin system. MPS IIIB top genes comprises the ontologies acetylation and chromatin regulation. The MPS IIIB top 10 genes were related to the activation of the mRNA cap-binding complex. Finally, MPS VII top genes were present in the ontologies C-MYB transcription factor network. Moreover, we identified several immune system processes like adaptive and innate immune systems, Class I MHC mediated antigen processing and presentation; and activated TLR4 signaling across the different MPS types. Other ontologies were also present in all the MPS types, like axon guidance, Calcium signaling, PI3K-Akt signaling pathway, and Wnt signaling pathway. We hypothesize that these pathways are deranged because glycosaminoglycans play an essential role in the extracellular matrix composition, helping to regulate several processes. System biology approaches may help to understand the mechanisms of neuropathology in the different types of mucopolysaccharidoses.

doi:10.1016/j.ymgme.2020.12.268

263

PREDIGA project: Preliminary results of the Spanish multicenter epidemiological and medical education project in acid sphingomyelinase deficiency disease (ASMD) and Gaucher disease (GD)

Jesus Villarrubia[a], Enrique Calderon[b], Miguel Angel Torralba[c], Isidro Vitoria[d], Marta Morado[e], Victor Quintero[a], Monserrat Morales[f], Juan Luis Carrillo-Linares[g], Gema Muñoz[h], *[a]Hospital Universitario Ramon y Cajal, Madrid, Spain, [b]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [c]Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [d]Hospital Universitari i Politecnic La Fe, Valencia, Spain, [e]Hospital Universitario La Paz, Madrid, Spain, [f]Hospital Universitario Doce de Octubre, Madrid, Spain, [g]Hospital Universitario Virgen de la Victoria, Malaga, Spain, [h]Complejo Hospitalario Universitario A Coruña, A Coruña, Spain*

Introduction

GD and ASMD are lysosomal disorders caused by deficiency of lysosomal enzymes acid beta-glucosidase and acid Sphingomyelinase. These enzyme deficiencies cause accumulation of glucocerebroside and sphingomyelin, respectively, mainly in macrophages, inducing deterioration of the organs in which they accumulate. Theoretical prevalence of ASMD is 0.4 per 100,000 and GD is 1 per 40,000 inhabitants. The absence of epidemiological studies in Spain lead us to believe that ASMD is highly underdiagnosed, and that the incidence of GD data is still to be defined.

Aim

To put in place a national medical education program to increase knowledge of the pathophysiology of ASMD and GD, as well as dissemination of diagnostic algorithms for these diseases. An epidemiological study of unknown origin splenomegaly was planned as a 3–5 years retrospective search and as a 2 years prospect for new patients, implementing the diagnostic algorithms defined for both, ASMD and GD. The epidemiological results obtained will be analysed.

Methods

A total of 52 HCPs (22 Hematologists / 18 Internal Medicine / 12 Pediatricians) from 34 hospitals in Spain are implementing the medical education program and epidemiological searching in their health area of influence for two consecutive years. It is planned to impart about 100 clinical sessions within the medical education program and reach 200

patients fulfilling diagnostic criteria for ASMD and GD in the recruitment process.

Results

In the first 6 months of the project, 12 educational sessions were held with more than 220 assistants (1 GD patient diagnosed) and 39 patients with diagnostic criteria were reviewed with the result of 1 positive for ASMD and 3 positives for GD.

Comments

Medical education plan and epidemiological study have increased awareness of these conditions allowing the diagnosis of new patients and can further define the prevalence of these two lysosomal diseases in Spain.

doi:10.1016/j.ymgme.2020.12.269

264

First in-human intracisternal dosing of RGX-111 (adeno-associated virus 9/human α-L-iduronidase) for a 20-month-old child with mucopolysaccharidosis type I (MPS I): 1 year follow-up

Raymond Y. Wang[a], Tammam Beydoun[a], Nina Movsesyan[b], Shih-Hsin Kan[b], Mery Taylor[b], Winnie Stockton[b], Igor Nestrasil[c], Bryan Pukenas[d], Paulo Falabella[e], Yoonjin Cho[e], Marie-Laure Névoret[e], *[a]CHOC Children's Specialists, Orange, CA, United States, [b]CHOC Children's Hospital, Orange, CA, United States, [c]University of Minnesota, Minneapolis, MN, United States, [d]Hospital of the University of Pennsylvania, Philadelphia, PA, United States, [e]REGENXBIO, Inc., Rockville, MD, United States*

