

**ABSTRACT BOOK**



### **Diagnostic Dilemmas - how not to miss MPS**

Christina Lampe

*University of Giessen, Center for Rare Diseases, Germany*

Recurrent infections of the airways and ears, inguinal and/or umbilical hernia in combination with joint stiffness and contractures as well as other skeletal abnormalities may lead to the diagnosis of a rare, inherited disease: mucopolysaccharidosis.

The mucopolysaccharidoses (MPS) are one group of lysosomal storage disorders caused by a deficiency of lysosomal enzymes, that are responsible for the degradation of glycosaminoglycans (GAGs), important components of the connective tissues. This is accomplished by complex pathophysiological cascades and results in a storage of GAGs in the cells. Almost all organs and organ systems are affected.

The accumulation of undegraded GAGs leads to a progressive variety of somatic and neurological symptoms, including skeletal, musculoskeletal and cardiorespiratory complications. Some MPS types show also a mental development decline. Early diagnosis, appropriate management and – in some MPS types available- therapies affect the quality of life of patients and can lead to a slowdown or a prevention of irreversible complications.

Since there is not a typical “MPS-symptom”, but only the sum of many nonspecific and variable symptoms may lead to the diagnosis, in particular in attenuated / milder MPS types, they are often diagnosed late and mistaken for an (uncharacteristically running) rheumatologic or skeletal disease.

## **Neuronopathic Gaucher Disease**

Raphael Schiffmann  
*Baylor Scott & White Health, USA*

Gaucher disease is an autosomal recessive disorder that is caused by mutations in the *GBA1* gene leading to insufficient activity of the hydrolase acid beta-glucosidase (glucocerebrosidase). Patients are classified into three phenotypes depending on whether the central nervous system (CNS) is involved and on the age of onset of clinical manifestations. Neuronopathic Gaucher disease (nGD) has a very wide clinical and genotypic spectrum. However, there is no consensus definition of nGD, including no description of how best to diagnostically separate the acute form—Gaucher type 2—from the subacute or chronic form—Gaucher type 3. We recently positively defined the various forms of Gaucher disease with particular emphasis on the presence of gaze palsy in all patients with nGD. We discuss the features that suggest nGD and what clinical features differentiate between Gaucher type 2 and type 3. This consensus definition will help in both clinical diagnosis and appropriate patient recruitment to upcoming research studies. Enzyme replacement therapy is the standard medical treatment for nGD. Substrate reduction therapy with venglustat is in clinical trial and gene therapy trials will likely start very soon.

## Clinical Manifestations of Lysosomal Acid Lipase Deficiency (LAL-D): The International LAL-D Registry

**Manisha Balwani**<sup>1</sup>; William Balistreri<sup>2</sup>; Lorenzo D'Antiga<sup>3</sup>; Shona Fang<sup>4</sup>; Simon A. Jones<sup>5</sup>; Emilio Ros<sup>6</sup>; Florian Abel<sup>4</sup>; Don P. Wilson<sup>7</sup>

<sup>1</sup>*Icahn School of Medicine at Mount Sinai Hospital, New York, New York*; <sup>2</sup>*Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*; <sup>3</sup>*Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy*; <sup>4</sup>*Alexion Pharmaceuticals, Inc., Boston, Massachusetts*; <sup>5</sup>*Manchester University Hospital NHS Trust, Manchester, UK*; <sup>6</sup>*Hospital Clinic de Barcelona, Barcelona, Spain*; <sup>7</sup>*Cook Children's Medical Center, Fort Worth, Texas*

