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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

XII PUNTA CANA DOMINICAN REPUBLIC SLEIMPN 2022

XII Latin American Congress of Inborn Errors of Metabolism and Newborn Screening
IN THE AGE OF OMICS

PUNTA CANA, DOMINICAN REPUBLIC - MAY 4-7, 2022

FOREWORD FROM SLEIMPN

The Latin American Society of Inborn Errors of Metabolism and Neonatal Screening (SLEIMPN), in collaboration with the Dominican Republic, is pleased to celebrate our XII Congress as an irrefutable testimony of the resilient character of both the human condition and the commitment of health care providers.

After our last meeting in Buenos Aires, Argentina, in May 2019, we are finally able to meet again and fulfill the main purpose of our Society, established in 1997: to contribute to the development of neonatal screening (NS) and the proper management of inborn errors of metabolism (IEM) from all corners of our Latin America.

It has been a difficult journey that began with the unexpected transfer of the headquarters from Panama to the Dominican Republic, continued through years of uncertainty due to the COVID-19 pandemic, and now ends with the joy of being able to welcome each and every one of you in Punta Cana.

Our Scientific Committees has developed a great scientific program under the theme "Inborn errors of metabolism and neonatal screening in the era of Omics". During the event we´ll have leading international speakers sharing their knowledge through simultaneous and plenary sessions as well as two pre-congress courses on neonatal screening and nutrition. Additionally, 185 scientific abstracts will be presented, either as posters or oral communications, and all of them published in this special issue of JIEMS. We will also benefit from interesting symposiums sponsored by the industry.

We feel proud and happy to contribute once again to the advancement of knowledge and integration of Latin America in the areas of IEM and NS. We are sure that, in this way, we are getting closer to achieving a better quality of life for our patients and a better world for all.

Ceila Pérez de Ferrán
President of SLEIMPN
President of the XII Latin American Congress of Inborn Errors
of Metabolism and Neonatal Screening

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 ***12th Congress of the Latin American Society of Inborn Errors of Metabolism and Neonatal Screening*** (Punta Cana, Dominican Republic, May 4-7, 2022).

In this special supplement you will find 185 abstracts submitted as free communications and accepted for presentation. In the index you will find first those abstracts accepted as oral communications and then those presented as posters, sub-divided in different categories.

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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TOPIC INDEX

Book of Abstracts

ABSTRACTS SELECTED FOR ORAL PRESENTATION

O-001 - INVESTIGATION OF MUCOPOLYSACCHARIDOSES BY MEASUREMENT OF DISEASESPECIFIC OLIGOSACCHARIDES IN CEREBROSPINAL FLUID USING TANDEM MASS SPECTROMETRY

Faqueti L 1,2, Iop GD 1,2, Kubaski F 1,2,3, Corte AD 4, Baldo G 5,6, Herbst ZM 7, Pereira D 8, Silva C 8, Bender F 9, Trapp FB 1,9, Civallero GE 1, Soares J 1, Giugliani R 1,2,4,9,10

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INTRODUCTION (faltou as divisões): Lysosomal storage diseases (LSDs) are caused by defects in lysosomal function that may result in deficiency of lysosomal hydrolases, membrane-associated transporters, or other non-enzymatic proteins. Mucopolysaccharidoses (MPS) lead to the impaired metabolism of glycosaminoglycans (GAGs). GAG quantification has been the most used screening method for the identification of MPS patients and several methods have been employed for their identification such as ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). As an alternative to urine samples, it is possible to use cerebrospinal fluid (CSF) because of its importance to assess disease progression and the therapeutic efficacy on the neurodegenerative forms of MPS. In this study, we have quantified diseasespecific oligosaccharides in CSF of 45 untreated MPS patients (MPS I=16, MPS II=9, MPS IIIA=1, MPS IIIB=3, MPS IIIC=1, MPS IVA=9, and MPS VI=6) and 18 age-matched controls by UPLC-MS/MS (Xevo TQ-S micro, Waters). CSFs were derivatized with PMP before the UPLC-MS/MS analysis. All MPS samples had elevated levels for each specific signature. The results for specific-signature oligosaccharides for each MPS subtype were: MPS I (UA-HNAc (1S), early retention time)= 47 ng/mL (range= 5-121 ng/mL), control reference range= 0); MPS II (UA-HNAx (1S), late retention time)= 11 ng/mL (range= 4-22 ng/mL), control reference range= 0); MPS IIIA (HN-UA (1S))= 107 ng/mL, control reference range= 2.28; MPS IIIB ((HNAcUA) 2 (1S))= 4.9 ng/mL (range= 3.8-6.2 ng/mL), control reference range= 0.01; MPS IVA (HNAc(1S))=688 ng/mL (range=183-1,284), control reference range=255 and for MPS VI 1,141 ng/mL (range=722-1,560); MPS IVA (HNAc-UA (1S))= 11.5 ng/mL (range= 4-34 ng/mL), control reference range= 0.11; MPS VI (HNAc-2S)= 219 ng/mL (range= 150-288 ng/mL), control reference range= 27. Thus, this method is suitable for the analysis of CSF in MPS patients and this methodology can be applied for the phenotype characterization and treatment monitoring.

O-002 - PROGRESSION OF CARDIOVASCULAR MANIFESTATIONS IN PATIENTS WITH MUCOPOLYSACCHARIDOSES

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INTRODUCTION: Cardiovascular involvement is among the main features of MPS disorders and it is also a significant cause of morbidity and mortality. The range of manifestations includes cardiac valve disease, conduction abnormalities, left ventricular hypertrophy and coronary artery disease. OBJECTIVES: To assess the cardiovascular manifestations in a cohort of patients with MPS I, II, IV and VI, as well as the impact of enzyme replacement therapy (ERT) on those manifestations. **MATERIALS AND METHODS**: We performed a chart review of 76 patients with different types of MPS that had performed echocardiograms from January 2000 until October 2018. Standardized Z scores were obtained for heart chamber sizes according to the body surface area. When available, echocardiographic measurements that were performed before ERT and at least 18 months after that date were used for the assessment of pre-and post-treatment parameters. RESULTS: Left side valvular disease was a frequent finding, with mitral and aortic thickening being reported in most patients in all four MPS types. Left atrium dilatation was present in 26% of the patients; 25% had increased relative wall thickness; 28% had pulmonary hypertension. The cardiovascular involvement was, in general, more prevalent and more severe in adults than in children, including conduction disorders (40% vs 16%), mitral stenosis (26% vs 6%), aortic stenosis (13% vs 4%), and systolic

dysfunction (observed in only one adult patient). ERT promoted a significant reduction of the left ventricular hypertrophy parameters, but failed to improve valve abnormalities, pulmonary hypertension, and left atrial dilatation. **CONCLUSIONS**: Adult patients with MPS may develop severe cardiovascular involvement, not commonly observed in children, and clinicians should be aware of the need for careful monitoring and timely management of those potentially lifethreatening complications. Our results also confirm the impact of long-term ERT on left ventricular hypertrophy and its limitations in reversing other prevalent cardiovascular manifestations.

O-003 - BRAIN GENE EDITING AFTER NASAL ADMINISTRATION OF THE CRISPR/CAS9 SYSTEM IN MPS II MICE

Pimentel Vera LN, Schuh RS, Barcelos P, Gonzales E, Poletto E, Tavares A, Kubaski F, Matte U, Teixeira H, Giugliani R, Baldo G

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INTRODUCTION*:* Hunter syndrome is a multisystemic disease characterized by impairment in glycosaminoglycans (GAG) heparan and dermatan sulfate breakdown pathways due to the lack or malfunction of the lysosomal enzyme Iduronate-2-sulfatase (IDS). Current treatments fail to reach the central nervous system, which is the main affected system in most patients with the severe form. Many experimental approaches based on viral vectors have been proposed, but safety concerns are still unsettled. Previously, we reported a liposomal vector as a carrier for the CRISPR-Cas9 gene-editing system for brain tissue targeting via nasal administration in MPS I mice. **OBJECTIVE*:*** In this work, we evaluate the proposed system in the MPS II mouse model. **METHOD*:*** Untreated mice were compared to MPS II mice treated with the CRISPR-Cas9 system for 30 days, inserting a copy of the IDS gene in the safe harbor ROSA26. All animals were sacrificed at 6 months. **RESULTS*:*** Results showed that repeated administrations of our system caused long-lasting benefits, including an increase in IDS activity in the olfactory bulb and brain cortex ($p<0.01$), reduction in serum and urinary GAG levels ($p<0.05$) and improvement in cognitive function, assessed by behavioral tests ($p<0.05$). **CONCLUSION*:*** Overall, our results show that this is a promising non-invasive method to treat MPS II.

