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Editor-in-Chief: Roberto Giugliani

Latin American Society of Inborn Errors of Metabolism and Neonatal Screening

SPECIAL SUPPLEMENT WITH THE ABSTRACTS

IGSD2019

5th International GSD Conference

BarraShoppingSul
Porto Alegre/RS - Brazil

14 -16 November 2019

FOREWORD FROM IGSD 2019

Two and a half years have passed since the International Glycogen Storage Disease Conference in Groningen (4th IGSD 2017). At that time, I could not foresee the major challenge we would have to face by bringing for the first time to Latin America, and to Brazil, an international conference dedicated entirely to glycogen storage diseases.

An event that brings together scientists, physicians, dietitians, students, patients and their families from around the world to seek a better understanding of this group of rare diseases, new treatments, and new alternatives to improve quality of life and, especially, to enhance research and knowledge capacity.

The conference program includes plenary and parallel sessions covering relevant topics on hepatic and muscle glycogen storage diseases. The conference will be preceded by a day of 3 pre-conference courses on hepatic glycogen storage diseases, Pompe disease, and ventilatory support in neuromuscular disorders as well as by a sponsored satellite symposium. More than 30 faculty members from around the world will be generously sharing their knowledge with different specialty physicians, patients and their families.

Forty abstracts were submitted for consideration by the scientific committee. All abstracts were of a high standard, including case reports of scientific interest. After a careful and difficult analysis, 11 were selected for Oral Communication at the conference and 2 others were incorporated into the scientific program for being considered very important topics that warrant a plenary session.

We believe that the publication of this special JIEMS supplement dedicated to up-to-date research on glycogen storage diseases will contribute to building a network in Latin America connected to the rest of the world that will encourage further studies, publications, connections, projects, and partnerships to better understand and treat this rare group of genetic diseases.

Carolina Fischinger Moura de Souza, MD, PhD
President of IGSD 2019

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FOREWORD FROM JIEMS

The ***Journal of Inborn Errors of Metabolism and Screening***, the official journal of the **Latin American Society of Inborn Errors of Metabolism and Neonatal Screening**, is pleased to introduce this special supplement with the abstracts accepted for presentation at the ***5th International Glycogen Storage Disease Conference*** (Porto Alegre, Brazil, November 14-16, 2019).

In this special supplement you will find 39 abstracts submitted as free communications and accepted for presentation. In the supplement you will find first those abstracts accepted as oral communications and then those presented as posters.

This supplement is also available online (open access) at the JIEMS website **(www.jiems-journal.org)**.

We hope that this JIEMS supplement contributes to disseminate the scientific output of this major event in the IEM field.

Roberto Giugliani
JIEMS Editor-in-Chief

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Book of Abstracts

ABSTRACTS SELECTED FOR ORAL PRESENTATION

2462 - FIRST-IN-HUMAN STUDY OF ATB200/AT2221 IN PATIENTS WITH POMPE DISEASE: 24-MONTH FUNCTIONAL ASSESSMENT RESULTS FROM THE ATB200-02 TRIAL

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INTRODUCTION: Pompe disease is a rare lysosomal disorder characterized by progressive loss of muscle and respiratory function due to acid α-glucosidase (GAA) deficiency, for which recombinant human GAA enzyme replacement therapy (ERT) is available. Here, we report the 24-month interim functional results from ATB200-02 (NCT02675465). **METHODS:** ATB200-02 is a first-in-human, phase 1/2, open-label study assessing safety/tolerability, pharmacokinetics/pharmacodynamics, and efficacy of ATB200/AT2221, a next-generation ERT/chaperone coadministration therapy, in adults with Pompe disease. **RESULTS:** Twenty-two patients were enrolled: ERT-switch (n=11), ERT-switch non-ambulatory (n=6), and ERT-naive (n=5). The 6-minute walk test improved in ambulatory ERT-switch patients (mean [SD], meters: Month 6, +23.9 [52.2], n=10; Month 12, +42.2 [46.5], n=10; Month 24, +53.6 (36.4), n=8) and ERT-naive patients (n=5; Month 6, +41.8 [29.4]; Month 12, +63.1 [29.1]; Month 21, +54.8 [34.7]). Other motor function tests were generally consistent with these results. Non-ambulatory ERT-switch patients demonstrated increases in upper extremity strength per quantitative and manual muscle testing. Forced vital capacity increased in ERT-naive patients (n=5; mean, % predicted: Month 6, +4.2; Month 12, +4.5; Month 21, +6.1) and was generally stable in ambulatory ERT-switch patients (Month 6, −1.2, n=9; Month 12, −3.0, n=9; Month 24, −0.6, n=7). ATB200/AT2221 was associated with reductions in creatine kinase and urine Hex4. Improvements in patient-reported outcomes (Rasch-built Pompe-specific Activity Scale, Rotterdam Handicap Scale, Fatigue Severity Scale, Subject Global Impression of Change) were reported. Most treatment-emergent adverse events (TEAEs) were transient and generally mild or moderate in severity. The most common TEAEs were nasopharyngitis, fall, and abdominal pain. Six patients reported infusion-associated reactions. **CONCLUSIONS:** Data from this interim analysis show clinical benefits of ATB200/AT2221 in ERT-naive and ERT-experienced patients, suggesting that ATB200/AT2221 can be an effective and well-tolerated treatment for adults with Pompe disease.

2463 - LNP-HAGL MRNA REDUCED LIVER GLYCOGEN ACCUMULATION AND DECREASED HEPATIC HYPERTROPHY IN A MOUSE MODEL OF GLYCOGEN STORAGE DISEASE III

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INTRODUCTION: Glycogen storage disease type III (GSDIII) is an inherited metabolic disorder caused by the deficiency of the glycogen debranching enzyme (GDE, gene name: AGL), which catabolizes glycogen into glucose. Deficiency in GDE results in pathological accumulation of glycogen and limit dextrin in tissues, directly affecting primarily liver and muscle. Patients with GSDIII are at increased risk for hypoglycemia, liver damage and myopathy later in life. **METHODS:** Here, we examined the pharmacology associated with treatment of a lipid nanoparticle (LNP) containing a codon-optimized AGL mRNA payload in an AGL-/- mouse model, which mimics the clinical, biochemical and pathological phenotypes of human GSDIII. **RESULTS:** We showed that a single bolus systemic injection of LNP-hAgl mRNA resulted in reduction of liver glycogen and decreased liver hepatocyte size. This effect was dose dependent and was observed as early as 24 hours after the single dose. The liver glycogen reduction effect was maintained for at least 10 days in Agl-/- animals with ad hoc feeding and standard diet. **CONCLUSIONS:** Our results demonstrated that treatment with LNP-hAGL mRNA effectively rescued the liver phenotype caused by AGL mutation in a mouse model of GSDIII and supports continued development of an LNP-hAgl mRNA as a therapeutic approach for the treatment of GSDIII in humans.

2472 - ANALYSIS OF THE IMPACT OF GLYCOGEN STORAGE DISEASE TYPE IX-ALPHA MUTATIONS ON CLINICAL SYMPTOMATOLOGY

Corbinian N. Wanner (Connecticut Children's, United States), **Patrick T. Ryan** (University of Connecticut School of Medicine/Connecticut Children's, United States), **David A. Weinstein** (University of Connecticut School of Medicine/Connecticut Children's, United States)

INTRODUCTION: Glycogen storage disease type IX alpha (GSD IXa) is caused by a deficiency of the phosphorylase kinase enzyme. This enzyme has multiple subunits (alpha, beta, and gamma) that serve a vital role in the phosphorylating capability of the enzyme. GSD IXa has a wide range of severity and clinical presentation. Therefore, this study was conducted to compare whether the location of a mutation has a correlation to the subject's clinical symptomatology. **METHODS:** A single-center retrospective chart review was completed as part of the institutional review board approved Natural History Study protocol administered to GSD IXa patients at the University of Florida and Connecticut Children's. This review included the collection of the following items: documented hypoglycemia at birth, history of infantile irritability, delay in developmental milestones, age of appreciated hepatomegaly, growth history trends, history of seizures or neurological complications, cornstarch dosing amounts, and markers of metabolic control after cornstarch therapy treatment: AST, ALT, Creatinine Kinase (CK), Cholesterol (Chol.), and Triglycerides (TG). The variables were then compared to the subject's mutation location. **RESULTS:** 28 subjects (all males) were included within the study with a mean age of 11.8 (SD ±5.0; Range: 1-20). Collectively, 18 unique mutations were found. From a metabolic marker perspective, the following mutations have the most severe and pronounced abnormalities; listed in decreasing severity. AST & ALT: c.3505C>T, c.3027+1G>A, and c.557G>A. CK: c.4C>G, c.3027+1G>A, and c.3666A>C. Chol.: c.345delG, c.133C>T, and c.557G>A. TG: c.893G>C, c.3505C>T, and c.345delG. In terms of cornstarch treatment, the following mutations have the highest requirement measured as grams per kilogram, bodyweight per day in decreasing order: c.893G>C (10.3g/kgBW/day), c.3666A>C (8.8g/kgBW/day), and c.3505C>T (8.4g/kgBW/day). **CONCLUSION:** Collectively, 8 of the 18 mutations are associated with the most severe abnormalities of metabolic control and subsequent cornstarch dose requirement. Specifically, this group of mutations overlapped in more than one marker: c.3505C>T, c.3027+1G>A, c.557G>A, c.3666A>C, c.345delG, and c.893G>C. In conclusion, these eight mutations likely have a more detrimental impact on the functionality of the phosphorylase kinase enzyme and therefore lead to a more severe clinical presentation.

2476 - RESEARCH PRIORITIES FOR LIVER GLYCOGEN STORAGE DISEASE: AN INTERNATIONAL PRIORITY SETTING PARTNERSHIP WITH THE JAMES LIND ALLIANCE

Fabian Peeks (Section of Metabolic Diseases, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands), **Willemijn F Boonstra** (Section of Metabolic Diseases, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands), **Camilla Carøe** (Paediatric Nutrition, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark), **Thomas Casswall** (Department of Pediatric Gastroenterology, Hepatology and Nutrition, Karolinska University Hospital, and CLINTEC, Karolinska Institutet, Stockholm, Sweden), **Damian Cohen** (Patient representative, Director of Glucolatino, Argentina), **Katherine Cowan** (James Lind Alliance, University of Southampton, Southampton, United Kingdom), **Iris Ferrecchia** (Glycogen Storage Disease Program, University of Connecticut, Farmington, and Connecticut Children's, Hartford, United States), **Alberto Ferriani** (Patient representative, Associação Brasileira de Glicogenose - ABGLICO - Brazil), **David A Weinstein** (Glycogen Storage Disease Program, University of Connecticut, Farmington, USA and Connecticut Children's, Hartford, United States), **Terry G J Derks** (Section of Metabolic Diseases, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, The Netherlands).