An international registry (NCT01633489; Alexion Pharmaceuticals, Inc.; 2013–ongoing) was established to better understand the natural history of lysosomal acid lipase deficiency (LAL-D) and to evaluate long-term treatment outcomes. Baseline findings for patients enrolled through July 1, 2019 are presented. Of 190 patients enrolled, 35 were excluded from this analysis (*LIPA* carrier, deceased at enrollment, unconfirmed LAL-D diagnosis); 155 patients with confirmed LAL-D diagnosis were included (12 infants, 143 children/adults). LAL enzyme activity analysis was performed for 145/154 patients (94%) and genetic testing for 128/154 patients (83%). Of 105 children/adults with reported *LIPA* mutations, 39 were homozygous and 34 were compound heterozygous for the common *LIPA* mutation E8SJM (c.894G>A); 6 infants with reported *LIPA* mutations were homozygotes and 2 were compound heterozygotes. Of the 155 patients, 62% were <18 years, 52% were male, and 85% were white. Median (range) age at clinical onset was 0.2 years (0.0–0.7) among infants and 6.0 years (0.0–41.3) among 133 children/adults with data; median (range) age at diagnosis was 0.2 years (–0.1 to 1.2) among infants and 10.8 years (0.2–53.6) among 135 children/adults with data. Manifestations that raised suspicion of LAL-D were reported in 149/155 patients. Infants (12 with data) presented predominantly with hepatomegaly (75%), splenomegaly (58%), nausea/vomiting (58%), and diarrhea (50%), and 50% had a known family history of LAL-D. Children/adults (n=143) presented predominantly with elevated alanine aminotransferase levels (67%), hepatomegaly (66%), and elevated aspartate aminotransferase levels (65%). Of 74 children/adults with baseline liver biopsy, 58% had microvesicular steatosis, 16% had micro- and macrovesicular steatosis, and 32% had lobular inflammation. Of the 155 patients, 6% had a medical history of cirrhosis. Analyses exploring the genotype-phenotype relationship will be presented. Registry data of >150 LAL-D patients demonstrate early symptom onset, variable clinical manifestations, and a significant diagnostic delay in children/adults.

### Disclosures:

**Balwani:** Alexion Pharmaceuticals, Inc., honorarium, advisory board; Lysosomal Acid Lipase Deficiency Registry, scientific advisory board.

**Balistreri:** Otsuka, Alexion Pharmaceuticals, Inc., consultant; Gilead, AbbVie, Merck, research grants.

**D'Antiga:** Alexion Pharmaceuticals, Inc., advisory board, honorarium, grants, speaker; Lysosomal Acid Lipase Deficiency Registry, scientific advisory board.

**Fang and F. Abel:** Alexion Pharmaceuticals, Inc., employment.

**S.A. Jones:** Alexion Pharmaceuticals, Inc., honorarium, grants, speaker.

**Ros:** Alexion Pharmaceuticals, Inc., honorarium, grants, speaker; Lysosomal Acid Lipase Deficiency Registry, scientific advisory board.

**D.P. Wilson:** Osler Institute, National Lipid Association, Insulet Corp., Alexion Pharmaceuticals, Inc., speaker; Aegerion, Alexion Pharmaceuticals, Inc., Merck Sharp & Dohme, Novo Nordisk, advisory board; Merck Sharp & Dohme, Novo Nordisk, research funding.

## **Lentiviral Gene Therapy for Patients with Lysosomal Disorders (LDs): Clinical Data Update**

Birgitte Volck  
*AVROBIO, USA*

AVROBIO, a clinical-stage gene therapy company with a mission to free people from a lifetime of genetic disease, aims to develop potential one-time lentiviral-based gene therapies to treat patients with LDs caused by the mutation of a single gene. Our gene therapies employ patient-derived hematopoietic stem cells modified with a lentiviral vector to insert a therapeutic copy of the mutated gene. Our clinical stage programs include Fabry disease (AVR-RD-01), cystinosis (AVR-RD-04) and Gaucher disease (AVR-RD-02).

AVR-RD-01 is being evaluated in an investigator-sponsored Ph1 trial and AVROBIO-sponsored Ph2 trial. Nine classic male Fabry patients have been dosed to date. Initial data suggest durable effect, including up to 32 months in one patient, as demonstrated by VCN, AGA enzyme activity in leukocytes and plasma and associated reductions in plasma lyso-Gb3. An 87% reduction in average number of kidney peritubular cell Gb3 substrate deposits was reported in the first treatment naïve patient at 48 weeks. Per the last safety data cut-off date, there have been no SAEs associated with AVR-RD-01 and the safety profile reported is consistent with conditioning and underlying disease.