O-004 - PARKINSON'S DISEASE IN ADULT PATIENTS WITH GAUCHER DISEASE TYPE 1: FREQUENCY OF PRE-MOTOR SYMPTOMS AND LYSOSOMAL ENZYMES PROFILE IN CEREBROSPINAL FLUID AND PLASMA

Wilke MVMB [1,2], Poswar FO [2], Borelli WJV [3], Kubaski F [4], Randon DN [5], Burin MG [6], Tirelli KM [6], Sebastião FM [6], Bender F [6], Lopes F [6], Schuh AS [3], Schwartz IVD [2,5,7]

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INTRODUCTION*:* Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. Its classic motor symptoms may be preceded by non-motor symptoms (NMS). Population studies have identified *GBA1* variants as risk factors for idiopathic PD. Na increased risk of PD has also been suggested in other Lysosomal Storage Disorders (LSDs). **OBJECTIVE*:*** To assess the evolution of the prevalence of NMS of PD in a cohort of South Brazilian adult patients with Gaucher Disease (GD) type 1, already evaluated in 2018. **METHODOLOGY*:*** This is a case-control study approved by the local Research Ethics Committee (reference number 200358). Cerebrospinal Fluid (CSF) and plasma were also collected to assess the levels of other LSD enzymes (hexosaminidase, beta-glucuronidase) and biomarkers of macrophage activation (chitotriosidase), compared to controls (metachromatic leukodystrophy, MLD). Cognition was evaluated by the MoCa questionnaire, daytime sleepiness by the Epworth Scale, depression by Beck´s Inventory, constipation by the UMSARS scale, and REM sleep behavior disorder by the single-question screen. Hyposmia was assessed with Sniffin' Sticks (SS). **RESULTS*:*** Sixteen patients were included (mean age: 41.35 ±13.8, range: 25-70 years old). A PD family history was found in two. The patient with the highest number of NMS at the baseline (4 including the lowest SS score) was diagnosed with PD four years later. No statistical significance was found between the number of NMS evaluated in 2018 and 2021, nor between patients with one L444P variant (n=6) and the rest of the cohort. CSF was collected in three patients (mean age = 38.3). Mean chitotriosidase (CSF) was 70 nmol/h/mL in GD patients and 142 in MLD (n=7) patients. Mean total hexosaminidase and β glucuronidase were 107 and 2.47 nmol/h/mL in GD and 208

and 1.13 nmol/h/mL in MLD, respectively. The patient with more NMS (n=3) appears to have overall less enzyme activity**. DISCUSSION*:*** The patient with the highest number of NMS in our 2018 cohort was the one that developed PD, corroborating the importance of this longitudinal follow-up. CSF and plasma analysis might allow a better understanding of the neurodegenerative processes connecting PD and the lysosomal environment. Further analysis is needed to understand this relationship.

O-005 - MAGNETITE NANOPARTICLES AS VEHICLE TO TRANSPORT RECOMBINANT HEXOSAMINIDASE A AND B THROUGH AN IN VITRO MODEL OF BLOOD-BRAIN BARRIER

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INTRODUCTION*:* Nanoparticles are efficient vehicles for pharmacological delivery to different target tissues. Currently, magnetite nanoparticles (MNP) conjugated to lysosomal recombinant enzymes, have been proposed as an alternative carrier to allow the enzymes penetration through the blood-brain barrier (BBB) during the intravenous enzyme replacement therapy (ERT) administration in lysosomal storage disorders with central nervous system involvement. This novel strategy would avoid the use of invasive approaches such as intrathecal or intracerebroventricular injections to reach the cell target. In preliminary assays, we have observed that MNP/HexA-conjugates are uptake and sorted to the lysosomes reducing the stored lipids after 24 and 48 h of incubation with a single administration on GM2-gangliosides fibroblast models. **OBJECTIVE*:*** In this work, a BBB in vitro model was used to evaluate the ability of MNP/HexA and MNP/HexB nanobioconjugates to cross throughout. **MATERIAL AND METHODS*:*** Magnetite nanoparticles were synthesized, conjugated with recombinant hexosaminidases (HexA and HexB), and characterized to obtain adequate size nanobioconjugate. Cytotoxicity assays were performed on endothelial cells using MTT approach. Moreover, the BBB in vitro model was generated using the endothelial cells in the upper chamber and fibroblasts from Tay Sachs and Sandhoff patients in the bottom chamber of transwell plates. Trans-endothelial resistance (TEER) was measured up to 6 days with and without nanobioconjugates and recombinant protein administration. To assess passage through the endothelial layer, FITC-labeled nanoparticles were used, and fluorescence was measured in the bottom medium. Finally, enzyme activity was evaluated on culture medium and fibroblasts lysate. **RESULTS*:*** Endothelial cells maintain a stable TEER for 7 days without treatment. Upon nanoparticles administration, a TEER variation was observed on the third day of treatment. Fluorescence increase in the bottom chamber was observed after one day of incubation with FITC-nanoparticles. Likewise, changes in the fibroblast's activity levels were observed in the first two days of treatment, where TEER was not altered**. CONCLUSIONS*:*** Nanobioconjugates are promissory carriers in the development of ERT in patients with LSD involving CNS.

O-006 - CRISPR-MEDIATED GENOME EDITING ALLOWS THE PHENOTYPE RECOVERY OF THREE LYSOSOMAL STORAGE DISEASES

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Lysosomal storage diseases (LSD) are a group of several pathologies all of them characterized by mutations on genes encoding for proteins related to the lysosomal function. Consequently, partially, or not degraded substrates are accumulated into the lysosomal lumen leading to mechanisms that active pathophysiological events such as oxidative stress. Given that, delivering the therapeutic gene could resolve the genetic problem and related altered process as well. To test our presumption, we decided to use CRISPR/nCas9 to modify the AAVS1 locus using lipofection as a delivery strategy. Initial validation of our system showed that donor vector was successfully introduced on the AAVS1 region with nondetectable Off-target effect, using HEK293FT as an easy cell transfection model. Also, we used primary fibroblasts isolated from patients suffering Tay-Sach, Sandhoff and mucopolysaccharidoses IVA diseases and we subjected them to transfection of CRISPR/nCas9 and donor plasmids during 7, 15 and 30 days. Upon the time of transfection, we measured enzyme activity, lysosomal mass, total GAGs accumulation, and mitochondrial oxidative stress. Our results show an increase up to 10%, 12% for HEXA, and HEXB, with respect to wild-type levels Also, a reduction in lysosomal mass was reached with consistent GAGs level decrease, as well as mitochondria-dependent oxygen species. With GALNS, we found the highest levels reaching 100% at 30 días post-transfection, reduced lysosomal mass and the normalization of GAGs to lower levels of wild type. Similar behavior was observed on the ROS assays. In conclusion, we have designed a system able to recover partially the fibroblast phenotype of three LSD.

O-007 - HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE DEFICIENCY: HIGH CLINICAL VARIABILITY IN ARGENTINEAN PATIENTS WITH *HPRT1* C.584A>C MUTATION. CASCADE GENETIC SCREENING FOR IDENTIFICATION OF NEW CASES AND CARRIERS.

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INTRODUCTION: Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is an inborn error of purine metabolism with X-linked inheritance responsible for Lesch-Nyhan disease (LND) and its attenuated variants (LNV). LND shows total enzyme deficiency and is characterized by hyperuricemia, self-mutilation, neurodevelopmental delay, intellectual disability, etc. LNV shows a partial enzyme deficiency that results in hyperuricemia, gout, nephrolithiasis, renal failure, and variable neurological compromise; these variants are considered underdiagnosed because they are misclassified as gout or hyperuricemic syndrome. Both presentations of the disease were diagnosed in our center. **OBJECTIVES:** To show the wide variability in the onset and phenotype of related patients with LNV diagnosis and HPRT1 c.584A>C mutation, and to carry out a cascade genetic screening of family members to identify new cases and carriers. **MATERIAL/METHODS:** Eleven patients with LNV and c.584A>C mutation were compared according to disease onset, age at diagnosis and first/main manifestations. The cascade genetic study included 8 women and 8 men with different degrees of kinship and a common ancestor of 5 generations. The c.584A>C mutation analysis was performed by PCR and restriction enzyme digestion. **RESULTS:** The patient average age of onset was 9.23 years (range 0.1-24). Nephrological manifestations predominated as presenting symptoms in 54% (6/11) subjects, followed by joint disease 27% (3/11) and motor retardation 18% (2/11). The average age of diagnosis was 12.5 years (range 0.1-24). Regarding clinical outcome, 91% (10/11) patients presented different degrees of cognitive impairment, 72% (8/11) nephrological manifestations, 64% (7/11) joint disease. Cascade screening allowed to identify 7 female carriers and 6 hemizygous males (4 had symptoms related to hyperuricemia and 2 asymptomatic minors but with hyperuricemia subsequently confirmed). **CONCLUSIONS:** Although LND and its variants are rare diseases, they should be considered in the differential diagnosis of hyperuricemia. Cascade genetic screening allowed to make an early diagnosis of affected males and to establish treatment with allopurinol in order to prevent gouty manifestations and kidney failure. In women, the importance of identifying carriers is essential to provide genetic counseling. The clinical heterogeneity observed in affected subjects of this family was very high; the outcome and complications were strongly related to the age of diagnosis.

O-008 - EPIDEMIOLOGY OF UREA CYCLE DISORDERS: COHORT OF 134 ARGENTINAN PATIENTS FROM THE LAST 20 YEARS.