INTRODUCTION: The international liver glycogen storage disease (GSD) priority setting partnership (IGSDPSP) was established to identify the top research priorities in this area. **METHODS:** The multiphase methodology followed the principles of the James Lind Alliance (JLA) guidebook. An international scoping survey in seven languages was distributed to patients, carers and healthcare professionals to gather uncertainties, which were combined into summary questions. The existing literature was reviewed to ensure that the summary questions had not been answered yet. A second survey asked responders to prioritize these summary questions. A final shortlist of 22 questions was discussed during an international multi-stakeholder workshop, and a consensus was reached on the top 11 priorities using an adapted nominal group technique. **RESULTS:** In the first survey, a total of 1388 questions were identified from 763 responders from 58 countries. These original uncertainties were refined into 72 summary questions for a second survey. In total 564 responders from 58 countries answered the second survey. The final shortlist of 22 questions included the top 10 questions identified by patients, carers and healthcare professionals. **CONCLUSION:** This unique priority setting

partnership has been the first international, multilingual priority setting partnership focusing on ultra-rare diseases. By involving patients, carers and healthcare professionals from in total 73 countries, we have identified the worldwide top 11 priorities for research related to liver GSD. This process provides a valuable resource for researchers and funding agencies to foster interdisciplinary and transnational research projects with a clear benefit for patients.

2483 - FUNCTIONAL AND METABOLIC ANALYSIS OF GLYCOGEN STOREAGE DISEASE TYPE IB MACROPHAGE

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INTRODUCTION: Glucose-6-phosphate(G6P) transporter (G6PT), encoded by the SLC37A4 gene, is a ubiquitously expressed protein. The primary role of G6PT is transporting G6P from the cytoplasm to the ER lumen, to enable hydrolysis step for glucose production. Glycogen storage disease type Ib (GSD-Ib) is a rare disease caused by a deficiency in G6PT. GSD-Ib patients exhibit enlarged liver and kidney with glycogen accumulation and recurrent hypoglycemia with disturbed metabolites in the blood. Neutropenia and neutrophil dysfunction which result in recurrent bacterial infections are well known disease phenotypes of GSD-Ib. In addition to the abnormalities of the neutrophils, we also focused monocytes and macrophages. It has been known that macrophages along with neutrophils are the first line of defense against invading bacterial pathogens. And especially, alveolar macrophages are critical for the defense against bacterial and viral infections. In this study, we investigated effects of G6PT gene knockout on metabolism and cellular functions such as anti-bacterial and anti-viral activity in the cells. **METHODS:** We established G6PT knockout porcine alveolar macrophages cell line using CRISPR/Cas9 system and analyze cell growth rates, cell cycle, apoptosis, metabolites, cellular functions, gene expressions and protein expression to evaluate the role of G6PT in the macrophages. **RESULTS:** The loss of G6PT activity reduced the proliferation of alveolar macrophages. We found that key effector functions of macrophage such as phagocytosis, cell migration, oxidative burst, and antiviral responses were impaired in the G6PT-deficient macrophages. Compared to the wildtype macrophages, G6PTdeficient macrophages showed lower glycolytic rate, glycolytic capacity, ATP production and maximal respiration than wildtype macrophages. **CONCLUSION:** We observed the G6PT-deficient macrophages were impaired in anti-bacterial/viral activity and role of G6PT is critical for metabolism and functions in macrophage. It is very important to recognize the pathogenesis implicated in GSD-Ib such as recurrent bacterial infections can be attributed not only to neutropenia and neutrophil dysfunction but also to impaired functions of macrophages by aberrant energy metabolism.

2484 - FASTING HYPOGLYCEMIA AGGRAVATES DYSLIPIDEMIA IN GSDIA MICE VIA ENHANCED ADIPOCYTE LIPOLYSIS AND IMPAIRED VLDL CATABOLISM

Joanne A Hoogerland (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands), **Fabian Peeks** (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands), **Brenda S Hijmans** (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands), **Justina C Wolters** (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands), **Sander Kooijman** (Department of Medicine, Division of Endocrinology and Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, The Netherlands), **Trijnie Bos** (Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands), **Aycha Bleeker** (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands), **Theo H van Dijk** (Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands), **Terry G J Derks** (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands), **Maaike H Oosterveer** (Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands).

INTRODUCTION: Hypertriglyceridemia is clinically used as a maker for glycemic control in patients with Glycogen Storage Disease type Ia (GSD Ia), however how poor glycemic control aggravates dyslipidemia is unclear. **MATERIALS AND METHODS:** To establish the physiological link between metabolic control and hypertriglyceridemia, we systematically analyzed whole-body triglyceride (TG) metabolism in fed (normoglycemic) and fasted (hypoglycemic) hepatocyte-specific glucose-6-phosphatase deficient (L-G6pc-/-) mice, a model for GSD Ia. **RESULTS:** De novo fatty acid synthesis contributed substantially to hepatic TG accumulation in fed L-G6pc-/- mice. In fasted L-G6pc-/- mice, hepatic steatosis was mainly caused by enhanced adipose tissue lipolysis, which was further supported by elevated free fatty acid levels in GSD Ia mice as well as patients. Plasma VLDL-TG and VLDL-cholesterol levels were increased in GSD Ia patients and fed L-G6pc-/- mice and further increased upon fasting in L-G6pc-/- mice. VLDL-TG secretion rates were doubled in fed and fasted L-G6pc-/- mice, while VLDL-TG catabolism was selectively inhibited in fasted L-G6pc-/- mice. **CONCLUSIONS:** Our data show that fasting-induced hypoglycemia in hepatocyte-specific GSD Ia

mice promotes adipose tissue lipolysis and arrests VLDL catabolism. A similar mechanism likely contributes to aggravated liver steatosis and hyperlipidemia in GSD Ia patients with poorly controlled glycemia, and to clinical heterogeneity in hypertriglyceridemia between individual patients.

2537 - DIETARY LIPIDS IN HEPATIC GLYCOGEN STORAGE DISEASES: A SYSTEMATIC LITERATURE STUDY, CASE STUDIES AND FUTURE RECOMMENDATIONS

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INTRODUCTION: Dietary management is the cornerstone of treatment for hepatic GSD. Traditionally, carbohydrates and proteins have received most interest. The role of dietary lipids is still a matter of debate. The aim of this study was to describe experiences with dietary lipid manipulations in patients with hepatic GSD to provide recommendations for patient care and future clinical studies. **METHODS:** This is an international study including published and unpublished experiences on dietary lipid manipulations in patients with hepatic GSD. A systematic literature search was conducted according to the Cochrane Collaboration methodology. All metabolic dieticians who attended the special dietetic session of the International GSD Conference 2017 Groningen, The Netherlands were asked to share data of unpublished patients who received modified lipid diet (age, dietary composition, diet duration, indication, blood tests, diagnostic imaging, growth). **RESULTS:** 69 cases (30 male, 25 female, 14 unknown, age 0-41 years) were collected including GSDI (n=36), GSDIII (n=28), GSDVI/IX (n=5), including 32 unpublished cases from 8 metabolic centers. A large variation in age range (0.33-41 years), lipid amount (14-87% total daily intake), follow-up duration (0.5-144 months) and outcome parameters was found. The most common interventions were MCT supplementation in GSDI and high fat diet in GSDIII patients. Hypertriglyceridemia and muscle weakness and cardiomyopathy were the main indication to start MCT supplementation and high fat diet, in GSDI and GSDIII, respectively. Among GSDI patients, 68% showed improved triglycerides (TG) (<15% or more); 80% showed no or positive effect on liver adenomas; 5/10 patients showed improved growth. Among GSDIII patients, 80% showed improved CK levels (<20% or more). Z-scores of interventricular septum dimension significantly decreased in pediatric GSDIIIa patients after high fat diet ($p<0.05$); 1/10 patients also showed improved growth. **DISCUSSION:** This study aimed to review all experiences with dietary lipid manipulations in hepatic GSD patients. MCT supplementation seems to improve TG levels and high fat diet may improve (cardio)myopathy in selected patients with GSDI and GSDIII, respectively. Standardized intervention and outcome measures are strongly needed. This study offers guidance for future studies to determine the efficacy (and safety) of lipid dietary interventions in hepatic GSD.

2538 - MEASURING BODY COMPOSITION IN PATIENTS WITH HEPATIC GLYCOGEN STORAGE DISEASES BY DUAL ENERGY X-RAY ABSORPTIOMETRY

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BACKGROUND: The hepatic glycogen storage disorders (GSDs) are a group of inherited metabolic diseases associated with fasting-related hypoglycemia and usually treated with periodic administration of uncooked cornstarch (UCCS). The main objective of the treatment is to promote adequate growth and development through the maintainance of normoglycemia. Some authors suggest that the frequent intake of UCCS is associated with excess adiposity. The present study aimed to evaluate the body composition of patients with hepatic GSDs through dual-energy X-ray absorptiometry (DXA). **METHODS:** Twenty-four patients (GSD Ia= 12; GSD Ib= 5; GSD III= 3; GSD IXα/β/γ= 4; female = 13), with median age 11.86 (IQR = 10.51-20.49) were included in the study. Findings were compared with clinical parameters, UCCS regimen, and markers of treatment adherence (serum lactate and triglycerides), all obtained through a review of medical records. **RESULTS:** Overall, 10 out of 14 patients aged 8–19 years and 6 of 7 adult patients had excess body fat as measured by fat mass index (FMI). Two adult patients had relative skeletal muscle index (RSMI) values below the cutoff point for their age group. Total UCCS intake (g/day) correlated positively with fat mass in grams (FM/kg) and FMI ($p < 0.01$ for all variables). On the other hand, relative UCCS intake (g/kg body weight) was negatively associated with FM/kg ($rs = -0.4$, $p = 0.02$). A stronger correlation was observed between relative UCCS intake and total lean body mass in grams (LM/g; $rs = -0.7$; $p < 0.01$). Among the treatment adherence markers evaluated, only lactate correlated with FMI ($rs = 0.4$, $p = 0.04$). All body fat parameters of interest (FM%; FM/kg; Android fat; Gynoid fat; FMI) were higher in patients with GSD I than in those with GSD III or IXα/β/γ. **CONCLUSION:** Our data suggests that the treatment of hepatic GSDs with UCCS may be associated with a trend toward greater lean mass loss, making patients more susceptible to sarcopenia.

2539 - A NEW IMAGE-BASED HIGH THROUGHPUT SCREENING ASSAY DISCOVERS A POTENT LEAD COMPOUND FOR THE TREATMENT OF GLYCOGEN STORAGE DISORDERS

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INTRODUCTION: Glycogen Storage Disorders (GSDs) are a versatile group of 15 incurable diseases. GSDs are caused by intracellular accumulation of normal, or malconstructed insoluble glycogen called polyglucosan. Thus, any strategy curbing glycogen over-production or facilitating its degradation is expected to be curative for GSDs. **METHODS:** We have developed a high throughput image based screening assay for detecting molecules capable of lowering polyglucosans in skin fibroblasts from patients afflicted with the prototypical GSD Adult Polyglucosan Body Disease (APBD, Solmesky et al (2017) Biochem J 474:3403). Computationally determined Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET)-compatible molecules were then tested for safety by the Irwin test and for efficacy in APBD modeling (glycogen branching enzyme knocked in) mice by accepted behavioral tests. Histopathological efficacy (lowering of tissue polyglucosan) was determinized by Periodic Acid-Schiff reagent staining and in vivo metabolism by metabolic cages. **RESULTS:** Administered subcutaneously at up to 250 mg/kg, our selected compound (compound A) caused no adverse effect after either short (1 week), or long (3 months) term exposures. This includes lack of lesions and fibrosis in histopathological assays. Importantly, compound A has demonstrably improved animal survival and reduced polyglucosans in the liver, brain, peripheral nerve, and heart. This result is in line with the enhanced carbohydrate catabolism observed in vivo. In addition, locomotive and reflex parameters were ameliorated by compound A, when administered before disease onset. **CONCLUSIONS:** Our published results showing that compound A is a mild glycogen synthase inhibitor (Solmesky et al, see above) and our promising safety and efficacy results in the APBD mouse warrant testing the efficacy of compound A as a pan-GSD treatment, particularly in GSDIa and GSDII models. Especially encouraging are the ameliorating effects of the compound on liver histopathology and its enhancement of systemic carbohydrate catabolism. At the mechanistic level, current experiments aimed at discovering the intracellular targets of compound A will shed light on its mode of action and enable its potentiation and personalization.