AVR-RD-04 is being studied by UCSD collaborators in a Ph1/2 investigator-sponsored trial to treat cystinosis. Three-month data from the first dosed patient demonstrated a reduction in granulocyte cystine levels and positive trends across multiple clinical measures. Per the last safety data cut-off date, no SAEs were reported and AEs were consistent with conditioning and underlying disease.

The Ph1/2 trial in Gaucher disease Type 1 investigating AVR-RD-02 has enrolled the first patient.

## **Biomarkers for the Mucopolysaccharidoses**

Maria Fuller

*Genetics and Molecular Pathology, SA Pathology, Australia  
School of Medicine, University of Adelaide, Australia*

**Background:** The mucopolysaccharidoses (MPS) are a family of LSD characterised by impaired degradation of glycosaminoglycans (GAG) which subsequently accumulate in affected cells and are excreted in the urine. Rare disorders, with broad clinical heterogeneity, accurate diagnosis of MPS can be protracted and predicting clinical course and treatment response challenging.

**Objective:** To improve the diagnostic efficiency of MPS through mass spectrometric detection of small, specific GAG fragments with terminal residues characteristic of the enzyme deficiency.

**Methods:** A derivatizing agent is added to the biological sample (urine, blood, CSF) along with an internal standard and following partial chromatographic separation, GAG fragments (ranging in size from mono- to tetrasaccharides) are quantified by tandem mass spectrometry.

**Results:** All ten MPS subtypes were identified from a signature GAG fragment yielding 100% sensitivity and specificity for the diagnosis of 90 MPS patients from 2,500 tested. There is no requirement for age related reference ranges or depolymerisation of the high molecular weight GAG. Notably, two siblings were misdiagnosed as a result of normal urinary GAG but were later correctly diagnosed with MPS IVA using the signature GAG fragment. The MPS II GAG fragment confirmed an unaffected foetus in the prenatal setting with an equivocal enzyme activity result and a genetic variant of uncertain significance. A precipitous drop in the concentration of these fragments was shown in MPS I, III, IVA and VI following therapeutic intervention highlighting their utility for biochemical monitoring. Additionally, in 12 MPS IVA patients in receipt of enzyme replacement therapy, concentrations of the signature GAG fragment correlated with urinary keratan sulphate.

**Conclusion:** Advances in mass spectrometry technologies have enabled simultaneous measurement of small, naturally occurring, GAG fragments, providing a platform for improving the efficiency and accuracy of MPS diagnosis, biochemical monitoring of treatment response and they may also show promise for prognosis.

## **LSDs in Brazil**

Ida Schwartz

*Hospital de clinicas de Porto Alegre, Brazil*

Brazil is one of the largest and most populous countries in the world, full of inequalities. However, Brazilians are privileged in terms of access to health. They have a large public health system, which includes a unique Policy on Rare Disorders, which covers neonatal screening and reimbursement for high-cost treatments for lysosomal disorders through specific guidelines. These topics, and the need for advances, will be addressed in the lecture.

## **Role of Patients' Support Groups - IGA as a Model**

Tanya Collin-Histed  
*International Gaucher Alliance (IGA), UK*

Established in 1994 as an anarchy of patient advocates, the (then) EGA, now IGA is an umbrella organisation and its members are national patient led organisation for Gaucher, LSD or rare diseases. Today we have 56 member organisations representing 54 countries across the globe, with representation geographically across a large majority of the world, although there are still some areas that we lack presence. We recognise that in some countries there is little or no awareness of Gaucher, LSDs or rare diseases and here we build relationships with individual patients and parents/families to offer support mainly through supporting patients to get treatment through charitable access programmes.