Kleppe S [1], Spécola N [2], Núñez-Miñana M [2], Posadas L [1], Cabrera A [3], González E [4], Pereyra M [5], Amartino H [6], Raskovsky V [6], Durand C [7], Silvera-Ruiz SM [8], Bernal AC [9], Roa AC [1], Eiroa HD [9*], Laróvere LE [8*]

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INTRODUCTION: Urea cycle disorders (UCD) are a group of inborn errors of metabolism that involve the excretion pathway of ammonia, the end product of protein catabolism. The incidence and prevalence of UCDs are unknown and it is likely that these diseases are underdiagnosed. In Argentina, the unequal access to biochemical and molecular diagnostic tests, as well as specific treatments for hyperammonemia aggravates the situation. **OBJECTIVE:** To describe the epidemiology, the diagnostic itinerary, treatment and evolution of UCDs in Argentina. **METHODS:** Retrospective multicenter cohort of consecutive patients with clinical and/or genetic diagnosis during the period 2000-2021. Demographic, clinical, biochemical, epidemiological, clinical diagnosis, treatment characteristics were collected by reviewing the medical history and interviewing the treating physician. All patients were followed up for response to treatment and prognosis. Categorical data are described as a percentage and absolute frequency, numerical variables with median and interquartile range. **RESULTS:** During the period of interest, 134 patients with UCD were included from 10 centers in Argentina with Early-onset presentation 48.4%, Late-Onset 41.9% and asymptomatic 9.7%. The median ammonium at diagnosis was 340 mcg/dl and the most frequent presenting symptoms were neurological and digestive. The distribution of the enzyme

defects was OTC 60%, ASS 22.2%, ASA 9.6%, CPS and NAGS 2.2%, and HHH 1% confirmed molecularly in 74.4%. Socioculturally, only 36.8% had health insurance, 62.8% had good access to medication, 66.6% to diagnosis, 35.7% to low protein food and 24.7% to special formulas. Regarding treatment, 96% received a restricted protein diet and 100% dietary supplements. Mean weight was in the 40th percentile and height in the 50th percentile. 76% required chronic treatment: sodium benzoate 76%, sodium phenylbutyrate 27%, and glycerol phenylbutyrate 12%. Mortality was 39.1%**. CONCLUSION:** To our knowledge, it is the first collaborative work of UCD in Argentina. The access to diagnosis and treatment is clearly uneven. Of the 134 patients followed, there were 41 diagnosed in the last 10 years, clearly underdiagnosed. The objective of this presentation is to portray which variables are most related to worse results, in order to change them.

O-009 - THE USE OF SWEET MANIOC STARCH COMPARED TO CONVENTIONAL CORNSTARCH IN THE TREATMENT OF GLYCOGEN STORAGE DISEASE TYPE IA

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INTRODUCTION: The clinical management of Glycogen storage disease Ia (GSDIa) includes the administration of uncooked cornstarch (UCCS). Although such an approach is effective in achieving euglycemia, its impact on the quality of life of patients should be considered. **OBJECTIVES:** To compare the efficacy and safety of the administration of sweet manioc starch (SMS) and UCCS during a shortfasting challenge in patients with GSDIa and biochemically characterize studied starches. **MATERIALS AND METHODS:** Randomized, triple-blind, phase I/II, cross-over study, and biochemically characterized both brands of starches regarding moisture, sugar content and the rate of amylose and amylopectin. GSDIa patients aged ≥16 years and treated with UCCS were enrolled. Participants were hospitalized for two consecutive nights, receiving UCCS (Maizena®) or SMS (Fritz e Frida®) each night. After the administration of the starches, glucose and lactate levels were measured in 1-h intervals throughout the hospitalization period. The procedures were interrupted after 10h of fasting or in a hypoglycemic episode (<3.88 mmol/L). **RESULTS:** Eleven individuals (mean age: 21.6 ± 4.3 years; all presenting body mass index >25 kg/m2) participated in the study. The average fasting period was 8.2 ± 2.0 h for SMS and 7.7 ± 2.3 h for UCCS (p=0.04). SMS maintained euglycemia for a greater period over UCCS. Increased lactate concentrations were detected even in absence of hypoglycemia, not being influenced by the different starches investigated (p=0.17). No patient showed severe adverse events. The moisture analysis revealed the mean: 10.5 ± 0.09% in the SMS samples, while the mean moisture of UCCS was 11.1 ± 0.31%. Quantifiable sugar was detected in both samples (SMS: 38.0 ± 0.00 and UCCS: 22.0 ± 0.14g/100g). The amylopectin content was 78.9 ± 2.02% (SMS) and 77.0 ± 1.23% (UCCS). **CONCLUSIONS:** SMS appears to be non-inferior to UCCS in the maintenance of euglycemia, thus emerging as a promising alternative to the treatment of GSDIa. Further studies are warranted in order to investigate the therapeutic use of SMS samples that have higher levels of amylopectin and unquantifiable sugars.

O-010 - PLASMA LIPIDOMIC PROFILING HIGHLIGHTS SEVERE PERTURBATION OF LIPID METABOLISM IN SMITH LEMLI OPITZ SYNDROME

Catesini G, Sacchetti E, Boenzi S, Olivieri G, Liguori A, Dionisi-Vici C, Rizzo C

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BACKGROUND: Smith-Lemli-Opitz syndrome (SLOS) is a congenital disorder of cholesterol biosynthesis due to deficiency of 7-dehydrocholesterol reductase, accounting for a wide spectrum of clinical manifestations/multiple malformations, which include prenatal and postnatal growth retardation, microcephaly, and severe intellectual disability. In order to investigate the presence of wide perturbations of lipid profile, we performed lipidomics analysis in a series of SLO patients. **METHODS:** We analyzed plasma samples from 6 SLOS patients and 6 age-matching healthy subjects. Wide-targeted quantitative lipidomic analysis was performed by ION Mobility Mass spectrometry, LCIMS/MS (LipidyzerTM), allowing the quantitation of over 1100 lipid species, spanning 13 different lipid classes. Collected data

were studied by multivariate analyses using both supervised and unsupervised statistics. **RESULTS:** Supervised and unsupervised profiling, of single lipid molecules and of different lipid classes, allowed a clear separation between patients and controls. Cholesteryl esters (CE) and ceramides (CER) were the most significant lipid classes (p>0.01). CE showed the highest VIP-scores, while among the CER, the major compounds were hexosyl-CER and lactosyl-CER. Volcano plot representation showed that the most significantly reduced molecules were CER(16: 0), LCER(16: 0) and LCER(24: 1), HCER(22: 0), and CE(18: 2), CE(20: 0), CE(20: 4), and CE(22: 5)**. CONCLUSION:** Lipidomic analysis demonstrates significant differences between SLOS patients and controls, indicating clear perturbations of lipid metabolism which potentially contribute to disease pathophysiology. The reduced cholesterol synthesis in SLOS may explain the reduced formation of CE. Reduced CER, which are involved in various biological processes, spanning from stratum corneum formation to differentiation of embryonic stem cells, may play a role in structural embryonic changes and in intracellular signaling pathways abnormalities.

O-011 - GENE THERAPY USING CRISPR-NCAS9 SYSTEM IN PHENYLKETONURIA

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Phenylketonuria (OMIM # 261600) is a phenylalanine metabolism defect produced by mutations in the gene encoding phenylalanine hydroxylase (*PAH*) (EC 1.14.16.1) which catalyzes the conversion of phenylalanine to tyrosine. Consequently, patients with this disease have high levels of phenylalanine in the blood. If not treated in time, the increase in phenylalanine has a negative effect on the central nervous system, producing mental deficiency, epilepsy and behavioral disorders. The global incidence of this disease is estimated at 1: 10,000 births. Early and continuous treatment can mitigate the damage in cognitive development reaching average levels. The treatment most used to date consists of dietary phenylalanine restriction. Although this therapeutic strategy has proven to be effective, it still fails to correct the typical neurocognitive defect in these patients, not to mention the difficulty that patients find in adhering to the diet. Other treatment strategies have been implemented such as the use of tetrahydrobiopterin or the subcutaneous administration of phenylalanine ammonium lyase (Pegvaliase). However, limitations such as reduced effectiveness in patients with severe phenotype or immune reaction respectively are important limitations of these therapeutic approaches. To date, gene therapy studies using CRISPR-Cas9 or adeno-associated vectors have already been used in murine models with decreased serum phenylalanine. In this work, we tested the use of a nCas9 to direct an expression cassette for PAH directed towards the human AAVS1 locus in primary fibroblast lines GM00006 and GM00937 obtained from the Coriell Institute (NJ, USA) using a commercial system of cationic liposomes (Lipofectamine 3000 TheroFisher, Scientific) and a new transfection system based on magneto liposomes. The results showed a cell-to-cell variation in the reduction of phenylalanine in the culture medium, with one of the primary fibroblast lines showing a better response to the genome-editing treatment than the other. These results show the potential of this strategy for PKU treatment and highlight the importance to include different patient cell lines during the early evaluation of genome editing strategies.

O-012 - PILOT STUDY TO DESCRIBE THE DIET AND GUT MICROBIOTA IN SCHOOLS WITH PHENYLKETONURIA, HYPERPHENYLALANINEMIA AND CONTROLS FROM CHILE

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INTRODUCTION: Phenylketonuria (PKU) is caused by a defect in the enzyme Phenylalanine Hydroxylase, producing an accumulation of phenylalanine (Phe). The PKU diet is a Phe restricted that prohibits foods of animal origin. To complete nutritional contributions, a protein substitute without Phe (PS) must be provided. HPAs do not require a special diet. Studies observed that PKU subjects have lower bacterial diversity, the relative abundance of some butyrate-producing bacteria, and fecal concentration of butyrate, despite having a higher intake of fiber, fruit and vegetable (F&V). **OBJECTIVE:** To characterize the diet, the gut microbiota and the production of fecal short-chain fatty acids (SCFA) in schoolchildren with PKU, HPA and controls. **METHODS:** 3 PKU/HPA/control groups (n= 4/3/5), all schoolchildren with normal nutritional

status. The intake of energy, macronutrients, fiber, polyphenols and the NOVA system that classifies food through a 24-hour dietary recall questionnaire. The gut microbiota was identified by massive sequencing of the V3-V4 region of the 16S rRNA gene. The α diversity, measures the microbial richness, was determined with the Shannon index and the β diversity, measures the differences in the bacterial composition, by means of a principal coordinate analysis (PCoA) with the unifrac-weighted metric. The fecal SCFA quantification was performed by gas chromatography. **RESULTS:** The PKU group consumed less cholesterol and more ultra-processed foods, compared to the other groups, and 50 % of the fiber consumed came from special low-protein foods products. There was no difference in the α and β diversity of the gut microbiota or in the fecal production of butyrate between the groups. However, the PKU group had a lower relative abundance of Faecalibacterium and Bifidobacterium, and a higher abundance of Enterobacter and Oscillospira, compared to controls and HPA. The HPA group presented a higher total concentration of fecal SCFA**. CONCLUSION:** In this study, we did not observe a lower diversity and fecal concentration of butyrate in the PKU group, as reported by other studies. However, more PKU subjects should be studied to confirm these findings. This study is the first to describe the microbiota and SCFA composition of subjects Chilean PKU.