2543 - STEAROYL-COA DESATURASE INDICES AND BODY COMPOSITION OF BRAZILIAN PATIENTS WITH GLYCOGEN STORAGE DISEASES

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INTRODUCTION: Stearoyl-CoA desaturase-1 (SCD-1) is key lipogenic enzyme that catalyzes the biosynthesis of monounsaturated fatty acids. In human observational studies, higher hepatic SCD-1 activity is associated with obesity, metabolic syndrome, insulin resistance and bone fractures, among others. Disturbed lipid metabolism and overweight are common features in patients with hepatic glycogen storage diseases (GSDs), but the role of SCD-1 has not been explored in this disease. Aim: To describe SCD-1 indices in patients with hepatic GSDs and to explore the association of SCD-1 indices with body composition. **METHODS:** Cross-sectional study. The sample included 14 patients with hepatic GSD (type Ia=11; type III=3; 50% male, median age: 9 years) and 16 healthy controls with similar age, BMI and gender. Body composition was evaluated by bioelectrical impedance. Blood samples were taken after a 12-h overnight fast to measure free fatty acids by GC-MS/MS. To estimate liver SCD-1 activity, SCD-16 [16:1(n−7)/16:0] and SCD-18 [18:1(n−9)/18:0] desaturation indices were determined. Differences between groups were evaluated by chi-squared and Mann-Whitney tests. Associations between body composition and SCD-1 indices were evaluated with Spearman's correlation coefficient. **RESULTS:** Patients had shorter stature than controls (median: 1.34 vs 1.56 m, p=0.012). According BMI, 64% of patients had excess weight (n=9) and regarding body composition, patients had higher body fat percentage (median: 27 vs 20%, p=0.039) and lower fat free mass than controls (median: 73 vs 80%, p=0.039). SCD-16 index was 5 times higher and SCD-18 index was 4 times higher in patients (p<0.001). SCD-1 indices, however, were not statistically associated with body fat percentage. **CONCLUSIONS:** Patients with GSDs presented higher body adiposity and increased SCD-1 activity. A high carbohydrate diet is known to increase hepatic SCD-1 expression resulting in increased biosynthesis of monounsaturated fatty acids as found in our patient cohort. Increased SCD-1 is associated with unfavorable metabolic outcomes and might be responsible for some clinical and biochemical features observed in GSDs.

2544 - LIVER METABOLIC ABNORMALITIES AND GENE EXPRESSION VARIANCE IN THE KETOTIC FORMS OF GLYCOGEN STORAGE DISEASES

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INTRODUCTION: Glycogenolysis in the liver requires activation of the phosphorylase kinase (PhK) which phosphorylates and activates the liver glycogen phosphorylase (PYGL) that converts glycogen into glucose-1-phosphate monomers. Deficiency of PYGL or PhK enzymes are associated with the pathogenesis of glycogen storage disease type VI (GSD-VI) and IX (GSDIX). GSD-VI and IX share similar features to other GSDs including hepatomegaly and glycogen accrual; however, both present with ketotic hypoglycemia during fasting. From a paucity of literature on GSD-VI and IX, there is a need to delineate the metabolic profile and long-term liver complications as a result of severe variability in enzyme activity. To characterize the metabolic abnormalities reported in pediatric patients of GSD-VI and -IXβ, we examined the physical features of the liver and gene expression profiles in mouse models of GSD-VI (Pygl-deficient mice) and GSD-IXβ (Phkb-deficient mice). **MATERIALS AND METHODS:** For fasting studies, serum biochemistry and histological analyses, young mice (4-8 weeks) were used. Mice were fasted for 0, 2, 4, 6, hours prior to glucose determination or sacrifice. Liver RNA was used to prepare cDNA for real-time PCR analysis. **RESULTS:** Young GSD-VI and IX mice revealed hepatomegaly, excessive hepatic glycogen accumulation and low free hepatic glucose. Both ketotic forms exhibited elevated ketone levels during a prolonged fast (2-6 hours) and mild hypoglycemia compared to wild-type mice. Histological studies confirmed extensive glycogen accumulation in hepatocytes of both GSD- VI and IX mice. Fasted GSD-VI and IX mice displayed lower serum levels of triglycerides, cholesterol, lactate, and uric acid (mg/dl) compared to wild-type mice. Gene expression analyses revealed early hepatic stress characterized by elevated pro-fibrotic and inflammatory related genes. Additionally, genes that regulate glycogenolysis and gluconeogenesis were found to be significantly different in GSD-VI and IX mice. **CONCLUSIONS:** GSD-VI and IX mice mimic the metabolic abnormalities reported in GSD-VI and IX patients. Gene expression data in GSD-VI and IX mice demonstrated significant metabolic changes in gluconeogenesis, fatty acid beta-oxidation and activation of genes linked with increased risk of fibrosis development. Future metabolic studies will focus on characterizing the complete metabolic profile as well as assess the long-term complications for improved patient care and disease management.

2569 - HEPATIC GLYCOGEN STORAGE DISEASE: DOES THE GENETIC DIAGNOSIS CONFIRM THE DIAGNOSIS BASED ON CLINICAL AND BIOCHEMICAL MANIFESTATIONS?

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INTRODUCTION: The hepatic glycogen storage disease (GSD) comprises a group of inborn errors of metabolism related to dysfunctions in glycogen metabolism. Each type of GSD is caused by the genetic deficiency of a specific enzyme involved in glycolysis or glycogenolysis. A large phenotypic diversity is observed in GSD, with the definitive diagnosis being a combination of clinical presentation, biochemical abnormalities, determination of enzymatic activity in the liver and molecular genetic analysis. Objective: To verify if the diagnosis of the type of GSD, based on the biochemical and clinical aspects, is corroborated by the genetic findings from the Next Generation Sequence (NGS) technique. **METHODS:** Based on 118 patients genetic tested to hepatic GSD by NGS technique, 43 patient records were assessed, and the diagnostic hypothesis proposed by the treating physician was compared with the result obtained in NGS genotyping. This data provides us a preview analysis of how the clinical and biochemical information is enough to confirm the diagnose. **RESULTS:** From the 43 patient records assessed, 4 were not confirmed as hepatic GSD through NGS, and 9 did not present diagnostic hypothesis. From the 30 (100%) records that present diagnostic hypothesis and the patients were confirmed as hepatic GSD through NGS, 6 (20%) the diagnostic hypothesis did not match the genetic test, 8 (27%) matched only the GSD type, and 16 (53%) matched type and subtype. **DISCUSSION:** GSDs are well-recognized diseases that can occurs without the full spectrum, and with overlapping in symptoms. Based on this analysis, for a better understanding of hepatic GSD phenotypes, the patient records will be given to physicians experts in GSD to establish the diagnosis of the type of hepatic GSD that affects each patient, based only on the clinical and biochemical manifestations of the disease. From the joint analysis of the response of the specialists, it will be evaluated the percentage of correspondence between the diagnoses established by the specialists, based on the clinical and biochemical findings, in comparison with NGS sequencing, and reviewed according the literature.

2789 - OROFACIAL MYOFUNCTIONAL ASPECTS AND FEEDING DIFFICULTIES IN HEPATIC GLYCOGEN STORAGE DISEASES

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INTRODUCTION: The prevalence of feeding difficulties and orofacial myofunctional disorders (OMD) in hepatic GSD is little known in literature. **OBJECTIVE:** To investigate feeding difficulties and OMD in hepatic GSD. **MATERIAL AND METHODS:** A cross-sectional, prospective, of 36 patients (19 males, 17 females; median age, 12.0 years; range, 8.0– 18.7 years) with diagnosis of hepatic GSD (type Ia, n=22; Ib, n=8; III, n=2; IXa, n=3; IXc, n=1). The evaluation included: a questionnaire for evaluation of feeding behavior, the orofacial myofunctional evaluation (AMIOFE), olfactory performance (Sniffin' Sticks test), taste perception (Taste Strips test). Feeding difficulty was determined in presence of this following three aspects: patient or family self-report, speech pathologist evaluation, and presence of one or more of the behavioral items or issues. **RESULTS:** Twenty-six patients (72.2%) had feeding difficulties, and 18 (50%) had OMD. Among patients with feeding difficulties, 23 (63.9%) reported selective intake, and 11 (30.6%) had fear of feeding. Three patients did not accept any oral diet because the progressive food refusal until the total exclusion of eating by mouth, and consequently necessity of tube-fed. The median orofacial myofunctional score was 87.5 (83.0–92.7). OMD was significantly associated with feeding difficulty, alternative feeding routes, food selectivity, preference for fluid and semisolid foods, and mealtime stress ($p<0.05$). Lower swallowing and chewing scores were associated with feeding difficulty ($p=0.001$ and $p=0.009$, respectively) and with specific issues related to eating behavior. Nine (25%) patients had decreased olfactory perception and four (11%) had decreased taste perception. Eight (22.2%) had decreased perception of sour taste. **CONCLUSION:** There is a high prevalence of feeding difficulties and OMD in hepatic GSD, with higher prevalence of selective intake and fear of feeding in comparison with non-GSD subjetcs. Eating behavior, decreased taste and smell perception, and orofacial myofunctional issues are associated with hepatic GSD.

ABSTRACTS SELECTED FOR POSTER PRESENTATION

2444 - WHOLE EXOME SEQUENCING FOR ASSESSMENT OF UNCLASSIFIED GLYCOGEN STORAGE DISEASES AND DISORDERS OF ENERGY METABOLISM

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INTRODUCTION: There are currently 16 types of glycogen storage disease (GSD), each of which is associated with an enzyme that requires a type-specified treatment regimen. Approximately 4% of the patients followed by our program have liver biopsy proven GSD but no identified genetic etiology. These patients present with hypoglycemia, hepatomegaly, metabolic acidosis and other phenotypic characteristics consistent with GSD, but targeted genetic testing has failed to elucidate any underlying genetic mutations. The purpose of this study is to investigate these patients using whole exome sequencing (WES) to identify specific genetic mistakes and classify new uncharacterized disorders of energy metabolism. **METHODS:** Study enrollment was conducted during inpatient visits at the Connecticut Children's GSD program. Patients and immediate family members were enrolled as part of the study protocol. The patient DNA sample was obtained from blood, and family member DNA samples were collected via saliva kits. DNA extraction from blood and saliva was done in the GSD Program laboratory at the University of Connecticut School of Medicine. The purified DNA from blood was de-identified and sent to Novogene, Co. for WES, and the results were filtered to only include deleterious and damaging variants. The damaging effect of each mutation was elucidated using the PolyPhen-2 database, and a list of metabolically relevant genetic defects was compiled. The DNA from the saliva samples will be used to assess the pathogenicity of identified mutations by WES. **RESULTS:** The WES data from two subjects have been analyzed. Subject one has 10,100 deleterious and/or damaging mutations and subject two has 10,224. According to PolyPhen-2, 238 mutations (69 homozygous, 169 heterozygous) for subject one and 247 mutations (75 homozygous, 168 heterozygous) for subject two are likely damaging. Based on these mutations, 157 metabolically relevant genes have been identified as potentially disease causative; 57 of which have mutations in both subjects. **CONCLUSION:** The shared, potentially damaging mutations found in the 57 genes likely contribute to the clinical symptomatology of the untyped GSD patient population. These genes provide an opportunity to better understand and treat patients with untyped GSD and other metabolically related disorders. Future studies on the DNA extracted from relatives will help clarify which of these genetic variations may be pathologic.