- Built on a strong foundation of volunteers all with a connection to Gaucher disease the IGA board of directors, volunteers and CEO donated 2900 hours of their time to support the work of the IGA in 2019.
- In 2018 we introduced our regional manager programme that seeks to be the eyes and ears of the IGA in regions where there is little or no awareness of Gaucher disease and using volunteers from our 'Go with Gaucher' programme (taking forward the next generation of patient advocates) we have programmes in South Asia (north and south), Central America, Caucasus & Central Asia and Africa).
- Establishing ourselves as an independent, well respected and trusted organisation we are recognised as a sister organisation to the EWGGD, the 'go to' organisation for stakeholders to consult with regarding all Gaucher projects, and the global voice of the patient community.



## **Patients' Support Groups and Political Complexities**

Fernanda Torquati  
*Italian Gaucher Association, Italy*

Home therapy, international challenges, annual meetings, but also interviews with national media and conferences with political groups. Being a non-profit organization that helps patients with rare disease is not easy. Their voice needs to be amplified in order to be listed by institutions. Moreover, they need not be left alone. The story of AIG started 28 years ago and till now we are supporting Gaucher's patients. We are fighting to allow lysosomal patients to have access to home therapy. The possibility of practicing enzyme replacement therapies at home is not a simple convenience, but a fundamental step to guarantee a dignified quality of life for these people. Especially during COVID-19 pandemic, Home Therapy increases the safety of patients and family members by avoiding non-essential movements to hospitals and prevent patients from interrupting Lifesaving Therapy for fear of infection.

### **Fabry Patients` Perspectives on Multidisciplinary Clinics**

**Daisy Tapia**<sup>1</sup>, Jillian Thrall<sup>2</sup>, Marta Sabbadini<sup>3</sup>, Wendy Packman<sup>2</sup>, Janey Youngblom<sup>4</sup>

<sup>1</sup>*Pediatrics, University of California, Irvine, USA*

<sup>2</sup>*Psychology, Palo Alto University, USA*

<sup>3</sup>*Cancer Genetics and Prevention Program, University of California, San Francisco, USA*

<sup>4</sup>*Biological Sciences, California State University, Stanislaus, USA*

Fabry Disease (FD) is an X-linked inherited lysosomal storage disorder which leads to progressive tissue damage, particularly in the renal, cardiac, and cerebrovascular systems. Disease presentation can vary among FD patients, males tend to be more severely affected than females. The complexity of disease manifestation means that individuals affected with FD require multispecialty management. A Multidisciplinary Clinic (MDC) is a proposed care delivery model that can provide a more comprehensive approach to clinical management for complex diseases such as FD. This study aims to understand FD patients' opinions towards the use of an MDC for FD management. Thirty-two adult individuals with FD were interviewed over the phone using a semi-structured interview guide. Of the 32 participants, four were being seen at an MDC, and all four felt that they were getting better overall FD care from the MDC compared to a non-MDC setting and preferred the MDC to their previous clinic model. Additionally, all four would recommend the MDC to other individuals with FD. The remaining 28 participants had never been seen in an MDC. When asked about possible advantages to an MDC setting, the majority (26/28) mentioned the convenience of having various appointments in one day and several (16/28) mentioned the FD expertise of providers participating in the MDC. When asked about challenges, 12/28 participants mentioned that the clinic day could be long and time consuming, additionally 11/28 noted that travel to attend the clinic could be an issue. About half (16/28) said it would not be overwhelming to see multiple providers in one day. Most (20/28) reported that they would be interested in participating in an MDC. These findings suggest that patients see various benefits and are interested in a multidisciplinary approach for managing FD. Evaluating and incorporating the perspectives of patients with FD is essential for the improvement of health outcomes.

## **Multiple-Dose Administration of a Non-Viral Vector in Fabry Mice as an Endogenous Expression System of $\alpha$ -Galactosidase A**

**Julen Rodríguez-Castejón**, Mónica Vicente-Pascual, Itziar Gómez-Aguado, María Ángeles Solinís, Ana del Pozo-Rodríguez, Alicia Rodríguez-Gascón