O-013 - INCREASE IN BMI DURING COVID-19 PANDEMIC: AN OBSERVATIONAL STUDY BASED ON TWO BRAZILIAN REFERENCE CENTERS

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INTRODUCTION: The COVID-19 pandemic demanded the need for measures to reduce contamination through social isolation, changing people's routines. The investigation of the effects of the COVID-19 pandemic in the treatment of inborn errors of metabolism is essential for greater preparation for similar future situations. **OBJECTIVE:** To investigate whether PKU metabolic control and BMI were affected by the COVID-19 pandemic. **METHODS:** Retrospective study including two Brazilian reference centers for the treatment of PKU (center A at Southeast Brazil, center B at South Brazil). Patients with at least three Phe dosages in each year (2018, 2019 and 2020) and at least one dosage from January to April 2021 were included; 2018 and 2019 were considered as the pre-pandemic (preP) and 2020 and 2021 as the pandemic period (PP). In center 2, the BMI Z-score for age (BMI/A) was also retrieved. **RESULTS:** Center A: 26/84 (31%) patients were included (54% female), median age: 15.96 yrs. The median of Phe was 387.2 µmol/L in the preP and 425.92 µmol/L in the PP (p=0.195), with a median of 4 exams preP and 4.51 PP (p=0.731). Center B: 15/91 (16.5%) patients were included (60% female), median age: 6 yrs. The median of Phe was 381.75 µmol/L in the preP and 379.94 µmol/L in the PP (p=0.156), with a median of 9.5 exams PreP and 6.01 in the PP (p = 0.027). The BMI/A Z score increased from 1.16 in the PreP to 1.74 in the PP (p= 0.016)**. CONCLUSION:** Although we were not able to demonstrate a significant increase in the Phe levels in the PP, the rate of patients included in each center probably reflects a decrease in the number of Phe measurements during the PP. COVID-19 pandemic is associated with an increased sedentary lifestyle, raising the BMI/A Z score.

O-014 - HOMA2 AND METABOLITES CHARACTERIZATION IN 26 CHILEAN PKU ADULTS WITH AND WITHOUT NONCOMPLIANCE TREATMENT.

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BACKGROUND: The Phenylketonuria (PKU) treatment consists in low phenylalanine (Phe) diet with supplementation of protein substitute without Phe (PS-PheFree). The evidence has shown some aromatic and branched amino acid as Phe and leucine, are strongly associated with obesity and insulin resistance (IR). It is possible that subjects who are non-compliance with the treatment increase the risk to develop IR and Metabolic Syndrome (MS). **AIM:** Compare the suspension of PS-PheFree and non-compliance to diet in PKU subject with glucose, insulin amino acids and acylcarnitine profile. **METHODS:** Group1(G1): PKU with PS-PheFree (n=10), Group2(G2): PKU without both, treatment and PS-PheFree (n=16) and Group3(G3): control (n=26), matched by age, sex, and body mass index (BMI). Amino acid and

acylcarnitine profile (AAP) in dry blood spot (DBS) was determined by Tandem mass spectrometry (MS/MS) and plasma amino acids by LC-MSMS. Principal component analysis (PCA) was performed to reduce the dimensionality and consolidate the variables. Statistical significance $p<0.05$. **RESULTS:** Average age was 23±4 years (46% female). Plasma Phe concentration (PheC) was lower in G1 than G2 (407±308 µmol/L vs 747±298 µmol/L; $p<0.05$; rv: 120-360µmol/L). Both G1 and G3, presented insulin levels in the normal range (10±8µIU/mL; 13±8µIU/mL; rv: ≤16µIU/mL), compared with G2 (18.1±13 µIU/mL), with a significate difference between groups ($p<0.03$). Regarding, HOMA2-IR, HOMA2-S and HOMA2-B we observed a significant difference between groups ($p<0.05$), specifically between G1 and G2. We obtained a negative correlation between PheC with HOMA2-S ($p=0.02$); and a positive correlation with HOMA2-IR ($p=0.02$) and waist circumference (WC) ($p=0.04$). With PCA multivariate analysis we could observe a group separation in function to a correlation of variables associated with IR and MS, obtaining G1 and G3 in PCA1, represented 58% of the total variance, which are similar, and G2 moves to the opposite side mainly by HOMA-IR, HOMA-B indexes, were PheC also contributed for that. When analyzing the AAP, we observed a positive correlation between fasting glucose with leucine/isoleucine ($p<0.01$), arginine ($p<0.01$) and a positive correlation between leucine and valine ($p<0.01$), mainly represented by G2 subjects**. CONCLUSION:** Noncompliance treatment without PS-PheFree is correlated with a higher risk of IR and developing MS, worsening their quality of life.

O-015 - MEDIUM-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD) IN COSTA RICA: MOLECULAR CHARACTERIZATION OF 38 PATIENTS IDENTIFIED THROUGH THE NATIONAL NEWBORN SCREENING PROGRAM.

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INTRODUCTION: Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is an autosomal recessive disorder of fatty acid β-oxidation (OMIM: 201450). Usually, the onset of symptoms in MCADD patients is between the third and the twenty-fourth month. These symptoms include lethargy, hypoglycemia, vomiting, and seizures. It is one of the inborn errors of metabolism detected in Costa Rica through the newborn screening program since 2006. **OBJECTIVE:** To describe the genotype and estimate the frequency of mutations detected among the 36 MCADD patients. **MATERIALS AND METHODS:** 36 patients were analyzed, 33 of which were born in the period between 2006-2021 and detected through the newborn screening test, the rest were not detected in neonatal age. Acylcarnitine analysis was performed on dried blood spots (DBS) using a non-derivatized method and triple quadrupole tandem mass spectrometry (MSMS). Genetic testing of the 12 exons of ACADM (NM_000016.5) gene was performed by Sanger sequencing in our laboratory, and the detected large deletion was confirmed through a Next-Generation Sequencing (NGS) panel referred to an external laboratory. **RESULTS:** In Costa Rica, a total of 1.091.624 children were screened from 2006 to 2021. In this period, the estimated prevalence for MCADD in the screened newborns was 1: 33079. High frequency of the c.985G>A variant was found in homozygous state in 57% of the individuals confirmed by molecular analysis. Seven patients have the genotype: c.[443G>A]; [985G>A]. Three mutations were found in lower frequency: c.[355dupG], c.[999_1011dup] and [Exon 1-10 del]**. CONCLUSIONS:** As reported in the literature, the c.985G>A variant is the most frequently found in patients with MCADD in Costa Rica. Reclassified in 2017 as pathogenic, the c.443G>A variant is the second most frequent one found in our patients. According to the Genome Aggregation Database, this variant seems to have a high frequency in the Latin American population. Dosage analysis (e.g., MLPA, CGH array, or NGS) should be considered in cases where sequencing analysis does not confirm the diagnosis.

O-016 - GENETIC DIAGNOSIS AND GENOTYPE-PHENOTYPE ASSOCIATION IN 126 BRAZILIAN INDIVIDUALS WITH REDUCED BIOTINIDASE ACTIVITY

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INTRODUCTION: Biotinidase deficiency (BD) was included in the Brazilian Neonatal Screening Program 10 years ago. Since then, our group has been studying the BTD gene, publishing the profile of 72 Brazilian individuals detected with low biotinidase levels. **OBJECTIVE:** To provide an update of the genetic diagnosis for BD in Brazil, including the results by Borsatto et al. (2014 and 2017). **METHODS:** Multicentric, observational, cross-sectional study with a convenience sampling strategy. The study protocol was approved by the local Research Ethics Committee, in accordance with the Brazilian regulations for human subject research (reference number 2012-0186). The entire analyzed population, with the inclusion of the new samples (N=54), comprised 126 individuals (aged 1 month to 18 years old; male N=63). Quantitative enzymatic activity values were available for 110/126 (current normal=7, heterozygous=60, partial BD=25, borderline heterozygous/partial BD=8, profound BD=7, and borderline heterozygous/normal=3). Genomic DNA was extracted from blood samples in EDTA or buccal epithelial cells using commercial kits followed by PCR, purification, and sequencing of exons 2, 3, and 4 of the BTD gene. The reference sequence NG_00819.1 and the American College of Medical Genetics and Genomics guidelines were employed to identify and classify novel variants. **RESULTS:** Considering the whole sample, 24 different pathogenic variants were identified, being c.1330G>C, c.755A>G, c.[511G>A;1330G>C], and c.1368A>C the most frequent ones (43.4%, 4.9%, 4.1%, and 3.7% of allele frequency, respectively). Three novel variants were found in addition to the six previously published: c.269T>A, c.1321G>A (both pathogenic), and c.1004C>T (likely pathogenic). BD classification according to the genotype was: heterozygous=44; partial BD=30; normal=27; profound BD=8; and undetermined=17. The genotype-phenotype comparison was available for 93/126 individuals, and the genotype-based classification matched the biochemical phenotype in 65 (69.9%) of the cases. **CONCLUSIONS:** The Brazilian neonatal screening program is effective to detect profound and partial BD patients. However, it seems to be including very often heterozygous –non-affected- individuals. The Brazilian mutational profile of BTD is more heterogeneous than in other countries. Although the genotype-phenotype association is not always consistent, genetic analysis is useful for clarifying borderline and consecutive discordant biochemical results.