Mucopolysaccharidosis (MPS) type I is a lysosomal disorder caused by mutations in the *IDUA* gene and resultant deficiency of lysosomal α-L-iduronidase (IDUA) enzyme. Patients with severe MPS I have mutations encoding completely inactive IDUA enzyme, and have early-onset developmental delay and cognitive regression in addition to multisystemic manifestations. Treatment for severe MPS I involves intravenous recombinant human IDUA (rhIDUA) enzyme infusions followed by stem cell transplant (SCT). However, SCT carries risks of engraftment syndrome, graft failure, graft-versus-host disease, death, and potentially incomplete correction of neurodevelopmental manifestations. We will report one-year follow-up in a child with severe MPS I (*IDUA* p.R628*/R628*, absent IDUA activity) treated with intracisternal RGX-111 (recombinant adeno-associated virus serotype 9 capsid containing the human *IDUA* expression cassette – AAV9.CB7.hIDUA) at age 21 months utilizing a single-patient investigator-initiated investigational new drug application, due to two MPS I-affected older siblings having died of SCT-related complications. Following baseline volumetric brain imaging, the child received a dose of 1×10^{10} genome copies/g brain mass. Prednisone (12 weeks), tacrolimus (32 weeks), and sirolimus (48 weeks) were administered. As of 8 months after dosing, the child has experienced no drug-related serious adverse events. Cerebrospinal fluid (CSF) biomarkers indicated increased IDUA activity (12 weeks) over baseline levels below the limit of quantification. High heparan sulfate (HS) levels in CSF were measured at baseline, and initial data demonstrated sustained decreases in total HS levels with a 50% reduction from baseline at Week 12 and a 45% reduction from baseline at Week 33. At Week 32 post-administration of RGX-111, neurocognitive evaluations indicated that the patient, who was then 29 months of age, continued to acquire cognitive developmental skills at a normal rate. Regular biomarker and neurodevelopmental assessments are ongoing.

doi:10.1016/j.ymgme.2020.12.270

265

Adults with chronic acid sphingomyelinase deficiency show significant visceral, pulmonary, and hematologic improvements after enzyme replacement therapy with olipudase-alfa: 1-year results of the ASCEND placebo-controlled trial

Melissa Wasserstein[a], Laila Arash-Kaps[b], Antonio Barbato[c], Renata C. Gallagher[d], Roberto Giugliani[e], Norberto B. Guelbert[f], Carla Hollak[g], Takayuki Ikezoe[h], Robin Lachmann[i], Oliver Lidove[j], Paulina Mabe[k], Eugen Mengel[l], Maurizio Scarpa[m], Ebubekir Senates[n], Michel Tchan[o], Jesus Villarrubia[p], Yixin Chen[q], Patricia A. Fraser[q], Beth L. Thurberg[q], Atef Zaher[q], Monica Kumar[q], *[a]Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, United States, [b]University Medical Center Mainz, Mainz, Germany, [c]Federico II University Hospital, Naples, Italy, [d]University of California San Francisco, San Francisco, CA, United States, [e]Hospital de Clínicas de Porto Alegre/Federal University of Rio Grande do Sul, Porto Alegre, Brazil, [f]Hospital de Niños de la Santísima Trinidad, Córdoba, Argentina, [g]Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands, [h]Fukushima Medical University, Fukushima, Japan, [i]National Hospital for Neurology and Neurosurgery, London, United Kingdom, [j]La Croix St Simon Hospital, Paris, France, [k]Clinica Santa Maria, Santiago, Chile, [l]Clinical Science for Lysosomal Storage Disorders, SpinCS, Hochheim, Germany, [m]University Hospital of Udine, Udine, Italy, [n]Istanbul Medeniyet University, Istanbul, Turkey, [o]Westmead Hospital, Sydney, Australia, [p]Hospital Universitario Ramón y Cajal, Madrid, Spain, [q]Sanofi Genzyme, Cambridge, MA, United States*

Acid sphingomyelinase (ASM) deficiency (ASMD) is a rare and debilitating lysosomal disease with no available treatment. ASCEND (NCT02004691/Sanofi Genzyme) is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled trial of olipudase alfa (recombinant human ASM) enzyme replacement therapy in 36 adults with chronic visceral ASMD. Inclusion criteria included spleen volume ≥ 6 multiples of normal (MN), percent-predicted diffusion capacity for carbon monoxide (DLco) ≤ −70%, and abnormal (≥5) Splenomegaly Related Score (SRS, a patient-reported outcome). Patients were randomized 1:1 to placebo or olipudase alfa (intravenous every 2 weeks with a ~ 16-week dose-escalation from 0.1 to 3.0 mg/kg or maximum tolerated dose). Independent primary efficacy endpoints were percent change in percent-predicted DLco and percent change in spleen volume MN (for the USA, combined with change in SRS) at Week 52. Other endpoints included percent change from baseline in liver volume, platelet count, lipids, chitotriosidase, and lyso-sphingomyelin. Least-square (LS) mean differences at Week 52 between olipudase alfa and placebo groups favored olipudase alfa for percent predicted DLco (+22.0% vs. +3.0%, $p = 0.0004$), spleen volume (−39.4% vs +0.5%, $p < 0.0001$), liver volume (−31.7% vs. 1.4%, $p < 0.0001$) and platelets (+16.8% vs +2.5%, $p = 0.019$), with clinical differences seen by Week 26. SRS decreased in both groups (−8.0 for olipudase vs −9.3 for placebo at Week 52, $p = 0.70$). LS mean differences from baseline to Week 52 favored olipudase alfa for HDL (33.5%, $p = 0.0016$), LDL (−25.9%, $p = 0.0021$), and chitotriosidase (41.9%, $p = 0.0003$). Pre-infusion mean plasma lyso-sphingomyelin decreased by 78.0% and 6.1% at Week 52 in olipudase-alfa and placebo groups, respectively. Olipudase alfa was generally well-tolerated with an acceptable safety profile. Most adverse events (AEs) were mild to moderate. There were no treatment-related serious AEs and no AE-related discontinuations. The study showed significant improvements in clinically relevant disease endpoints at Week 52 in adults with chronic ASMD treated with olipudase alfa compared to placebo.

doi:10.1016/j.ymgme.2020.12.271