2468 - NATURAL HISTORY OF PAEDIATRIC PATIENTS WITH GLYCOGEN STORAGE DISEASE TYPE 1B IN ENGLAND: RESULTS OF A MULTI-SITE SURVEY

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INTRODUCTION: Glycogen storage disease type 1b (GSD1b) is caused by a defect in glucose-6- phosphate translocase (G6PT) and is characterized by hepatomegaly and fasting hypoglycaemia, as well as neutropaenia and frequent infections. The neutrophil dysfunction predisposes patients to severe infections and is reported to cause inflammatory bowel disease (IBD). There is widespread variation in the dietary and pharmacological management of GSD1b across the world, with some centres advocating liver transplantation as an option for severe fasting intolerance. The aim of this study was to classify the genotype, phenotype and management of paediatric patients with GSD1b across the United Kingdom. **METHODS:** A multi-site survey was distributed to all metabolic centres in the United Kingdom. We collected data retrospectively on patient genotype and a range of phenotypical features in 2 yearly intervals up to the age of 16 years. This included fasting tolerance and feeding regimens, growth parameters, biochemical data (neutrophil count, urate, cholesterol, triglyceride, lactate, erythrocyte sedimentation rate, urine protein: creatinine ratio) and the incidence of hepatic adenomas. We also recorded the incidence of gastrointestinal symptoms and the number of hospital admissions per year. All data was anonymised. **RESULTS:** Data was collected from 4 major metabolic centres in England. A total of 27 patients were included with 15 female patients and 12 male patients with a median age of 97 months. This represents almost the entire paediatric GSD1b cohort in the United Kingdom. Five patients were homozygous for the c.92_94delTCT mutation and four patients were homozygous or compound heterozygous for the c.1042_1043delCT

mutation. Most patients were homozygous for frame shift mutations. Most children had short stature (median height of 25th percentile at diagnosis and age 8 years) and with all having an elevated weight percentile relative to their height (median weight of 75th percentile at age 8 years). Most children had a persistent short fasting tolerance of less than 2 hours for much of their childhood. All patients had elevated urate, triglyceride and lactate levels at diagnosis. Seven patients had liver transplants and two patients had haematopoietic stem cell transplantation (HSCT). Neutropaenia was observed in 26 patients usually by the age of 2 years. Only 1 of the post-HSCT patients developed normal neutrophil levels. A number of patients reported gastrointestinal symptoms; however, none had a formal diagnosis of IBD made by a gastroenterologist. No patients received typical treatment for IBD, and an improvement in symptoms was often reported post an increase in the dose of granulocyte-colony stimulating factor. The number of infections recorded did not change post-liver transplant. **DISCUSSION:** The information obtained from this multi-site study shows that GSD1b is a severe disease with a short fasting tolerance that persists for most of early childhood. Patients who are homozygous for frame shift mutations tend to have a more severe phenotype. Liver transplantation is a valid option to improve fasting tolerance and quality of life, although it does not seem to improve neutropaenia or limit hospital admissions secondary to infection. A formal diagnosis of IBD was not observed in any of our cohort.

2474 - INTERVENTIONS AND OUTCOMES IN ADULT GSD III: A THREE CENTRE STUDY IN COLLABORATION WITH ASSOCIATION FOR GLYCOGEN STORAGE DISEASE (AGSD-UK)

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INTRODUCTION: Glycogen Storage Disease type III (GSD III) is a genetic metabolic disorder of glycogen. In adults un-metabolised glycogen accumulates in organs, primarily the liver (GSD IIIa and b), muscles (GSD IIIa) and heart. This cross-sectional study looks at clinical outcomes in a patient cohort from three UK adult metabolic centres, Salford (S, n=14), Birmingham (B, n=5) and London Guys and St. Thomas's Hospital (L, n=3) part of the AGSD-UK working group. **METHOD:** Data were retrospectively collected for all patients with GSD III seen in the last year at the three centres. Analysis focused on biomarkers of liver disease (AFP, ALT), radiological evidence of liver disease (MRI/USSA), evidence of muscle (creatine kinase, CK) and cardiac disease (ECHO) and hepatic interventions required in this cohort. Data are shown as median (range). **RESULTS:** 22 patients' data; 10 female (F) 12 male (M), age 29. 5 (17-56 yrs), were included. 16 patients had GSDIIIa and 6 GSDIIIb. All patients were diagnosed in early childhood except one milder phenotype diagnosed at age 5. Biochemical markers of the liver disease: AFP in 19/22 patients was 2.0 (1.1 to 9.0) KU/L and ALT 105, (30-229) 22/22. Hepatic imaging showed fatty infiltrate in 11/22 patients; 6/22 had single or multiple liver lesions, classified as adenoma in 5. Cirrhosis was observed in 4/22 patients. Four patients (1 F, 3 M, age 38.5 (33-50yrs)) required hepatic interventions. In this sub-cohort biomarker results were higher; AFP 7.4 (7.3-9.0,3/4), ALT 140 (88-226)U/L. One patient underwent liver transplant for cirrhosis age 31. Following multiple adenoma resection surgery one patient suffered severe postoperative complications. Liver adenoma ablation was performed in one patient who now has cirrhosis, currently listed for transplantation. One patient developed hepatocellular carcinoma age 31 with AFP > 300, had embolisation and sadly died age 33. In GSDIIIa patients CK was 3360 (169-5821). Cardiac data were available in 17/22 patients. One patient had required an implantable cardioverter defibrillator for arrhythmia. 8/17 patients had cardiac hypertrophy and mitral valve regurgitation was observed in 3/17 patients. **DISCUSSION:** Anecdotally hypoglycaemia seems to improve with age but life-threatening hepatic and cardiac complications emerge as the patients get older (21% in this cohort). This study highlights the need for ongoing holistic monitoring and intervention and guidelines in adults with GSDIII disease.

2475 - FREQUENCY OF RS2229611 SNP IN 3'UTR OF G6PC IN BRAZILIAN PATIENTS WITH GLYCOGENOSIS TYPE IA

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BACKGROUND: The rs2229611 (c.*23T>C) SNP located in the 3'UTR of the G6PC gene was suggested as a biomarker of glycogenosis type Ia (GSD Ia). Studies have demonstrated that this SNP is in linkage disequilibrium (LD) with common pathogenic variants in different ethnicities. Besides that, it was evidenced that the rs2229611 affects the mRNA stability of G6PC, and this can be associated with the GSD Ia severity. So, this study verified the frequency of the rs2229611 in Brazilian patients with GSD Ia. **METHODOLOGY:** Fifty unrelated Brazilian patients with a genetic diagnosis of GSD Ia were included in this study. These patients were analyzed by next-generation sequencing (NGS) in Ion Torrent PGM platform

with a panel of genes involved in hepatic GSDs, including G6PC gene. The Enlis software was used to analyze the dataset. The linkage disequilibrium between pathogenic variants and the rs2229611 SNP was evaluated by calculation of the D' and R2 parameters for variants present in more than five alleles. **RESULTS:** The genetic analyses evidenced that the rs2229611 is present in 93% of the patients with GSD Ia. Seventeen pathogenic variants were identified and the c.247C>T (p.Arg83Cys) allele is the most frequent (38%) in the Brazilian patients. The LD analysis indicated that the c.247C>T allele is present in two haplotypes in the Brazilian population, one in LD with the rs2229611 (D'=0.73; R2=0.029) and another linked with the ancestral allele (T) in this position. **DISCUSSION AND CONCLUSION:** The data reinforce the previous findings that showed the higher frequency of the rs2229611 SNP in patients with GSD Ia, when compared with healthy individuals. In gnomAD database the frequency of rs2229611 is 71.15%. However, the frequency observed in this study is higher than the observed in other ethnicities as Indian (71%), Czech and Slovac (80%). Besides that, is the first time that the c.247C>T pathogenic variant is evidenced linked with the ancestral allele. So, this study indicates that the rs2229611 SNP associated with other clinical findings can be used as a biomarker of GSD Ia in Brazilian patients with clinical suspicion of GSD Ia in cases that no was founded two pathogenic alleles in the G6PC.

2479 - CRISPR/CAS9-MEDIATED EDITING OF HEPATIC G6PC IN MICE ALLOWS TO INVESTIGATE THE CLINICAL SPECTRUM OF GLYCOGEN STORAGE DISEASE TYPE IA

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INTRODUCTION: Glycogen storage disease type 1 (GSD Ia) is an inborn error of metabolism caused by a defect in glucose-6-phosphatase (G6PC) activity and primarily results in fasting hypoglycemia. Evidence is accumulating that glycemic control in GSD Ia patients affects the risk of long-term complications such as liver tumor development. Moreover, large heterogeneity in biochemical symptoms is observed between individual patients. Because the available mouse models do not cover the spectrum of disease phenotypes in GSD Ia patients, we used CRISPR/Cas9 gene editing technology to generate hepatocyte-specific GSD Ia mice with variable G6PC activities in the liver. **MATERIALS AND METHODS:** Male hepatocyte-specific Cas9-expressing mice (ROSA26-LSLCas9 knock-in mice x Alb-Cre mice) were injected with either high (H, 1.0x1011 particles), middle (M, 0.5x1011 particles), or low (L, 0.1x1011 particles) titers of adenovirus particles containing three sgRNAs targeting G6pc exon 1 in comparison to mice administered control adenovirus (empty vector, 1.0x1011 particles). Animals were sacrificed 4 weeks after virus injection for organ and blood collection. **RESULTS:** sgRNA-G6pc injection in Cas9-expressing mice led to dose-dependent reductions in hepatic G6PC expression, residual G6Pase activities (H: 2%, M: 5%, L: 50%), and fasting blood glucose levels. Furthermore, it resulted in a dose-dependent increase in hepatomegaly and hepatocyte vacuolation, hepatic glycogen, glucose-6-phosphate, and lipid contents, as well as plasma triglyceride levels. **DISCUSSION:** CRISPR/Cas9-mediated inactivation of hepatic G6pc elicits the biochemical symptoms of GSD Ia in a dose-dependent fashion. Hence, this novel approach can be employed to induce a spectrum of disease phenotypes, thereby enabling mechanistic investigation of the relationship between glycemic control and long-term complications in GSD Ia. Moreover, this system allows to systematically evaluate gene-gene interactions in the pathophysiology of GSD Ia.

2481 - DISEASE BURDEN AND UNMET NEEDS IN POMPE DISEASE: RESULTS FROM A PATIENT SURVEY IN THE UNITED KINGDOM

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INTRODUCTION: Pompe disease is a rare autosomal recessive lysosomal disease caused by a deficiency of acid alpha-glucosidase, which presents with progressive muscle weakness and respiratory insufficiency. Without treatment, disease progression leads to increased morbidity and mortality. A survey was conducted to understand disease burden, unmet treatment needs, as well as expectations of new therapeutic options, from individuals living with Pompe disease.