O-017 - CFTR MUTATIONS IN DOMINICAN REPUBLIC POPULATION

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INTRODUCTION: The population of the Dominican Republic (DR) is heterogeneous, due to the ethnic mixture that arises from colonization and migration. In addition, it shares Hispaniola Island with the Republic of Haiti, being ethnically different from the other Caribbean countries. Our population has a higher percentage of African ethnicity and lower percentage of European and native ethnicity than Puerto Rico and Cuba. It is known that Cystic Fibrosis (CF) is a genetic condition caused by the mutation of the gene coding for the transmembrane conductance regulator protein of Cystic Fibrosis (CFTR). Due to the miscegenation, there is variation of mutations seen in the Latin American population specifically those of the DR. **OBJECTIVES:** To evaluate CFTR mutations detected in the patient population seen in the CF clinic of the Robert Reid Cabral Children's Hospital. **MATERIALS AND METHODS:** a descriptive, crosssectional study was carried out; the samples were collected for convenience. All patients who met the clinical criteria for CF with sweat chloride testing greater than 60 mmol/L had genetic test with mutations identified in the CFTR. **RESULTS:** We identified 63 different CFTR mutations, of which more than 50% of patients have c.1521_1523del (F508del). We identified 7 mutations of uncertain clinical significance, 9 mutations not described in the CFTR 2 database, and 5 mutations not described in the Cystic Fibrosis Mutation Data of the sick kids children's Hospital (CFDB). Additionally, we found 3 mutations noted to be of uncertain clinical significance that are not described in CFTR2 or CFDB, which makes us think that they are mutations exclusive to the Dominican population, never described worldwide**. CONCLUSIONS:** Countries with great miscegenation, such as the DR, may present CFTR mutations of uncertain clinical significance and not described in the global databases for CF. This makes us think that they are unique in this population, which due to their low prevalence are not included in the agreed panels of research of CFTR mutations and therefore, limiting their timely diagnosis, adequate therapeutic intervention in time to avoid the deterioration of the condition. Researching these populations is an opportunity to learn more about how ethnic combinations affect them.

O-018 - POPULATION VALUES OF NEONATAL TSH AS AN ESTIMATE INDICATOR OF IODINE

SUFFICIENCY/DEFICIENCY STATUS IN BUENOS AIRES PROVINCE – ARGENTINA.

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INTRODUCTION: Incidence of Congenital Hypothyroidism (CH) has showed a continuous worldwide increasing during the last two decades and iodine deficiency has been recognized as one of its possible causes. In 1994 the World Health Organization (WHO) described the usefulness of the TSH population values from newborns aged 48-96 hrs as an estimate indicator of iodine sufficiency/deficiency status according to the percentage of newborns with TSH above 5.0 µU/ml of whole blood (%NB-TSH>5). **OBJECTIVE:** To describe the %NB-TSH>5 annual variation in newborns from the Buenos Aires Province – Argentina, aged 48-96 hrs, screened at Fundación Bioquímica Argentina between 2002–2020, and to analyze its behavior as an estimate indicator of iodine sufficiency/deficiency status.**MATERIAL AND METHODS:** Newborn Screening for CH was conducted along the evaluated period (January/2002 October/2020) measuring TSH with the AutoDelfia Neonatal hTSH Kit - PerkinElmer. Results interpretation was done regarding a cut-off of 11.0 µU/ml. Databases corresponding to each year were exhaustively cleaned according to the WHO requirements. TSH results corresponding to 1.436.667 newborns were included in the study. %NB-TSH>5 was calculated for each year, its variation was graphically analyzed and results were interpreted regarding the WHO criteria. **RESULTS:** Annual %NB-TSH>5 (number of newborns analyzed) were as follows: - 2002: 2,27 % (76.326); - 2003: 2,56 % (76.624); - 2004: 2,87 % (79.346); - 2005: 2,88 % (80.911); - 2006: 3,66 % (79.231); - 2007: 3,34 % (77.575); - 2008: 2,60 % (84.254); - 2009: 3,23 % (69.906); - 2010: 3,92 % (85.159); - 2011: 4,16 % (85.487); - 2012: 3,85 % (85.073); - 2013: 4,35 % (78.251); - 2014: 5,09 % (81.701); - 2015: 5,06 % (78.279); - 2016: 5,12 % (70.832); - 2017: 4,66 % (69.352); - 2018: 4,77 % (69.476); - 2019: 4,93 % (63.898); - 2020: 4,64 % (44.986)**. CONCLUSIONS:** %NB-TSH>5 showed a continuous increasing from 2002 to 2014 with values > 3,0 % from 2006 onwards, marking the beginning of a potential mild iodine deficiency status. A plateau around 4,9 % was reached from 2014 onwards. In spite %NB-TSH>5 only is an estimate indicator of iodine sufficiency/deficiency status, the study characteristics, its duration, the sample size, the use of the same TSH methodology along the complete evaluated period and the %NB-TSH>5 behavior confer the results a high predictive value. Mild iodine deficiency may be related to changes in population dietary habits that decrease iodine intake, like low-salt diets.

O-019 - NEWBORN SCREENING CELEBRATES 20 YEARS IN SOUTH BRAZIL

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INTRODUCTION: Newborn screening (NBS) began in Brazil in 1976, initially carried out by isolated and private few centers. In 2001, NBS National Program was born, sponsored by federal laws to perform actions in Public Health System, and Regional References Centers (NBSRC) were created in each brazilian state: Hospital Materno Infantil Presidente Vargas (HMIPV) was nominated in the state of Rio Grande do Sul (NBSRC-RS). **OBJECTIVE:** Retrospective review of NBSRC-RS data between 2001-2021, historical evolution in 20 years. **RESULTS:** More than 2 million newborns have been screened to date (around 100,000 NB/year). NBS coverage has been rising more than 55 % (2001 = 27 %/2021 = 82 %) and the ideal first collection time (3-5 days of age) rose from 8 % (2001) to 75 % (2021). All the detected babies are referred to NBSRC-RS multidisciplinar team (physician, dietitian, psychologist and social worker) in HMIPV (114,000 ambulatory assistence/year) and confirmatory diagnosis is provided within the first weeks of life. This resulted in the diagnosis of 2,198 sick children with Phenylketonuria (133), Congenital Hypothyroidism (1,402), Sickle Cell Disease (300), Cystic Fibrosis (101), Biotinidases Deficiency (44) and Congenital Adrenal Hyperplasia (218), and a higher number of carriers detected. The management of these children has improved over time, in particular thanks to the public health professional efforts, improved techniques of biochemistry and molecular genetics which lead to an accurate diagnosis and the arrival of new treatment options**. CONCLUSION:** We should celebrate twenty years of NBSRC-RS: good results that allowed early management and prognosis of our selected babies surely transformed (although clinical and/or social problems may arise), we contributed to fact of these patients are living healthy today.

O-020 - NEWBORN SCREENING OF CONGENITAL ENDOCRINE-METABOLIC DISEASES IN A PEDIATRIC HOSPITAL, MENDOZA-ARGENTINA

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INTRODUCTION: It is important that the detection, diagnosis, treatment and follow-up of congenital endocrine-metabolic diseases (CEMD) are developed in Reference Centers. Therefore, our Program performs the mandatory newborn screening (NS) of primary congenital hypothyroidism (PCH), congenital adrenal hyperplasia (CAH), phenylketonuria, galactosemia, biotinidase deficiency (BTDdef), cystic fibrosis (CF) and maple syrup urine disease (MSUD). **OBJECTIVES:** Present results and indicators of the NS Program. **MATERIALS AND METHODS:** From 1999 to 2009, the Program carries out the NS of PCH and phenylketonuria; newborns in hospitals of the state and private sector of Mendoza-Argentina. In 2010, the detection of CAH, galactosemia, BTDdef, and CF was incorporated; and in 2021, MSUD. The analytical process was carried out in two stages. 1st stage, Zentech reagents were used: phenylalanine, galactose and branched chain amino acids (BCAA) (enzymatic colorimetric methods); biotinidase (colorimetric method) and TSH, 17OHP, IRT (ELISA). 2nd stage: re-evaluation of samples with "border-line and positives" results; phenylalanine and biotinidase (fluorometric methods-Perkin Elmer reagents); galactose (enzymatic fluorometric method-Perkin Elmer reagent); TSH, 17OHP, IRT (DELFIA) and BCAA (enzymatic fluorometric method-in house reagent). **RESULTS:** NS, 1999-2021: 442585 newborns. Indicators 2021, mean: days of life (DOL) at the sample collection: 2 days. Time of transit of the sample from the Maternities to CE.P.E.I.I.: 3 days. DOL to get the result: 7 days. DOL to deliver the report: 9 days. Diagnosis and start of treatment: 12 days. Rejected and insufficient samples: 0.59%. Recall rate: total (newborns gestational age ≥ 37 weeks): 3.10 % (1.50 %); 100% of the newborns were located. Coverage; publics hospitals/private: 99 %/39 %. Children in treatment-follow-up: 229 PCH (incidence = 1/1933); 9 phenylketonuria and 22 persistent hyperphenylalaninemias (incidence = 1/14277); 19 CAH (incidence = 1/12767); 36 CF (incidence = 1/6738) and 1 BTDdef (incidence = 1/242581)**. CONCLUSIONS:** In the context of a Reference Center/cost-effectiveness, mandatory NS was performed for 7 CEMD using an analytical algorithm in stages with validated methodologies. Indicators were optimized from sample collection to diagnosis, treatment and follow-up of affected children.