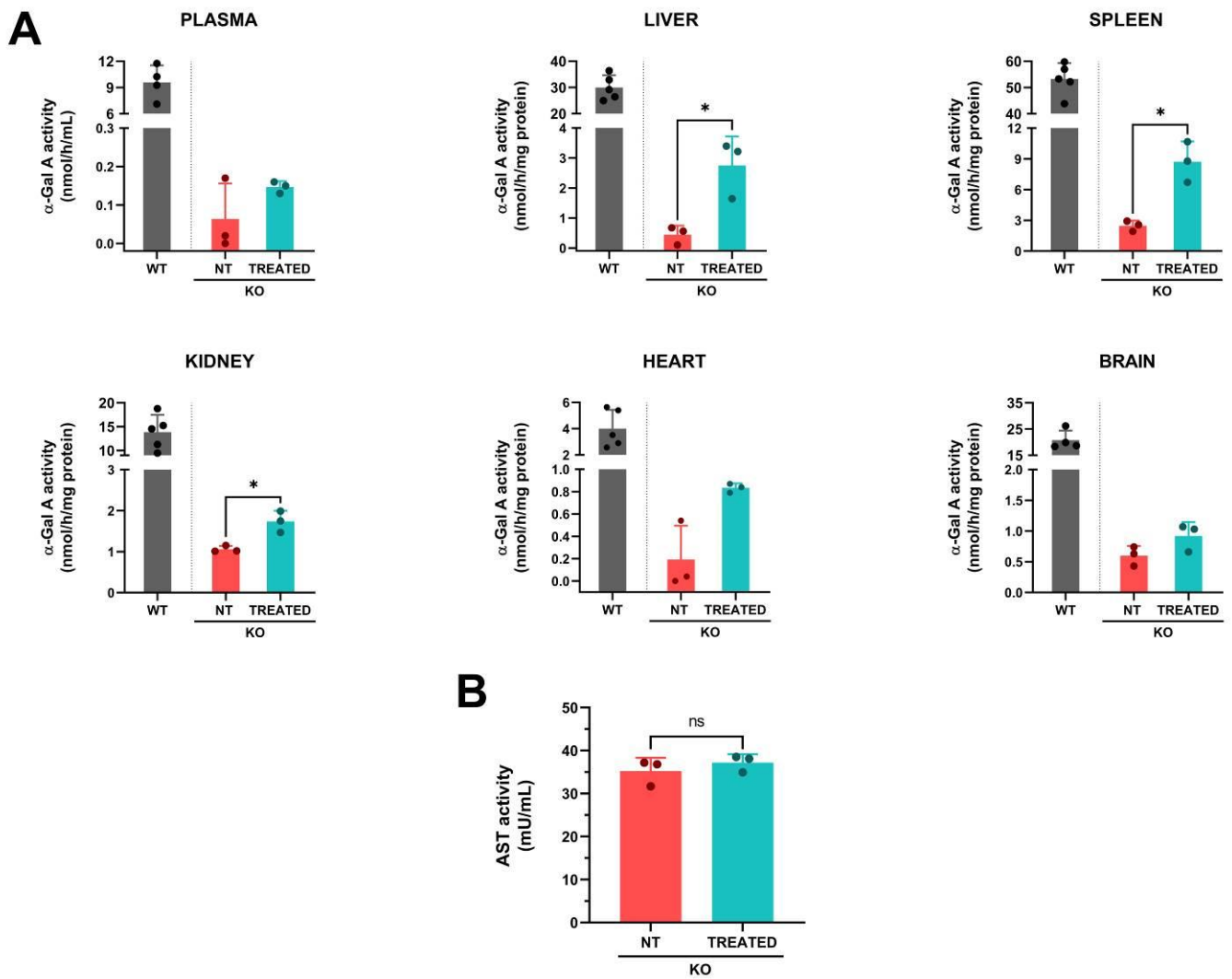
*Pharmacokinetics, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, University of the Basque Country UPV/EHU, Spain*

**Background:** Fabry disease (FD) is an X-linked lysosomal storage disorder caused by loss of  $\alpha$ -galactosidase A ( $\alpha$ -Gal A). Gene augmentation therapy is an ideal option to restore the endogenous expression of  $\alpha$ -Gal A.

**Objective:** To evaluate the potential of a solid lipid nanoparticle (SLN)-based vector to increase  $\alpha$ -Gal A in plasma and tissues in  $\alpha$ -Gal A knockout (KO) mice (JAX stock #003535).