METHODS: Adult members of the Association for Glycogen Storage Disease (AGSD)-UK were invited to complete a new 88-question online survey to collect data on demographics, treatment, symptoms, and activities of daily living. Participants had to be receiving enzyme replacement therapy (ERT) for Pompe disease. **RESULTS:** Survey completion rate was 92%. Mean age (n=25) was 51.6 years (range, 25-81); mean age at diagnosis was 36.8 years (range, 2-60). The average duration of ERT treatment was 8.7 years. Respondents reported significant impairment of motor and respiratory functions: 86% required walking assistance and 62% required a ventilator. Most reported difficulty with employment (84%), social (65%), and household (90%) activities. Progressive decline occurred despite ERT (mean age at initiation, 42.4 years): >40% of patients reported some functional decline. **CONCLUSIONS:** Pompe disease places great burden on physical and social aspects of patients' lives. Despite the availability of ERT, significant unmet medical needs remain.

2541 - CLINICAL AND MOLECULAR CHARACTERISTICS OF FRUCTOSE 1,6 BISPHOSPHATASE DEFICIENCY (FBP1D) PATIENTS IN ISRAEL

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BACKGROUND: FBP1D is a rare autosomal recessive inborn error of carbohydrate metabolism caused by mutations in FBP1 gene which affect the process of gluconeogenesis .Patients present with ketotic hypoglycemia and lactic acidosis triggered by catabolic events and excessive fructose ingestion. **METHODS:** Clinical and molecular data of 18 patients from Israel was retrospectively collected. **RESULTS:** The cohort included 11 males and 7 females. Most of the patients presented in the first year of life (14/18), one third of the patient presented during the neonatal period (6/18). The main presenting features were: hypoglycemia (18/18), lactic acidosis (14/18),elevated transaminases (12/18) and hepatomegaly (6/18). The average number of metabolic crises was one in a year. Ten patients (55%) were admitted to the intensive care unit (ICU) during metabolic crisis at least once during their life. Most of the ICU admissions were during the first year of life. All of the patients are currently alive (current ages 3-31 years) and have normal development. Molecular diagnosis was performed in 13 of the patients (11 homozygous, 2 compound heterozygous), two mutations were novel (c.706- 1G>A, 690_705+11del). The remaining five patients were diagnosed based on their clinical and biochemical features. **DISCUSSION:** Our Israeli FBP1D cohort highlights the typical features of the disorder including hypoglycemia, lactic acidosis and, elevated transaminases. This disorder of carbohydrate metabolism can be life threatening especially during the first year of life but disease course thereafter is relatively benign. It is crucial to consider FBP1D diagnosis in every patient presenting with ketotic hypoglycemia and lactic acidosis and to accomplish definitive molecular diagnosis.

2545 - FIBROBLAST GROWTH FACTOR 21 (FGF21) IS A NOVEL SENSITIVE BIOMARKER FOR THE DIAGNOSIS AND CONTROL OF HEPATIC GLYCOGENOSES

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BACKGROUND: Fibroblast growth factor 21 (FGF21) is a growth factor with regulatory effects on glucose and lipid metabolism. Previous studies have shown that elevated serum FGF21 levels can serve as a diagnostic biomarker for various mitochondrial diseases. Recently, serum FGF21 was associated with long term complications in organic acidemias. **OBJECTIVE:** To study the utility of serum FGF21 levels as a biomarker in patients with confirmed diagnosis hepatic glycogenoses **METHODS:** FGF21 serum levels were assayed by ELISA kit in patients with various hepatic glycogen storage diseases (GSD). Three separate samples (random, fasting and postprandial) were obtained in each patient and were compared with normal controls. Fasting and postprandial levels were compared in each individual. **RESULTS:** The cohort included 11 patients with various hepatic GSDs as follows: two patients with GSD1a, one patient with GSD1b, 4 patients with GSD3, one patient with GSD6 and one patient with GSD9b. Serum FGF21 were significantly elevated at all three conditions compared to normal levels; random samples 564±720pg/ml (normal level 0-250pg/ml, $p<0.001$), fasting sample 1446±1755pg/ml (normal level 0-250pg/ml, $p<0.001$), post prandial samples 759±509pg/ml (normal level 0-250pg/ml, $p<0.001$). In the same individual serum FGF21 levels were significantly higher during fasting compared with postprandial condition ($Z=-2.52$, $p<0.04$) **DISCUSSION:** Our results suggest serum FGF21 can serve as a reliable biomarker for the diagnosis of hepatic GSD. We demonstrate that its levels are dependent on fasting/satiation state. Future studies are needed to confirm its role in better metabolic control of GSD patients.

2554 - LIVER TRANSPLANT FOR GLYCOGEN STORAGE DISEASE TYPE IIIA: A CASE REPORT

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INTRODUCTION: Glycogen Storage Disease (GSD) type III is related to glycogen debranching deficiency. The most frequent type is IIIa, which has manifestations of distinct predominance in childhood (ketosis, dyslipidemia and hepatomegaly) and adulthood (muscular disease and cardiomyopathy). A hyperproteic, sucrose-free diet, and the use of uncooked cornstarch, are the basis of the treatment. **CASE REPORT:** A 42y old Brazilian man was referred to the Genetics Service at 37y10m due to cirrhosis secondary to probable unconfirmed GSD. The patient's family reported that by six months of age he had hepatomegaly and at 1y7m liver biopsy was compatible with GSD. Since then, he follows a diet of frequent food intake and using large amounts of sucrose. At 34y of age, he was hospitalized due to hematochezia and diagnosed as having ulcerative colitis and cirrhosis. In the first consultation at the Genetics Clinics, he presented jaundice, weakness, muscular hypotrophy, increased erythrocyte glycogen and CPK 714U/L. Exome sequencing was requested, which showed two pathogenic mutations in the AGL gene (c.3980G>A/c.2728C>T) compatible with GSD III. A high protein diet with regular use of cornstarch (6/6h) was prescribed. Due to the cirrhotic condition, he underwent liver transplantation at 38y10m, with early biliary stenosis. After transplantation, free diet and protein supplementation were introduced, with low adherence. He presented two episodes of acute rejection with good response to immunosuppression and subsequent remission of inflammatory bowel disease (IBD). Left atrial dilatation was identified 43 months after transplantation. The patient has presented progressive reduction of muscle strength and trophism; progressive increase of CPK (R^2=0.298) and fasting glycemia (R^2=0.293), maintaining normoglycemia even during acute rejection. **CONCLUSIONS:** The present case report reinforces that liver transplant could be considered as a therapeutic option only for selected cases in GSD III. This procedure may prevent hypoglycemia in GSD IIIa, but skeletal and cardiac muscle diseases seem to remain in progress, requiring nutritional and clinical monitoring after transplant. Ulcerative colitis was associated to GSD Ib, but it is not a condition usually observed in type III, and it is estimated that immunosuppression may have contributed to the control of IBD. This case emphasizes the importance of the multidisciplinary collaboration in the treatment of hereditary metabolic diseases.

2556 - HEPATIC NON-GSD-IB: IS THE IMMUNE SYSTEM CHALLENGED BY THE METABOLIC DEFECT?

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INTRODUCTION: Cytokines are soluble factors that mediate several fundamental biological processes, including body growth, adiposity, hematopoiesis, inflammation, and immunity. In this study, we evaluated the cytokine profiling of hepatic non-GSD-Ib patients compared to healthy controls. **METHODS:** Observational, cross-sectional, and controlled study approved by the local IRB. All participants/legal guardians signed an informed consent. Twenty-one genetic-diagnosed GSD patients on UCCS treatment [Ia=16, III=2, IX=3; median age= 13 (IQR=20.7-10.5); male=11] and 24 unrelated healthy controls [median age= 12 (IQR=21.0- 9.25); male=11] were sampled by convenience. Inclusion criteria were: (i) ≥3 years of age; (ii) no signs of infection; (iii) not being vaccinated in the 15 days prior to sample collection; (iv) no use of antibiotics; (v) not designated to receive or received organ transplant. Twenty cytokines (GCSF, GM-CSF, IFNy, GRO, IL-10, MDC, IL-13, IL-17A, IL-1α, IL-1β, IL-4, IL-6, IL8, IP10, MCP-1, MIP1α, MIP-1β, TNFα, TNFβ e VEGF) were quantified in blood through a multiplex assay kit. Data were analyzed using the MILLIPLEX® Analyst 5.1 Software (Millipore Sigma). Duplicates with divergence ≥ 30% between measurements were excluded from the analysis. Statistical analysis was done using the Mann-Whitney U test. **Results:** Affected individuals had reduced levels of IL-4 [patient= 0.16 pg/ml (0.09-1.79); control= 0.58 pg/ml (0.22-12.86); p=0.040], MIP-1α [patient=1.38 pg/ml (0.88-8.14); control=11.05 pg/ml (4.27- 36.30); p=0.003], MDC [patient= 397.49 pg/ml (335.46-520.92); control= 686.91 pg/ml (534.27-894.43); p<0.001], TNF-β [patient= 0.00(0.00-0.94); control= 0.65 pg/ml (0.01- 45.47); p=0.045] and VEGF [patient= 1.17 pg/ml (0.55-172.96); control=145.33 pg/ml (5.54- 272.17); p=0.043]. **DISCUSSION/CONCLUSION:** IL-4 is a key regulator in humoral and adaptive immunity, while MDC plays role in the amplification loop of polarized type-II responses. MIP1α has pro-inflammatory activities, and can negatively regulate the proliferation of hematopoietic

stem/progenitor cells. TNF-β has been shown to play an essential role as an anti-inflammatory cytokine. VEGF is linked to several biological effects in healthy and disease main due its angiogenic activity. Altogether, low levels of these cytokines in patients may reflect an imbalance in the immune system regulation with possible long-term implications such as HCA, predisposition to infections, and chronic anemia.

2558 - PRECLINICAL DEVELOPMENT OF SPK-3006, AN INVESTIGATIONAL LIVER-DIRECTED AAV GENE THERAPY FOR THE TREATMENT OF POMPE DISEASE

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INTRODUCTION: Pompe disease is a lysosomal storage disease caused by loss-of-function mutations in the acid alpha-glucosidase (GAA) gene, which lead to significant accumulation of glycogen in many tissues resulting in multi-system pathology. Enzyme replacement therapy (ERT) increases survival, slows disease progression, and is the current standard of care for Pompe disease patients. However, ERT has several potential drawbacks such as limited biodistribution and insufficient uptake in certain affected tissues, immunogenicity of recombinant GAA, and high treatment burden. We have shown that investigational liver-directed adenoassociated viral (AAV) gene therapy expressing a novel secretable GAA transgene results in decreased glycogen accumulation, increased survival, and improvement of cardiac, respiratory, and muscle phenotypes in the Gaa-/- mouse model of Pompe disease. Here we provide additional updates on preclinical development of an investigational liver-directed AAV gene therapy for Pompe disease. **MATERIALS AND METHODS:** In an effort toward clinical translation we further optimized the expression cassette and selected a highly hepatotropic capsid. The clinical candidate, SPK3006, was tested in non-human primates at three doses. Additional in vitro and in vivo studies are ongoing to further characterize SPK-3006 and to determine the biochemical properties of the transgene-derived protein product following liver expression of secretable GAA. **RESULTS:** Secretable GAA vectors demonstrated greater efficacy in restoring Gaa-/- mouse muscle strength when compared to the standard-of-care regimen of biweekly 20 mg/kg ERT. In non-human primates, a single infusion of investigational SPK-3006 demonstrated dose-dependent expression of GAA in plasma with no associated adverse histopathological findings and no significant changes in clinical pathology parameters. **CONCLUSIONS:** These studies demonstrate the potential of an investigational liver-directed gene therapy approach with secretable GAA and support initiation of clinical studies utilizing SPK-3006.