O-021 - NORMAL REFERENCE VALUES OF ACYLCARNITINE AND AMINO ACIDS IN THE ITALIAN POPULATION DETECTED IN DBS AND PLASMA BY TANDEM MASS SPECTROMETRY

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BACKGROUND: Tandem Mass Spectrometry (TMS) assay of Acylcarnitines (AC) and Amino Acids (AA) on DBS is used in Extended Neonatal Screening (ENS), while Plasma assay is preferred for diagnostic confirmation and follow-up. Up today, references ranges of AC and AA in DBS and plasma in MS by age groups are not available in literature for the specific Italian population. The AC and AA in DBS and plasma of 270 healthy Italian subjects were analyzed in TMS (age groups: 1-6 months, 6-12 months, 1-6 years, 6-18 years and >18 years), in order to obtain the normal reference values and to evaluate the quantitative differences found between the two biological matrices. **RESULTS:** The study of AC and AA showed specific correlation with age in DBS and plasma. In DBS as age increases, AC (C0, C2, C8: 1, C14, C14-OH and C16-OH) decrease; AC (C5: 1, C5, C5-OH, C4DC and C5DC) increase; AC (C3, C4, C4-OH, C6, C8, C3DC, C10: 1, C10, C12: 2, C12: 1, C12, C6DC, C12-OH, C14: 2, C14: 1, C14: 1-OH, C16: 1, C16, C16: 1-OH, C18: 2, C18: 1, C18, C18: 2-OH, C18: 1-OH, C18-OH, C16DC and C18DC) are constant. In plasma as age increases, AC (C0, C2, C4-OH, C5-OH, C8: 1, C4DC, C14, C16, C16-OH and C18: 2) decrease; C5DC increase; AC (C3, C4, C5.1, C5, C6, C8, C3DC, C10: 1, C10, C12: 2, C12: 1, C12, C6DC, C12-OH, C14: 2, C14: 1, C14: 1-OH, C14-OH, C16: 1, C16-OH, C18: 1, C18, C18: 2-OH, C18: 1-OH, C18-OH, C16DC and C18DC) are constant. In DBS as age increases, AA (MET, GLU, ORN and PRO) decrease; AA (GLY, VAL, PHE, ASP, CITR and ARGSUCC) increase; AA (LEU, TYR and ARG) are constant, while ALA and HOMOCITR have a variable trend. In plasma as age increases, AA (ALA, MET, TYR, ASP, GLU, ARG, PRO and ARGSUCC) decrease; AA (VAL and CITR) increase; AA (GLY, LEU, PHE and ORN) are constant. The comparison between plasma and DBS matrices showed significant quantitative differences: - Increase in plasma levels of AC (C0, C2, C4, C5, C6, C8, C3DC, C10: 1, C10, C5DC, C12: 1, C12, C14: 2, C14: 1, C16DC and of the ratio CPT1). - Decrease in plasma levels of AC (C3, C4-OH, C5-OH, C4DC, C14: 1-OH, C16, C16: 1-OH, C16-OH, C18: 2, C18: 1, C18 and C18: 1-OH) - No differences for AC (C5: 1, C8: 1, C12: 2, C6DC, C12-OH, C14, C14-OH, C16: 1, C18: 2-OH, C18-OH and C18DC) In plasma all the AA show significantly increased values than in DBS. **CONCLUSIONS:** The quantitative and age-related differences of the Acylcarnitine and Amino Acids in the two analysed matrices add new information never described in the Italian population previously, giving new

reference ranges useful in the early diagnosis and followup of Inherited Metabolic Disorders (IMDs) screened by ENS.

O-022 - IS MATERNAL VITAMIN B12 DEFICIENCY A SUITABLE CONDITION TO BE INCLUDED IN NEWBORN SCREENING PROGRAMS? RESULTS OF THE EXPERIENCE IN SOUTHERN SPAIN

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BACKGROUND: Although vitamin B12 deficiency is not a primary target of expanded newborn screening (NBS) programs, markers for methylmalonic and propionic acidemias (C3 and C3/C2) may identify vitamin B12-deficient newborns. **OBJECTIVE:** The principal aim of this study was to describe the birth prevalence of maternal vitamin B12 deficiency detected through newborn screening in our population and to compare the sensitivity of NBS markers for this condition. **METHODS:** Amino acid and acylcarnitine levels were determined from 368,152 newborns' single DBS samples between April 2010 and December 2018 by tandem mass spectrometry (MS/MS) using a commercial kit (MassChrom, Chromsystems, Germany). A cutoff point of p99.9 was set for the healthy population (C3<3.87 µmol/L, C3/C2<0.17). Another sample was requested if increased levels of C3 and/or C3/C2 were present. All cases with persistently high levels were studied further, evaluating mother and child's CBC; plasma acylcarnitine and homocysteine, serum vitamin B12 levels; and urine organic acids. Mothers were also tested for anti gastric parietal cells (GPC) and intrinsic factor (IF) serum antibodies. **RESULTS:** C3 and/or C3/C2 levels were persistently high in 84 cases. Further biochemical tests showed 69 vitamin B12 deficiencies. The C3/C2 ratio (64/69) was a more sensitive marker than C3 (31/69). Most newborns were exclusively breastfed at diagnosis (50/69). One severe case presented with hypotonia and metabolic acidosis at detection, the rest ot the newborns were asymptomatic. 24 cases of probable maternal pernicious anemia were found. Newborns of mothers with pernicious anemia had a much more severe deficit than other newborns (tHcy: 40.6 µmol/L vs 16.6 µmol/L, p<0.0001; urine MMA: 321 mmol/mol Crea vs 68 mmol/mol Crea, p=0.01). All confirmed cases (infants and mothers) were treated with oral or intramuscular vitamin B12 and did not present hematological or neurological symptoms during follow-up**. CONCLUSIONS:** Nutritional vitamin B12 deficiency is very frequent in our population (1: 5,335). Sensitivity of MS/MS biomarkers for vitamin B12 deficiency in NBS is still unknown, but including the C3/C2 ratio as a primary marker increases a program's sensitivity. Systematic maternal screening for pernicious anemia is recommendable as it may identify the cause in a significant percentage of cases, which are also the most severe. Given a suitable screening strategy and a specific diagnostic and therapeutic protocol, vitamin B12 deficiency could be an appropiate candidate for systematic inclusion into NBS programs.

O-023 - SIMPLE AND FAST UPLC-MS/MS METHOD FOR QUANTIFYING 3-O-METHYLDOPA IN DBS: AN OPPORTUNITY FOR NEWBORN AND HIGH-RISK SCREENING OF L-AMINO-ACID DECARBOXYLASE DEFICIENCY

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Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive disorder caused by mutations in the *DDC* gene, which affects enzyme activity. This enzyme deficiency leads to increased levels of the L-dopa metabolite 3-O-methyldopa (3-OMD). Most patients present symptoms within the first years of life and they may have severe developmental delay. Diagnosis has been based on the sequencing of the *DDC* gene and/or in the assay of AADC in plasma, which may limit the diagnosis of the disease due to high cost and/or unavailability. Levels of 3-OMD have been described as elevated in plasma, urine, and dried blood spots (DBS) of AADCD patients. In this context, a simple and fast UPLCMS/MS method was developed for the quantification of 3-OMD in DBS aiming the application of this metabolite for newborn screening (NBS) of AADCD patients. Analyses were

performed with a Xevo TQ-S micro (Waters), using a Pursuit PFP column (100 x 2.0 mm, 3 µm) and the mobile phase consisted of a gradient system combining 0.1% aqueous formic acid and methanol for 2.2 minutes. DBS of 7 patients with a confirmed diagnosis of AADCD were analyzed and compared with 38 age-matched controls. All seven patients had very high levels of 3-OMD (average = 3,308 ng/mL, range: 1,367-12,302 ng/mL). All controls had low levels of 3-OMD with an average of 34 ng/mL (range: 20 to 331 ng/mL). All 7 patients had a confirmed molecular diagnosis by sequencing of the DDC. Three patients were homozygotes for the p.Arg347Gln variant and four were compound heterozygotes, with the following genotypes: p.Arg347Gln/Trp121Arg, p.Ser147Ile/Val60Ala, p.Gln190Prof*13/Arg347Gln, p.Gln190Argfs*13/Leu288Pro. It is also interesting to point out that one homozygous patient for the p.Arg347Gln variant treated with L-dopa had the highest level of 3-OMD (12,302 ng/mL), while another homozygous untreated patient had a much lower 3-OMD level (1,504 ng/mL). The validation of the UPLC/MS-MS 3-OMD assay in DBS enables its use for newborn screening with a simple and low-cost method.

O-024 - IMPLEMENTATION AND VALIDATION OF A SECOND-TIER TEST FOR METHYLMALONIC ACID BY LC-MS/MS.