**Method:** The vector consisted of SLN, dextran, protamine and a plasmid encoding for  $\alpha$ -Gal A. A dose of the vector (60  $\mu$ g of plasmid) was injected through the tail vein once a week for 3 weeks. Seven days after the last administration, animals were sacrificed and  $\alpha$ -Gal A activity was measured in plasma, liver, spleen, kidney, heart and brain by an enzymatic assay, along with samples obtained from wild-type (WT) and non-treated KO mice. Aspartate aminotransferase (AST) activity was measured in liver with a commercial assay kit.

**Results:** An increase in  $\alpha$ -Gal A activity was detected in plasma and tissues, which was significant in liver, spleen and kidney (6, 4 and 2-fold with respect to non-treated KO animals, respectively). Depending on the tissue, the enzyme activity reached levels ranging from 9% to 21% of those in WT (Figure 1A). The vector did not increase AST activity (Figure 1B).



*Figure 1.* (A)  $\alpha$ -Gal A activity in plasma and tissues of wild-type ( $n=4-5$ ) and untreated and treated Fabry mice ( $n=3$  per group). (B) AST activity in liver. Results are plotted as individual values and mean with standard deviation. \* $p<0.05$ . WT: wild-type; NT: non-treated; KO:  $\alpha$ -Gal A knockout mice; ns: non-significant.

Conclusion: The SLN-based vector increased  $\alpha$ -Gal A activity in plasma and tissues of  $\alpha$ -Gal A deficient mice; interestingly, the highest increment was detected in liver, which may act as a factory for the production and secretion of  $\alpha$ -Gal A.

## **Asymptomatic Family with Late Onset Pompe Disease: An Unexpected Diagnosis**

**Marcia Ribeiro**

*Pediatrics, Federal University of Rio De Janeiro, Brazil*

Background: Pompe disease (PD) is a genetic disease with broad spectrum of phenotypes, due to deficiency of acid  $\alpha$ -glucosidase (GAA) activity. PD manifestations may occur as soon as in the first months or as late as in the 60th decade of life. Objective: To describe a family with three asymptomatic individuals with PD with compound heterozygosity. Method: Case report. Results: PLC, a 7-year old asymptomatic boy was investigated for PD because of an increase of aspartate aminotransferase and alanine aminotransferase during an investigation of atopy. First and only child of a young and unrelated couple with a negative family history of PD. He presented low GAA activity in dried blood spot and in leukocytes, normal urinary glucose tetrasaccharide and a compound heterozygosity mutation on GAA gene: NM\_000152(GAA\_v001):c.-32-13TG, localized at chr17:78078341(GRCh37/Hg19) and a 5'UTR deletion, localized at chr17:75690146-75690211-Hg18. Further investigation of the family showed: a) his mother and maternal uncle with low GAA activity and NM\_000152(GAA\_v001):c.[-32-13TG(; )1123CT] mutations; the second mutation was localized at chr17:78082335(GRCh37/Hg19); b) his father with normal GAA activity and a 5'UTR deletion; c) his maternal grandfather with c.-32-13TG mutation in one allele; d) his maternal grandmother with a c.1123CT in one allele and; e) his paternal grandmother with the same 5'UTR deletion. All of them were asymptomatic. The c.1123CT mutation was classified as likely pathogenic and the c.-32-13TG, as pathogenic, related to late-onset PD. Normal evaluation of cardiac, respiratory and muscle function of the proband and his mother. Conclusion: PD presents a large variation in the age of onset and type of genetic alterations. Different types of mutations and deletions should be considered in the diagnostic investigation. As the proband, his mother and his uncle are asymptomatic at this moment. It is very important to follow them up to offer the proper treatment when it will be required.