2560 - HEPCIDIN, INTERLEUKIN-6 LEVELS AND IRON METABOLISM PARAMETERS IN PATIENTS WITH HEPATIC GLYCOGEN STORAGE DISEASES

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INTRODUCTION: Hepatic glycogen storage diseases (GSD) are genetic diseases characterized by recurrent episodes of hypoglycemia and anemia has been recognized as a frequent complication of these disorders. Hepcidin is a hormone produced by the liver which is a key regulator of iron homeostasis; it has been linked to hepatic adenomas in GSD and also anemia of chronic disease. **OBJECTIVE:** To evaluate hepcidin and IL-6 concentrations in patients with

hepatic GSD and their association with anemia and other parameters of iron metabolism. **METHODS:** This was a cross-sectional study with a convenience sampling strategy. Levels of hepcidin, IL-6, and markers of iron metabolism (hemoglobin, iron, ferritin, transferrin, and transferrin saturation) were measured in 32 patients receiving uncooked cornstarch therapy (GSD Ia= 18; GSD Ib= 7; GSD III= 3; GSD IXa= 3; GSD IXb= 1; median age 9.5 years). Additional data were obtained by means of a chart review. Nonparametric methods were used for data analysis. **RESULTS:** Nine patients (GSD Ia= 3/17; GSD Ib= 6/7) were anemic (mild= 4; moderate= 5). Five of 32 had inflammatory bowel disease (all with GSD Ib) and 5/28 patients had hepatic adenomas (all with GSD Ia). Eight patients had hyperferritinemia, and one had elevated transferrin saturation as well. Hepcidin correlated positively with ferritin levels (r=0.375; p=0.034). IL-6 correlated with hemoglobin (r=-0.572; p=0.001), iron (r=-0.538; p=0.001), transferrin (r=-0.550; p=0.001), and transferrin saturation (r=-0.425; p=0.015). There was no correlation between hepcidin and IL-6 levels (p=0.057). Patients with GSD Ib had the highest IL-6 levels. There was no difference between patients with and without anemia (p=0.182), and with and without liver adenoma (p=0.453), regarding hepcidin levels. **CONCLUSIONS:** Anemia is a common finding in hepatic GSD, especially in GSD Ib, the type of GSD associated with the highest IL-6 levels. These findings suggest that inflammation is strongly associated with development of anemia in hepatic GSD, particularly in GSD Ib. It is important to emphasize the need to regularly monitored patients with hepatic GSD are in relation to this complication.

2561 - THE COEXISTENCE OF GLYCOGEN STORAGE DISEASE TYPE 0 AND LIMB-GIRDLE MUSCULAR DYSTROPHY IN A PATIENT

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INTRODUCTION: Glycogenosis Storage Disease Type 0 (GSD0) is an autosomal recessive glycogen synthase 2 (GYS2) deficiency characterized by episodes of recurrent hypoglycemia. It is considered a rare disease, with less than 30 reported cases worldwide. Another atypical disease, with few cases reported, is autosomal recessive type 2 limb-girdle muscular dystrophy (LGMD2E), caused by a rare mutation in the beta-sarcoglycan gene (SGCB), which leads to progressive muscle weakness of the pelvic and scapular girdles and in advanced stages, cardiomyopathy and scoliosis. **CASE REPORT:** Child, female, 13 years old, born at 37 weeks of gestation and adopted at 14 days of age, with no available information about her affiliation. During lactation, the mother noticed slow sucking with choking episodes and deep sweating, and an extensive investigation was initiated in her first two years due to recurrent hypoglycemia, associated with delayed neuropsychomotor development, weight-to-height deficit, weakness and tiredness. However, no cause was found. At the age of nine, she resumed molecular investigation, which identified deletion of exon 5 from the GYS2 gene, located on chromosome 12p12.1, compatible with GSD0. However, the persistent finding of very high creatine phosphokinase justified further investigation. At 11 years of age, the child complained of persistent headache, and examination also revealed myopathic gait and static inspection with alterations. Exome sequencing was performed, which identified a pathogenic variant in homozygous gene SGCB, indicating LGMD2E muscular dystrophy. Results: We found two rare diseases never described concurrently in the literature. The girl has not adapted to the usual diet for GSD0 but has not manifested hypoglycemia for over a year. It has food selectivity and consumes the same family food associated with the use of a pediatric polymeric diet and frequent intake of pure cassava flour. Currently, she does not use medication, but supplements vitamin D and does night glycemic control. **DISCUSSION:** In such a peculiar case, the hypothesis of parental consanguinity is raised as a possible etiology. The simultaneity of two rare diseases is a challenge to the therapeutic proposal, mainly because there is no other identical case described, and few reported cases of individuals with one of these diseases. In addition, given the difficulty in adhering to the diet, it is possible for the patient to change on their own the indicated therapy.

2562 - INFLAMMATORY BOWEL DISEASE IN NON-IB HEPATIC GLYCOGEN STORAGE DISEASES: A CASE SERIES

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INTRODUCTION: Glycogen storage disease (GSD) type Ib has been classically associated with inflammatory bowel disease (IBD), however few is known about IBD in other GSDs besides some reports in GSD 1a. This study aims to describe a series of IBD among cases of non-Ib genetically diagnosed GSDs. **METHODS:** Observational retrospective case series study, based on review of medical records of cases

followed in one outpatient metabolic clinic from Southern Brazil. The inclusion criteria were having clinical and molecular diagnosis of non-Ib GSD, performed after signature of consent term. **RESULTS:** Four non-Ib cases of IBD were identified among 50 cases followed in this center (2 females, mean age 18 years, range: 7 to 43). Mean age at GSD diagnosis was 1.93 years (range: 0.5-5). Molecularly defined GSD types were Ia (n=2); III (n=1) and IXc (n=1). Mean age of onset of GSD treatment was 10.89 years (range: 0.5 to 38.5). First symptoms of IBD were hematochezia (3/4) and diarrhea associated to abdominal pain (1/4). Mean age at the diagnosis of IBD was 14,5 years (range: 4,4 to 34). Three out of four patients used cornstarch (mean dose 6,5±0,33 g/kg/day) and two received high-protein diet (GSD-III and IXc). All individuals underwent specific treatment for IBD: mesalamine (3/4); azathioprine (2/4); infliximab (1/4); and adalimumab (1/4). Two patients used oral glucocorticoid, which had been gradually suspended in both cases in order to obtain better metabolic control. Two subjects had transitory mesalamine-associated hepatitis. All subjects had colonoscopies compatible with colitis. Gastric biopsy revealed mild gastritis (n=1) and eosinophilic esophagitis (n=1). Elevations of erythrocyte sedimentation rate (4/4) and C-reactive protein (2/4) were observed. In three cases the possibility of GDS1b diagnosis was clinically considered before genetic confirmation. An adult male individual with untreated GSD type III, cirrhosis and IBD underwent liver transplantation at 38y10m. Transplant related immunosuppression was instituted with subsequent remission of IBD. **CONCLUSIONS:** This is the first series to report cases of IBD in GSD type III and IXc. The report of IBD in new GSD subtypes may provide new hypothesis on the physiopathology of GSDs-related IBD. This series also highlights the importance of molecular diagnosis for the definition of the GSD subtype and to consider the possibility of IBD in non 1b cases in front of suggestive manifestations.

2563 - HEPATIC GLYCOGEN STORAGE DISEASES: ANTHROPOMETRIC CHARACTERIZATION AT BIRTH AND AT THE BEGINNING OF TREATMENT

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INTRODUCTION: Glycogen storage diseases (GSD) are a group of inherited disorders of glycogen metabolism with abnormal concentration and/or structure of glycogen in different tissues. Disorders of glycogen metabolism may affect the liver and/or muscles. Hypoglycaemia, hepatomegaly, hyperlipidemia, and growth retardation are the main findings in hepatic GSDs. The most common types with hepatic involvement are GSD I, III and IX. **METHODS:** Retrospective observational study. Perinatal and first consultation data were collected from patients followed in an outpatient metabolic clinic from Southern Brazil. Individuals with clinical and molecular diagnosis of hepatic GSDs were included. **RESULTS:** Forty-four subjects met criteria for inclusion in this study (16 F; GSD type Ia [n=23], Ib [6], III [7], IXa [6], IXb [1] and IXc [1]). Regarding delivery, 23 (52%) were cesarean and 11 (25%) normal deliveries; 34 individuals (77.5%) were born at term and 2 (4.5%) were premature (32 and 35 weeks). One newborn was small for gestational age. Mean birth weight was 3.47kg (± 0.57; 2.07 to 4.75kg) and mean length was 48.9cm (± 2.7; 41 to 53cm). Mean height Z-score for age at birth was -0.07 (± 1.44; -4.37 to 2.72) and mean BMI Z-score for age was 0.66 (± 1.12; -1.61 to 2.12). Median age of the clinical diagnosis of GSD was 0.79 years (mean: 1.5 years ± 1.6; range: 0.083 to 7). GSD type I (a+b) diagnosis was achieved earlier when compared to ketotic GSDs (Mann Whitney, $p<0.018$). Follow-up at the referral center started at mean age 9.8 years (± 10.6; range: 0.88 to 5.6). Mean height Z-score for age at the first visit was -1.88 (± 1.64; range: -5.76 to 2.24) and mean BMI for age Z-score was 1.52 (± 1.37; range:-0.83 to 5.88). **CONCLUSION:** This is the first series to study perinatal characterization in hepatic GSDs. GSD individuals presented adequate weight and height at birth. In the course of the disease, even before treatment introduction, growth deficit, overweight and obesity were observed. GSD type I was diagnosed earlier. Further studies are warranted aiming for better knowledge on carbohydrate treatment and hormone balance. GSD type I was diagnosed earlier when compared to the other types in this sample, but there was still a large time gap between diagnosis and referral to outpatient reference metabolic clinic to start the best management.

2565 - FANCONI BICKEL SYNDROME. FIRST CASE REPORTED IN URUGUAY.

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INTRODUCTION: Fanconi-Bickel syndrome (FBS) is a rare clinical entity inherited in an autosomal recessive mode and characterized by hepatorenal glycogen accumulation,

proximal renal tubular dysfunction, and impaired utilization of glucose and galactose. It is caused by defects in the facilitative glucose transporter 2 (GLUT2), which transports glucose in and out of the hepatocytes, pancreaticβcells, and the basolateral membranes of the interstitial and renal epithelial cells. The affected child presents in the 1st year of life with failure to thrive, rickets, hepatomegaly, hypoglycemia and tubular nephropathy. Treatment is symptomatic replacement of water, glucose, electrolytes, vitamin D, and restriction of galactose. Is our aim, to present our first case of FBS. **CLINICAL CASE:** female patient, 5 months of age. She is product of the first pregnancy of healthy non consanguineous couple. She presented with hypoglycemia and metabolic acidosis with elevated lactic acid when she was 18 hours old. Laboratory workup showed: mild elevated liver enzyme and alkaline phosphatase, low serum phosphate, acidosis, urine glucose and protein elevated, generalized aminoaciduria. Normal anion gap. Hepatomegaly and polyuria were evident. Genetic analysis confirms the diagnosis of FBS. She is treated with replacement of water, electrolytes, calcitriol, sodium phosphate, galactose free diet, bicarbonate solution, glucose and frequent small meals. At 4 months of age, intermittent colestasis was evident that is constant at present. **CONCLUSIONS:** According to our knowledge, few cases of FBS have been reported in the neonatal period as our case. Establishing the diagnosis is important for performing adequate genetic counseling and to prevent metabolic complications such as rickets by the initiation of a proper diet and supplements.