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INTRODUCTION: To reduce the rate of recalls and false positives in expanded newborn screening (NBS) programs, the use of 2nd tier tests has become widespread, including the determination of MMA. We implemented a simple approach for methylmalonic acid (MMA) quantification in dried blood spot (DBS). We validate the method using follow-up samples of patients with confirmed Methylmalonic acidemia and controls subjects. **OBJECTIVE:** To implement and validate MMA determination by liquid chromatography–tandem mass spectrometry (LC-MS/MS) in DBS for its use as second tier test and evaluate MMA concentration in samples of different group of subjects. **METHODS:** MMA quantification by LC-MS/MS was implemented by isotopic dillution, using MMA-d^3 ($CD^3CH(COOH)_2$) as internal standard. DBS standard and control samples were made from normal donor blood spiked with MMA to final concentrations of 6 and 50 µmol/L. We collected and analyzed 61 samples of newborn controls (NBC) (age < 3 days, as defined in our NBS program), 64 samples of older controls (OC) (6 days to 30 years old), 3 Methylmalonic acidemia patients and 84 samples of patients with another IEM. DBS samples were extracted using 70% acetonitrile with 0,1% Formic acid. $ESI^{(-)}$ was used as ionization method and analytes were detected by Multiple Transition Monitoring (transitions 117 > 73 for MMA and 120 > 76 for MMA-d^3). **RESULTS:** The implemented LC-MS/MS method, showed good precision, accuracy and linearity with a recovery of 112 % and detection limit of 0,5 µmol/L (CV interday 5,95 % and 5,27 %; CV intraday 2,35 % and 1,44 %, for controls 6 and 50 uM respectively) for MMA in DBS samples. The levels of MMA we found for each group were: for NBC group ND-0,68 µmol/L, for OC ND-1,86 µmol/L, for patients with another IEM ND-2,28 µmol/L and for Methylmalonic acidemia patients 209,9-2104,8 µmol/L**. CONCLUSION:** We validated a simple and fast LC-MS/MS method for the quantification of MMA in DBS, allowing us to use it as a 2nd tier test in our newborn screening program. Quantification of MMA in samples from different groups of subjects is still under progress to establish our own reference range value.

O-025 - ADAPTATION OF THE AUTOMATED ARCHITECT TSH CHEMILUMINESCENT MICROPARTICLE IMMUNOASSAY (CMIA) FROM ABBOTT TO BE USED IN NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM.

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INTRODUCTION: Dried blood spot (DBS) are the recommended specimens for Newborn Screening (NBS) when biochemical markers are measured. Adaptation of methods designed for analytes determination in serum/plasma for use in DBS requires exhaustive adaptation and validation to guarantee results reliability. **OBJECTIVE:** To present the operative and analytical adaptations introduced to the Architect TSH kit from Abbott designed for human TSH quantification in serum/plasma, to be used in NBS for Congenital Hypothyroidism working on DBS. **MATERIAL AND METHODS:** Architect TSH is a third generation Chemiluminescent Microparticle Immunoassay (CMIA) (functional sensitivity: 0.0036 µU/ml), designed to be processed in a random access Architect autoanalyzer from Abbott. TSH determination requires 150 µL serum/plasma plus 50 µL of dead volume. Samples aspiration is made from primary tubes or sample cups. For assay adaptation, different variables were tried to optimize sample punching, elution and

aspiration, measurement and results calculation: a) elution buffers (PBS, PBS/Albumin 1 %, Tris pH=8.0, and AutoDELFIA® TSH buffer), b) elution volumes (250 to 400 µl), c) sample cups centrifugation (speed and time), d) elution conditions (60'/room temperature vs overnight/2-8 °C), e) postelution agitation (mode, speed and time), and f) calibration mode (dilution factor vs DBS calibration curve). Considering the DBS micro-volume, sample dilution and sample matrix, TSH calibrators on DBS (PerkinElmer) were run as unknown together with samples and controls. **RESULTS:** Final optimized assay conditions were as follows: a) punch 1/8" calibrators, samples and controls discs in sample cups, b) dispense 400 µl of PBS and allow to stand 10', c) centrifuge sample cups 5'/3400 rpm, d) elute overnight/2-8 °C, e) agitate 10'/210 rpm, f) load racks samples into the autoanalyzer, g) start the run, h) upload readings (RLUs), i) load RLUs in Multicalc Software, and j) calculate TSH concentrations regarding the DBS calibration curve. Autoanalyzer and assay performances were monitored processing serum and DBS controls, respectively**. CONCLUSIONS:** The Architect TSH adapted/optimized assay conditions allowed its implementation in NBS routine. In spite sample preparation is time- and labor-intensive, it can be put in line with the usual NBS Laboratory procedures. The Architect TSH functional sensitivity allowed optimal analytical responses despite the DBS micro-volume and sample dilution. To include DBS calibration curves was critical to optimize inter-run responses. Simultaneous work with 2 Architect $i2000_{SR}$ analyzers allows completing ≈ 1000 tests/4.5 hrs.

O-026 - DEVELOPMENT OF A WEB PLATFORM (INFORMATION SYSTEM) FOR THE COMPLETE COMPUTER MANAGEMENT AND INTEGRATION OF THE NEONATAL METABOLIC SCREENING PROGRAM IN MEXICO.

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INTRODUCTION: Neonatal screening programs operate a variety of information: It is essential that the information is organized, easily accessible and can be permanently audited. There are information systems that can carry out these functions, but not all of them meet the requirements of a comprehensive neonatal screening program that guarantees the user a correct follow-up of each case. **OBJECTIVE:** To report the results of a web platform developed and implemented for the management of the total information in real time of a comprehensive neonatal screening program in Mexico from September 2016 to December 2021. **MATERIALS AND METHODS:** The development of the platform was carried out with a multidisciplinary specialist team. Different technologies were analyzed, the web environment was chosen for its versatility. Quality metrics were considered to ensure usability and scalability. **RESULTS:** We developed a comprehensive Web platform (information system) that manages demographic information, statistics, sample traceability, results reporting by SMS and email services, online technical support, all from any electronic device that has an internet connection. 3,856,930 samples have been registered with an average daily record of 2,337 samples; 376,188 data capture errors have been detected and corrected, 45,583 suspected cases have been reported (repetition rate of 1.17%); 28,547 cases were confirmed with an incidence of 1: 644 and results reporting in an average of 2 days. **CONCLUSIONS:** The SySDQM (System & Screening de Químicos Maldonado) Web platform minimizes human error by sending automatic notifications for suspected and confirmed cases, automatically assigning status to samples, validating information and reporting results, for example it features an algorithm to detect second samples not identified by the user; the system also speeds up the availability of information, improves process times and audits indicators, generates the clinical history of each confirmed case and is an efficient system of documentation, statistical and epidemiological control, which optimizes the neonatal screening program for the achievement of their objectives.

O-027 - ANALYTICAL PERFORMANCE EVALUATION FOR NEONATAL TSH IN THE BUENOS AIRES CITY NEONATAL SCREENING PROGRAM USING THE CDC-QC MATERIAL AS INTERNAL QUALITY CONTROL AND SIGMA METRIC.

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INTRODUCTION: The Neonatal Screening Program (NSP) of the Buenos Aires City Government has four laboratories in networking, and uses de Six Sigma Metric Analysis (σ) to evaluate the analytical performance of Neonatal TSH (nTSH). **OBJECTIVE:** To assess the analytical performance of nTSH of the NSP during 2021 using Internal Quality Control (IQC) data, and to compare these results with the ones obtained in the period 2016-2018 using External Quality Control (EQC) data. **MATERIALS AND METHODS:** IQC data was collected from the specimens provided by the CDC (Atlanta, USA): lots F1901 and A2101 (mean value 12.00 and 14.35 uUI/ml blood respectively), since the concentration of these materials is near our cut-off level. The F1901 lot was used from January until October, and lot A2101 from August until December. The monthly results were analyzed: monthly Mean (mMean), monthly BIAS% (mBIAS%) and monthly CV% (mCV%). The Allowable Total Error (ATE%) stablished from the state of art of the method is 54%. Monthly Sigma (m_σ) was calculated according to m_σ=(ATE%-|mBIAS%|)/mCV%. All laboratories used DELFIA (PerkinElmer) reagents. The Sigma criteria adopted by de NSP considers the performance as Optimum if σ≥4.0, Desirable if 2.1<σ<4.0, and Minimum if σ≤2.0. The monthly number of IQCs among the laboratories varies, being 9 the monthly mean (with a minimum mean of 5 and a maximum mean of 16), with a total number of IQC results of 415 in the NSP. **RESULTS:** Out of the 47 m_σ results analyzed, 31.91% had Optimum Sigma, 57.45% had Desirable Sigma and 10.64% had Minimum Sigma. Comparing to the prior period of analysis (σ EQC results), it´s observed the concordance of results at the similar range of concentration (samples between 7 and 15 uUI/ml): 28.57% had Optimum Sigma, 57.14% had Desirable Sigma, and 14.29% had Minimum Sigma**. CONCLUSION:** The information provided by the Six Sigma Metric using the IQC data remarks the importance of this tool to control and follow-up the analytical performance of the test. It´s an advantage in temporal terms as the data is available before the release of the EQC reports, being this information used for the detection of improvement opportunities.

O-028 - PERFORMANCE INDICATORS OF A COMPREHENSIVE EXPANDED NEONATAL SCREENING PROGRAM IN YUCATAN, MEXICO.

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INTRODUCTION: Neonatal screening is a preventive medicine tool for the early detection of congenital diseases such as inborn errors of metabolism (IEM), which represent a public health problem that requires specific and comprehensive strategies for timely detection. In the state of Yucatan, Mexico, since 2008, a comprehensive expanded neonatal screening program (PITNA) has been implemented for 67 diseases. To ensure the efficiency and quality of the PITNA, the periodic evaluation and registration of different parameters is required. **OBJECTIVE:** To present the performance indicators of the PITNA of the Ministry of Health of Yucatan (SSY), Mexico. **MATERIALS AND METHODS:** Observational descriptive study of the PITNA of the SSY from 2008 to 2021. 67 diseases in blood samples on filter paper were analyzed by time-resolved fluorometry, MS/MS, isoelectric focusing and HPLC. The PITNA includes annual training for health personnel, collection of samples in the state's medical units, location and performance of confirmatory tests for suspected cases, and 5-year follow-up of confirmed patients. **RESULTS:** 230,638 births were registered, of which 92 % (211,683) were screened. 63 % of newborns (NB) were screened between 3 and 5 days of life. The results reporting was carried out in an average of 4 days from entry to the laboratory. 2,107 suspected cases were reported, with 100% recovery of these, allowing timely detection of 389 confirmed cases (1: 544 NB), repetition rate 0.10 %. The mean age at the start of treatment was 17.82 days. Congenital hypothyroidism (1: 1,091 NB) and glucose 6 phosphate dehydrogenase deficiency (1: 2,378 NB) were the most prevalent**. CONCLUSIONS:** The implementation of a PITNA contributes to improving public health services and provides timely detection of metabolic diseases to this sector of the population. Knowledge of these indicators allows us to identify opportunities for improvement in services: greater coverage, shorter results delivery times, recovery of suspected cases in less time, timely diagnosis and treatment of sick patients. A PITNA must be specific to each region, adaptable according to the geographic, social, medical capabilities and economic scope of each region or country.