### **Hip Pathologies and Influencing Parameters in Mucopolysaccharidosis Type III**

**Sandra Rafaela Breyer**<sup>1,4,5</sup>, Eik Vettorazzi<sup>2</sup>, Leonie Schmitz<sup>2</sup>, Amit Gulati<sup>2</sup>, Katharina Maria Von Cossel<sup>3,5</sup>, Alexander Spiro<sup>1,4,5</sup>, Martin Rupprecht<sup>1,4,5</sup>, Ralf Stuecker<sup>1,4,5</sup>, Nicole Maria Muschol<sup>3,5</sup>

<sup>1</sup>*Pediatric Orthopedics, Altonaer Children's Hospital, Germany*

<sup>2</sup>*Department of Medical Biometry, University Medical Center Hamburg-Eppendorf, Germany*

<sup>3</sup>*Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Germany*

<sup>4</sup>*Department of Orthopaedics, University Medical Center Hamburg-Eppendorf, Germany*

<sup>5</sup>*International Center of Lysosomal Disorders, University Medical Center Hamburg-Eppendorf, Germany*

**Background:** Mucopolysaccharidosis type III (MPS III) comprises a group of rare, lysosomal storage diseases. Although musculoskeletal symptoms are less pronounced than in other MPS subtypes, pathologies of hips and spine have been reported in several MPS III patients.

**Objective:** The purpose of this study was to describe hip pathologies and influencing parameters in MPS III patients.

**Methods:** A retrospective chart review was performed for 101 MPS III patients. Thirty-two patients met the inclusion criteria of enzymatically or genetically confirmed diagnosis and plain anteroposterior x-ray of the hips.

**Results:** The mean age at data assessment was 11.0 years. Osteonecrosis of the femoral head was observed in 17/32 patients. No statistically significant association was found between osteonecrosis and age, sex or MPS III subtype. Patients with a severe phenotype showed significantly higher rates of osteonecrosis (14/17) than patients with an intermediate phenotype. The modified Ficat classification, Wiberg's center-edge angle and Reimer's migration percentage were measured on plain anteroposterior radiographs of the hips. Hip dysplasia was present in 9/32 patients and was significantly associated with osteonecrosis of the femoral head (7/9).

**Conclusion:** MPS III is a severe, not yet treatable neurodegenerative disease. As new therapeutic strategies are under development and might significantly alter the course of the disease, detailed knowledge of hip pathologies and influencing factors is essential. Therefore, radiographs of the hips should be included in baseline and follow-up assessments of MPS III patients.

## **Neonatal Combination Therapy Improves Some of the Clinical Manifestations in the Mucopolysaccharidosis Type I Murine Model**

**Giada De Ponti**<sup>1</sup>, Ludovica Santi<sup>1,6</sup>, Giorgia Dina<sup>2</sup>, Alice Pievani<sup>1</sup>, Alessandro Corsi<sup>3</sup>, Mara Riminucci<sup>3</sup>, Shaukat Khan<sup>4</sup>, Kazuki Sawamoto<sup>4</sup>, Laura Antolini<sup>5</sup>, Silvia Gregori<sup>6</sup>, Andrea Annoni<sup>6</sup>, Andrea Biondi<sup>7</sup>, Angelo Quattrini<sup>2</sup>, Shunji Tomatsu<sup>4</sup>, Marta Serafini<sup>1</sup>

<sup>1</sup>*Department of Pediatrics, University of Milano-Bicocca, Centro Ricerca M. Tettamanti, Italy*

<sup>2</sup>*Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Experimental Neuropathology Unit, INSPE, Italy*

<sup>3</sup>*Department of Molecular Medicine, Sapienza University, Italy*

<sup>4</sup>*Department of Biomedical Research, Alfred I. duPont Hospital for Children, USA*

<sup>5</sup>*Department of Health Sciences, University of Milano-Bicocca, Centro di Biostatistica per l'epidemiologia clinica, Italy*

<sup>6</sup>*IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute for Gene Therapy, Italy*

<sup>7</sup>*Department of Pediatrics, Fondazione MBBM/San Gerardo Hospital, Italy*

Mucopolysaccharidosis type I (MPS-I), a lysosomal storage disorder caused by a deficiency of alpha-L-iduronidase enzyme, results in the progressive accumulation of glycosaminoglycans (GAGs) and consequent multiorgan dysfunction. Hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) are the currently available therapies for MPS-I patients. Despite their effectiveness in correcting clinical manifestations related to visceral organs, complete improvement of musculoskeletal and neurocognitive defects remains an unmet challenge and provides an impact on patients' quality of life.