2566 - BONE MINERAL DENSITY AND BONE TURNOVER MARKERS IN PATIENTS WITH HEPATIC GLYCOGEN STORAGE DISEASES

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INTRODUCTION: Reduced bone mineral density (BMD) has been described in patients with hepatic Glycogen Storage Disease (GSDs). Although its mechanisms are not well understood, these patients are at risk of developing osteoporosis. Fractures are directly linked to osteoporosis/osteopenia, but currently there is no clear evidence that fractures are more frequent in GSD patients. Bone turnover markers are a series of biomarkers released during bone remodeling that respond rapidly to changes in bone physiology, and have been employed to estimate fracture risk and monitoring the adherence and response to therapy in patients with osteoporosis. Aim**:** To evaluate bone turnover markers in patients with GSDs on treatment and to verify their association with BMD. **METHODS:** 25 patients with GSDs on uncooked cornstarch treatment at Hospital de Clínicas de Porto Alegre, Brazil, were recruited and agreed to participate of the study. In the same date, bone mineral density was assessed by dual X-ray absorptiometry (DXA) and blood samples were collected to assess bone turnover markers in plasma. Carboxy-terminal collagen crosslinks (CTX), Procollagen type 1 amino-terminal propeptide (P1NP) and Osteocalcin (OC) were measured through an electrochemiluminescence assay. Two patients were not able to perform DXA and had only clinical and biochemical measurements available. **RESULTS:** Out of the 25 patients, 19 (76%) had type I GSD, 14 type Ia and 5 Ib, 3 (12%) type III and 3 (12%) type IX. Mean age was 15$\pm$7.9 years, and 52% of patients were female. Median BMD Z-score for lumbar spine was -0.60 (range= -2.3 to +1.1) and for whole body was -0.20 (range: -2.1 to +1.6). Regarding bone turnover markers, 32% of patients had all three markers increased. P1NP was inversely correlated with whole-body BMD Z-score (r -0.593; p=0.03). Patients with GSDs type III and IX had higher CTX (mean=1.83$\pm$0.4) than patients with type I (mean=1.37$\pm$0.5) (p=0.026). All patients (n=3) that had lumbar spine BMD Z-scores lower than -2 had all bone turnover markers increased. One patient (4% of the sample) had history of a non-pathological fracture. He presented normal BMD and increased bone turnover markers, and was on calcium supplementation for about 3 years. **CONCLUSIONS:** Our results showed that bone turnover markers were increased in a great number of GSDs patients and were associated with reduced BMD, suggesting a role for these biomarkers in monitoring bone disease in hepatic GSDs.

2567 - PSEUDODEFICIENCY IN GLYCOGEN STORAGE DISEASE TYPE II: THE NEED OF ALLELE FREQUENCY STUDIES IN BRAZILIAN POPULATION

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INTRODUCTION: Glycogen Storage Disease type II, or Pompe disease (PD) is caused by mutations in the GAA gene that encodes for the lysosomal enzyme α-glucosidase (GAA), and, when deficient, leads to accumulation of lysosomal glycogen especially in cardiac and skeletal muscle. There are two phenotypes associated with Pompe disease, the classical infantile form (IOPD) and later form (LOPD). To date, over 580 distinct pathogenic variations in GAA gene have been identified. Furthermore, the so-called pseudodeficiency allele p.[Gly576Ser; Glu869Lys] (c.[1726G>A; 2065G>A]), complicates the diagnosis as it causes reduction of GAA activity, which could be as low as observed in affected patients, but does not lead to the development of the disease. Frequency of this allele can by quite high in some populations (3.9% in Japan and 3.3% in Taiwan) and lower in others (less than 1% of newborns in USA). There is no data on pseudodeficiency frequency for the Brazilian populations. Distinguish Pompe-affected individuals from those bearing pseudodeficiency alleles is only reached by molecular analysis. Objective: To investigate two individuals with GAA activity values close to found in PD affected patients. **MATERIALS AND METHODS**: 1) A four day-old boy with altered newborn screening results for PD was referred to our Service for further investigation. 2) A mother of a PD patient was studied as part of diagnosis algorithm. **RESULTS**: For the first case, GAA activity in leukocytes was 0.96 ± 0.03 nmol/h/mg protein [RV:1-7.6], molecular genetic studies revealed the presence of a pathogenic variant, c.-32-13T>G, and p.[Gly576Ser; Glu689Lys], both in heterozygous state. For the second case, biochemical results showed a low enzyme activity in leukocytes, 0.82 ± 0.32 nmol/h/mg protein. Molecular analysis revealed that she was a compound heterozygote for pathogenic variant p.Gly576Asp and p.[Gly576Ser; Glu869Lys]. **CONCLUSION**: Our findings, along with the previous results of a homozygous individual for the pseudodeficiency allele, reported by another Brazilian group, suggest that, indeed, this allele is present in our population and its frequency must be determined. This also reinforces the need of a comprehensive investigation protocol, including further biochemical and genetic analysis in order to provide an accurate diagnosis and to enable the prompt start of therapy in confirmed cases as the enzyme replacement therapy is available in many countries, including Brazil.

2568 - A RETROSPECTIVE COHORT STUDY ON B12 LEVELS IN HEPATIC GLYCOGEN STORAGE DISEASES

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INTRODUCTION: Dietary restrictions imposed by the treatment of hepatic Glycogen Storage Diseases (GSD) and the use of uncooked cornstarch (UCCS) as a carbohydrate source may lead to nutritional deficiencies. There are case reports of severe B-complex vitamin deficiencies in GSD patients. This study aims to evaluate the vitamin B12 levels presented by individuals with hepatic GSDs and its association with GSD subtypes and treatment variables. **METHODS**: Retrospective, longitudinal, observational study of patients with clinical and molecular diagnosis of hepatic GSDs followed in one outpatient metabolic clinic at Southern Brazil, from November 2010 to May 2019. Vitamin B12 measurements were processed in a single laboratory using electrochemiluminescence (upper limit of detection: 2000pg/dL). **RESULTS:** Forty individuals were included (42.5% female; mean age 15.6 years [±10,5]), with genetically confirmed GSD: 52.5% type Ia; 15% Ib; 15% IXa; 12.5% III; 2.5% IXb; 2.5% IXc. All patients were under use of UCCS and no individual was vegetarian. From one to 26 B12 dosages were performed per patient, with a total 225 dosages (mean: 668.9pg/dL ±516.1). Mean follow-up time was 3.97 years (±1.75; range: 0.33 to 8.42). Mean B12 levels in GSD Type Ia: 622.3 (±482.3), Ib: 1110.2 (±626.78), III: 608.8 (±241.32), IX: 555.5 (±399.3). GSD 1b group had significantly higher B12 levels ($p<0.01$). B12 levels below 400pg/ml were detected in 20 (50%) individuals and below 200pg/ml in 3 individuals. Nine participants received intramuscular replacement (hydroxycobalamin, 5000UI, weekly to monthly). GSD 1b group had significantly higher B12 levels ($p<0.01$). No individual diagnosed with GSD Ib used injectable B12. Oral supplements of polyvitamins including B12 (mean dose: 1.55mcg/day ±1.43) were used by 30 participants (75%). Three subjects received concomitant supplementation and replacement. **CONCLUSION:** Patients with GSD Ib had significantly higher B12 levels and only received oral supplementation. There is little information on vitamin B12 levels in GSD patients, and there is no consensus on the need or amount to be supplemented. It is possible to exist deficiency in both B12 consumption and absorption. Further research is warranted, and an investigation will be performed in this center on the whole B-complex vitamin profile in association with clinical, molecular and treatment variables.

2570 - ASYMPTOMATIC FAMILY WITH LATE ONSET POMPE DISEASE: AN UNEXPECTED DIAGNOSIS

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INTRODUCTION: Pompe disease (PD) is a genetic disease with a broad clinical spectrum of phenotypes, due to a deficiency of acid α-glucosidase (GAA) activity. The deficient percentage of enzymatic activity may be related to the type of genetic alteration. PD manifestations may occur as soon as in the first months of life or as late as in the 60th decade of life. The aim of this case report is to describe a family with three asymptomatic individuals with PD with compound heterozygosity. **MATERIAL AND METHODS:** Case report. **RESULTS:** PLC, a 7-year old asymptomatic boy was investigated for PD because of an increase of aspartate aminotramsferase (AST) and alanine aminotransferase (ALT) 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 (DBS) and in leukocytes, normal urinary glucose tetrasaccharide (Glc4) and a compound heterozygosity mutation on GAA gene: NM_000152(GAA_v001):c.-32-13T>G, 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.[-32-13T>G(;)1123C>T] 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.-32-13T>G mutation in one allele; d) his maternal grandmother with a c.1123C>T in one allele and; e) his paternal grandmother with the same 5'UTR deletion. All of them were asymptomatic. The c.1123C>T mutation was classified as likely pathogenic and the c.-32-13T>G, as pathogenic, related to late-onset PD. Evaluation of cardiac, respiratory and muscle function of the proband and his mother were normal. **CONCLUSIONS AND DISCUSSION:** PD is a heterogeneous disease, both genetic and clinically, with a large variation in the age of onset and type of genetic alterations. Until now, about 400 variants have been described. Besides different types of mutations, 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.

2571 - ALGLUCOSIDASE ALFA ENZYME REPLACEMENT THERAPY IN EARLY AND LATE-ONSET POMPE DISEASE: A SYSTEMATIC LITERATURE REVIEW

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INTRODUCTION: Pompe Disease (PD) is caused by deficient activity of acid alpha-glucosidase and has progressive glycogen storage in tissues. Previous systematic reviews (SR) on intravenous enzyme replacement therapy (ERT) with alglucosidase alfa (recombinant acid alpha-glucosidase) for early-onset PD (EOPD) and late-onset PD (LOPD) haven't evaluated important endpoints, as safety, quality of life (QOL) and time to onset ventilation (TOV). Objective: To evaluate efficacy and safety of alglucosidase alfa for both PD forms. **METHODS:** We systematically searched PubMed and Embase for prospective studies, such as randomized controlled trials and nonrandomized trials, published until September 2018 evaluating ERT with alglucosidase alfa for EOPD and LOPD. Outcomes of interest were defined a priori. Assessment of quality of evidence (QOE) was performed according to GRADE approach. **RESULTS:** In EOPD, 1470 articles were identified and 13 were eligible. Only 4/9 analyzed endpoints favored ERT (all with QOE very low) and will be detailed. Reduction in cardiomyopathy was shown in 8/10 studies. Increase in survival was shown in 6/6 studies. ERT delayed TOV in 4/6 studies evaluated. In LOPD, 1172 articles were identified and 23 were eligible. Only 4/8 analyzed endpoints favored ERT (all with QOE very low). FC was benefited by ERT due to effect on 6 Minute Walking Test (6MWT), with clinically significant effect showed on meta-analysis. Reduction on VT was shown in 5/5 studies. Reduction in the risk of death on the ERT group was showed on meta-analysis. Safety data were described in 21 studies (6 describing EOPD; QOE very low), mentioning severe adverse events (AEs), infusion-associated reactions (IARs) and antibody formation. Although frequently present, antibody titers were not correlated with severe AEs or IARs nor were associated with treatment efficacy in both PD types. Most IARs were mild to moderate in both forms. **DISCUSSION:** Our results add data over previous published SR on ERT for both PD forms, as it evaluated also observational prospective studies, showing benefit for cardiomyopathy, survival and TOV in EOPD, and on 6MWT, VT and survival in LOPD. Our findings also suggest that ERT is safe in both PD forms, once most AEs were mild to moderate and antibody formation did not seem to interfere with any outcome evaluated. Furthermore, in this case, when interpreting QOE, it should be taken into account that PD is rare, severe and without alternative specific treatment.