On the basis of these observations, we tested the therapeutic efficacy of the current standard of care treatments, such as ERT and nBMT, alone or in combination, in a mouse model of MPS-I during the neonatal period, which is proposed to be the best therapeutic window.

We evaluated IDUA enzyme activity, GAGs accumulation and the presence of vacuoles in visceral organs and plasma, performed radiographs and micro-CT analysis to measure the extent of the skeletal phenotype correction, and examined the neurological outcome.

We demonstrated that the combination therapy improved clinical manifestations in organs usually refractory to current treatment, such as kidney and heart, and that combination with HSCT prevented the production of anti-IDUA antibodies that negatively impact ERT efficacy. Synergistic beneficial effects of combining both treatments were also observed for the reduction of skeletal anomalies, with a trend towards normalization of the histomorphometric parameters of bone resorption, that are altered in the transplantation group, and modulated neuroinflammation and metabolic abnormalities at the brain level. As currently there are limited therapeutic options for MPS-I patients, our findings suggest that the combination of HSCT and ERT during the neonatal period may provide a further step forward in the treatment of this rare disease, promoting the idea of an early intervention supported by the development of newborn screening programs.

## **Fat Fraction Quantification of Lumbar Spine Bone Marrow using the LiverLab Assessment Tool in Adult Volunteers and Patients with Gaucher Disease**

**Calvin Gan<sup>1</sup>, Patricia Robertson<sup>1</sup>, Jeffrey Lai<sup>1</sup>, Jeff Szer<sup>2</sup>**

<sup>1</sup>*Radiology, The Royal Melbourne Hospital, Australia*

<sup>2</sup>*Clinical Haematology, The Royal Melbourne Hospital & Peter MacCallum Cancer Centre, Australia*

### Background:

Magnetic Resonance Imaging (MRI) is used for evaluation of bone disease in Gaucher disease (GD), but a widely available quantitative scoring method remains elusive. An MRI post-processing LiverLab tool using two-point-Dixon VIBE images to output a numeric fat fraction (FF) has not been validated in bone marrow.

### Objective:

To assess the reproducibility of the LiverLab tool for assessing bone marrow FF and to determine whether it can differentiate GD patients from healthy subjects.

### Method:

10 healthy volunteers (age range 28-65, 5 males, 5 females) and 18 GD patients (age range 27-74, 12 males, 6 females, 13 on enzyme replacement therapy (ERT)) were recruited with FF calculated at L3, L4 and L5 by two radiographers (two studies for volunteers, one study for GD patients). Bone marrow burden (BMB) score in GD patients was assessed by one observer.

Inter and intra-rater agreement was assessed with Bland-Altman data plots.

Differences in FF between healthy volunteers versus GD patients and between treatment versus no treatment were assessed using two-sample t-tests.

In GD patients, relationship between FF, BMB and Glucosylsphingosine were assessed with Pearson's correlation coefficient.

### Results:

#### Healthy volunteers:

Mean FF 0.36, standard deviation (SD) 0.10 (range 0.20-0.57). Intra and inter-rater SD were both 0.02.

#### GD patients:

Mean FF 0.40, SD 0.13 (range 0.09-0.57). No statistical difference between healthy volunteers and GD patients ( $p=0.44$ ) or between GD patients whether on ERT or not ( $p=0.09$ ).

No significant correlation between mean FF and total BMB ( $r=-0.53$ ,  $p=0.25$ ) or Glucosylsphingosine levels ( $r=0.29$ ,  $p=0.25$ ), but a trend to lower FF in patients with moderate versus mild categories of BMB score.

### Conclusion:

Excellent reproducibility of LiverLab FF measurements across studies and observers is comparable to QCSI. Lack of statistical difference between GD patients and controls may be explained by limited patient numbers, active treatment or mild disease severity in untreated patients.