2572 - GLIOMA IN GLYCOGEN STORAGE DISEASE TYPE IA: CORRELATION OR SPURIOUS ASSOCIATION?

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INTRODUCTION: Glycogen Storage Disease (GSD) type Ia is an inborn error of metabolism caused by glucose-6-phosphatase deficiency. The main clinical manifestation is fasting hypoglycemia, which treatment involves restriction of fast absorption carbohydrates and frequent administration of cornstarch. GSD Ia is associated with hepatic adenomas, which may progress to hepatocellular carcinoma in rare cases, but it has not been associated with other types of tumours in humans to date. **METHODS:** Case report and review of the literature. **RESULTS:** Female 13yo patient, born to consanguineous parents, was diagnosed with GSD Ia at 6 months due to hypoglycemia, hepatosplenomegaly and developmental delay, and had liver biopsy showing glycogen storage. Genetic investigation, performed later, showed homozygous c.563-3C>G known pathogenic variant in G6PC gene. At 10y11mo she had cardiogenic shock probably associated to vitamin B1 deficiency requiring intensive treatment. She was in regular follow-up with good metabolic control, when at 12y7mo she was hospitalized due to focal epileptic seizures in the right hemibody and labial commissure deviation. Due to risk of metabolic decompensation the first hypothesis were hypoglycemic seizures, but she presented normal glicemia and focal crisis. Tomographic investigation showed left frontoparietal intra-axial expansive lesion. Pathology was suggestive of grade III anaplastic glioma, astrocytoma subtype. She started radiotherapy at 12y8mo and chemotherapy at 12y11mo. Currently, her metabolic and epileptic control are stable and she is under regular use of cornstarch (0.98 g/kg/dosis). **CONCLUSIONS:** This is the first study to associate GSD Ia and glioma. Other studies described medulloblastoma in animal models of GSD. Gliomas are the most common primary tumours of the brain and spinal cord, and high grade types are the most commonly diagnosed in children. Due to insufficient evidence, a correlation between GSD Ia and glioma cannot be established as glucose-6-phosphatase enzyme is not constitutionally expressed in glial cells.

2603 - GLYCOGEN STORAGE DISEASE DIAGNOSIS OF TWO PATIENTS BY NEXT GENERATION SEQUENCING

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INTRODUCTION: Glycogen storage disease type I (GSDI) is a rare autosomal recessive disorder characterized by accumulation of glycogen and fat in the liver and kidneys. GSDIa is caused by mutations in G6PC gene, which encodes glucose-6-phosphatase catalytic subunit and GSDIb is caused by mutations in SLC37A4 gene that encodes glucose-6-phosphate transporter. Aim: To analyze in a panel of next generation sequencing (NGS) both genes G6PC and SLC37A4 in two Brazilian patients. **METHODS:** DNA samples were analyzed by NGS in IonTorrent PGM platform (Life Technologies) with a customized panel including the exonic regions and the intron-exon boundaries of the eleven genes causing GSD. The minimal coverage was 200X. Variants were filtered and classified by Enlis, Varstation and Ion Reporter softwares. The variants found were confirmed by automated Sanger sequencing. **RESULTS:** Patient 1 (3yo, female) presented with short stature and low weight (weight:12.16 Kg; height:83cm; BMI:17.65), high lactate levels, anemia, thrombocytopenia, liver dysfunction (Gluc 85; ALT 45, AST 67, Hb 9.0g/dL, white blood cels 4.990 platelet 810.000, neutrophils 1427mm3, lactate 10mmol/L). CT abdominal scans showed hepatomegaly, liver nodule and nephromegaly. She has recurrent infections with neutropenia. The NGS identified the mutations p.Arg300His and p.Leu348Valfs (exons 9 and 11) in compound heterozygosity in the SLC37A4 gene. Patient 2 (8 yo, male) presented with obesity (weight: 41.6 Kg; height: 121.6 cm; BMI: 28.13), moderate lactate levels (Gluc 72; ALT 33, AST 34, Hb 13.6,g/dL, white blood cels 5.400, platelet 372400, neutrophils 1250 mm3, lactate 3.85mmol/L). CT abdominal scans moderate hepatomegaly and mild splenomegaly. He has no recurrent infections. None of the patients had persistent neutropenia. Both patients are following up in a reference center for metabolic diseases. The NGS presented the mutations p.Leu186Pro and p.Val236del (exons 6 e 7) in compound heterozygosity in the SLC37A4 gene. All mutations were previously described, except for p.Leu186Pro, a novel mutation predicted by in silico analysis as probably pathogenic. **CONCLUSIONS:** Both patients had previous clinical diagnosis of GSDIa; however, the molecular analysis revealed that they were GSDIb cases. NGS with targeted multi-gene panel is a fast and effective method to elucidate diseases with common clinical and biochemical symptoms as GSDs.

2609 - LIVER TRANSPLANTATION IN HEPATIC GLYCOGEN STORAGE DISEASES: CASE SERIES STUDY FROM A REFERENCE CENTRE FOR RARE DISEASES IN SOUTHERN BRAZIL

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INTRODUCTION: Hepatic glycogen storage diseases (GSD) are genetic diseases caused by enzymatic deficiencies in the glycogen metabolism pathway. Treatment is type dependent and is usually performed by frequent meals, use of cornstarch and restricting fast-absorbing carbohydrates. Ketotic forms of GSD have an indication of a high-protein diet. Liver transplantation is reserved for cases at high risk of hepatocellular carcinoma or with evidence of cirrhosis. **METHODS:** Observational retrospective case series study, based on review of medical records of cases assisted in one outpatient metabolic clinic from Southern Brazil. **RESULTS:** Out of 103 cases treated at this center, three individuals underwent orthotopic liver transplantation (2 male; mean age: 36.91 years, range: 33.25 to 43; GSD type Ia [n=2], GSD type IIIa [n=1]). Mean age at GSD diagnosis was 2.22 years (range: 1.66 to 3). Mean age at the first consultation in the reference center was 30.6 years (range: 24 to 38) and mean age at introduction of specific GSD treatment was 30.83 years (range: 24 to 38.5). Mean age at the time of transplantation was 31.74 (range: 25.33 to 38.9). All transplants had deceased donors. Mean follow-up time after transplantation was 4.78 years (range: 1.5 to 9.1). The indications for transplant were hepatic cirrhosis (n=1, GSD III) and unresectable hepatic adenomatosis (n=2, GSD Ia). Events identified after transplantation included acute mild to moderate rejection (n=2); surgically treated biliary stenosis (n=1) and ureterolithiasis (n=1). Progression of muscle disease was identified in one case of GSD type IIIa. One patient is on high-protein diet (GSD IIIa). No deaths occurred after transplantation. **CONCLUSIONS:** Liver transplantation is a non-risk-free procedure and it should be reserved for specific cases. The transplantation rate in this center was 2.91% of cases. Mean time from clinical diagnosis of GSD until arrival at the referral center and specific treatment introduction was 28.38 years. This delay seems to have been decisive for the installation and aggravation of the secondary complications that led to transplantation in these cases. This series also highlights the importance of prompt introduction of therapy and referral to reference centers in front of GSD diagnostic suspicion.

2788 - NON-VIRAL AGL GENE DELIVERY AS A POSSIBLE THERAPEUTIC APPROACH FOR GLYCOGEN STORAGE DISEASE TYPE III (GSDIII)

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Glycogen storage disease type III (GSDIII) is a rare genetic disease caused by the lack of the “Glycogen Debranching Enzyme" (GDE), a large cytosolic protein (176 kDa) with two distinct enzymatic activities involved in glycogen degradation. Mutations along the Agl gene, encoding for the human GDE, are associated with loss of enzymatic activity. As a consequence, abnormal glycogen accumulates in both skeletal and cardiac muscle and/or liver, with great variability in the resultant organ dysfunction. No cure exists and the unique available treatment is based on a strict diet. The most frequent form of GSDIII (type IIIa) is considered a muscular dystrophy: muscle disorders, though minimal during childhood, may become more evident in adults with progressive weakness and distal muscle deterioration, and some patients eventually may require the use of a wheelchair for mobility. A synthetic Agl cDNA was engineered and expressed in Escherichia coli. The recombinant protein shows the same molecular weight of the human enzyme, holds debranching activity and is very stable. The same gene construct was inserted into a mammalian expression vector and successfully expressed in human cell lines. We will show results of our studies focused in introducing the synthetic Agl gene into defective human cell lines using physical (electro-gene transfer) and chemical transfection methods for delivery, with the long-term goal of contributing to an alternative non-viral gene therapy approach for GSDIII.

2790 - LYSINURIC PROTEIN INTOLERANCE AS A DIFFERENTIAL DIAGNOSIS OF GLYCOGEN STORAGE DISEASES: AN ILLUSTRATIVE CASE REPORT

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INTRODUCTION: Lysinuric protein intolerance (LPI) is an ultrarare aminoacidopathy with autosomal recessive inheritance that is associated with hepatosplenomegaly, intestinal malabsorption and vomiting. The diagnosis is made by detecting increased urinary excretion of dibasic amino acids, reduced plasma lysine, postprandial hyperammonemia and dyslipidemia. Maintenance treatment involves protein restriction and citrulline administration. In the literature, LPI is not usually cited as a differential diagnosis of Glycogen Storage Diseases (GSD). The objective of this report is to describe the investigational journey of a case with previous clinical diagnosis of GSD Ia, in which further investigation led to diagnosis of LPI. **METHODS:** Case report. **RESULTS:** A 11-year-old female patient born to consanguineous parents was referred for genetic evaluation due to suspicion of GSD. At 6 months, she started investigation due to progressive hepatosplenomegaly, growth restriction, chronic diarrhea, protein aversion and vomiting. At age 5, mild hyperlactacidemia was identified and liver biopsy was described as compatible with glycogen deposits and cornstarch and dietary treatment for GSD had been started for 4 years. She also underwent molecular and radiological investigation for hemochromatosis, with no evidence of iron deposition. At age 9, she was evaluated for the first time in a reference center for rare diseases and presented short stature, low weight, muscular fatigability, reduced muscle trophism, without any history of hypoglycemia. Laboratory tests revealed hyperferritinemia, dyslipidemia and mild hyperlactacidemia. Investigation for lysosomal diseases was normal. Amino acid dosage showed increase of alanine and glutamine and reduction of lysine. Urinary amino acid HPLC showed significant increase of lysine, alanine and glutamine, with increased postprandial ammonia, confirming LPI. SLC7A7 gene sequencing led to identification of the biallelic novel frameshift variant c.1109_1133del (p.Leu370Serfs*141). **DISCUSSION AND CONCLUSION:** LPI symptoms like hepatomegaly, bone, muscle and hematologic manifestations, growth restriction, lactate elevation and dyslipidemia could resemble GSD phenotypes. However the identification of chronic diarrhea, splenomegaly and protein aversion should lead to suspicion of LPI. The definitive clinical, biochemical and genetic diagnosis were fundamental to terminate a prolonged diagnostic search and allow adequate management and genetic counseling in this case.

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