ABSTRACTS SELECTED FOR POSTER PRESENTATION (IEM)

P-001 - GTP CYCLOHYDROLASE DEFICIENCY: AN UNUSUAL FORM OF

HYPERPHENYLALANINEMIA. A CASE REPORT.

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INTRODUCTION: The GTP cyclohydrolase deficiency is an autosomal recessive disease responsible for hyperphenylalaninemia and neurological impairment due to malfunction of certain neurotransmitters pathways related to tetrahydrobiopterin (BH4) deficiency. The GTP cyclohydrolase enzyme coded by GCH gene is the first step in the tetrahydrobiopterin synthesis pathway. The management of this disease includes a diet restricted in phenylalanine intake and prescription of forms of tetrahydrobiopterin like sapropterin and administration of neurotransmitters precursors like L-dopa/carbidopa and 5-hidroxytryptophane as well. **OBJECTIVES:** We report a female patient with hyperphenylalaninemia due to GTP cyclohydrolase deficiency as an infrequent etiology and also discuss the clinical and molecular outcomes **MATERIALS AND METHODS:** Retrospective medical record review of a female patient diagnosed with GTP cyclohydrolase. **RESULTS:** We report a female patient with high levels of phenylalanine detected by newborn screening into dried blood spot test samples. Phenylketonuria was suspected, so quantification of blood levels of phenylalanine and tyrosine were performed with abnormal results. The molecular panel of hyperphenylalaninemia was performed using next-generation sequencing technology. Two missense variants were detected on GCH gene of unknown significance on heterozygote state, c.664A>G and c.607G>A, resulting in protein changes p.Asn222Asp and p.Gly203Arg respectively. Pterins levels in urine were performed due to liquid chromatography-tandem mass spectrometry with low levels of neopterin and biopterin. Management was performed with a diet restricted in phenylalanine and then the use of sapropterin. Developmental delay and hypotonia are present although the lowering of levels of phenylalanine in the blood which were normal in further controls. L-dopa/carbidopa was initiated but not well tolerated. **CONCLUSION:** Two our knowledge this is the first report In patients GTP cyclohydrolase deficiency was reported in a Panamanian patient. The disease must be suspected in any patient with hyperphenylalaninemia and with unexplained neurological features. Molecular diagnosis should be performed in all patients with hyperphenylalaninemia.

P-002 - PTERIN DEFICIENCY: DIFFERENTIAL DIAGNOSIS IN A SERIES OF CHILEAN CASES.

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INTRODUCTION: Between 1 and 5% of Hyperphenylalaninemias (HPA) can be produced by BH4 deficiency, a group of disorders that affect biosynthesis and regeneration of this cofactor (BH4) of the enzyme Phenylalanine Hydroxylase (PAH) or by deficiency of DNAJC12 protein that acts as a PAH chaperone. Both defects present with a mild or moderate HPA, but with a neurological manifestation. **OBJECTIVE:** To describe a series of Chilean cases with DNAJC12 and pterin deficiency. Retrospective review of clinical records between 2010-2021. **RESULTS:** 7/8 patients with an HPA diagnosed by neonatal screening presented an altered neurological evolution, were studied to rule out pterin deficiency. 1/8 patients present after newborn period HPA and neurological symptoms. Were diagnosed with 3 due to DNAJC12, 4 cases PTS, and one secondary to GCCH1 mutation. The median age at diagnosis was x = 43.1 months, the most prevalent neurological symptoms were: 6/8 have developmental/cognitive delay, 3/8 have abnormal movement, 3/8 epilepsy and 2/8 have a neurodevelopmental disorder. All of them are on Phe restricted diet. 6/8 cases were supplemented with neurotransmitter precursors (levodopa/ carbidopa) according to specific diagnosis and international recommendations. 2 of them don't improve with the treatment, because of bad compliance to nutritional and pharmacological indications.2/8 responded well to dietary treatment only**.** **CONCLUSION:** Pterines deficiency or mutation in DNAJC12 must be suspected in patients whit HPA especially when appears neurological impairment despite a good Phe concentration, especially when its diagnosis is not considered in the neonatal screening program because the treatment could improve its neurological outcome. More studies are needed in order to evaluate different therapeutic recommendations for these patients and the inclusion of these genetic variants of HPA in neonatal screening programs.

P-003 - SAPROPTERIN DIHYDROCHLORIDE RESPONSIVENESS TEST IN THE MANAGEMENT OF PHENYLKETONURIA: CASE REPORT

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INTRODUCTION: Phenylketonuria (PKU) is a genetic disease caused by a congenital defect in phenylalanine (PHE) metabolism. Faulty phenylalanine hydroxylase (PAH) enzyme activity prevents the conversion of PHE to tyrosine, leading to an accumulation of phenylalanine in the blood (hyperphenylalaninemia). Patients with residual enzyme activity may benefit from the use of sapropterin dihydrochloride, a synthetic formulation of tetrahydrobiopterin (BH4) that acts as a cofactor of PAH, reducing PHE serum levels. **OBJECTIVE:** Responsiveness tests were performed in order to assess sensitivity to sapropterin dihydrochloride. **MATERIALS AND METHODS:** The tests occurred in November/2020 and May/2021, both lasting seven days. In total, we had the participation of n= 29 phenylketonuric patients undergoing treatment in the Newborn Screening Reference Center (NBSRC) of Hospital Materno Infantil Presidente Vargas (HMIPV), in Porto Alegre/RS. The participation of girls of childbearing age was recommended. Participants were instructed to administer 20 mg/kg of the drug once a day, associated with a source of dietary fat, in order to increase drug absorption. During this period, the patients had their blood drawn (DBS) on two occasions: before the drug administration and at 8h after it, as well as their food intake recorded. **RESULTS:** Responsiveness was assigned to patients who showed a 30% reduction in serum PHE concentration from the 0-48h prior pre-test levels. Twelve of twenty-nine patients were responsive to sapropterin dihydrochloride (41% responding). No adverse effects resulting from the drug were identified. Due to the covid-19 pandemic and other reasons, six participants dropped out of both trials**. CONCLUSION:** In general, patients responsive to sapropterin overload, besides the reduction in serum PHE levels, also reported an improvement in clinical symptoms. Some of the non-responsive patients reported improvement in symptoms, thus reinforcing the relevance of new studies that evaluate the use of sapropterin dihydrochloride in individuals who do not present a reduction in serum PHE concentration equal to or greater than 30% in relation to the mean before the use of the drug.

P-004 - DOES PHENYLALANINE PHYSIOLOGICAL FLUCTUATION AFFECT BH4 RESPONSIVENESS TEST RESULTS FROM A 24H-PROTOCOL?

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INTRODUCTION: Patients with phenylketonuria (PKU) can benefit from sapropterin dihydrochloride (BH4) if they are responsive. Protocols do not consider natural fluctuation nor variations in phenylalanine (Phe) intake in patients' responsiveness. ***OBJECTIVE:*** To describe BH4 responsiveness in PKU patients according to a 24-hour screening protocol and to assess the natural fluctuation and variation in Phe consumption in patients' responses. ***METHODS:*** An ambulatory test was performed. Day1: assessed the Phe natural fluctuation (collected in the morning, at baseline with 8h fasting, and after 8h); Day2: basal blood collection, followed by a 20mg/kg of BH4 single-dose ingestion. New collections were done 8h and 24h after BH4. Patients maintained their usual diet with Phe restriction and metabolic formula. Diet adherence was assessed by dietary records and Phe intake couldn't vary ≥30% between days. Patients were considered potentially responsive if they had a ≥30% reduction in Phe levels at 8h and/or 24h after 20mg/kg BH4 ingestion, considering the natural range of Phe plasma on day 1. Reduction between 28-30% (borderline) was considered responsiveness if the genotype was concordant. ***RESULTS:*** Twelve of the 15 were included in the analysis and one borderline patient (Phe reduction of -29.1%) without possibility to access the genotype was considered inconclusive. The median of Phe natural fluctuation was 5.9% (IQ25-75 -15.8: 16.8) and had no difference in responsiveness and non-responsiveness (p=0,059). Phe consumption had no correlation with pre-BH4 points (p= 0,760; p= 0,679; p= 0,788). Four mild PKU patients (33.3%) were responsive, being three responsive at 8h and 24h (Phe plasma reduction= -75.9±20.2% at 8h and -75.7±37.0% at 24h) and one in 8h (Phe plasma reduction -28.7%). The Phe median (IR 25-75) before and after BH4 in responsiveness was, respectively, 316.5µmol/L (235.2-613.9) and 187.27µmol/L (121.7-459.8), and in non-responsive was 435.0µmol/L (383.9-632.0) and

399.5µmol/L (348.1-548.3), respectively (p= 0.257 and p=0.136). If we don't consider the natural fluctuation, one responsive patient would be non-responsive**.** ***CONCLUSION:*** The 24-hour screening test with correction for the Phe natural range identifies a rate of potentially-responsive patients with mild PKU similar to that described in the literature. Phe intake should be objectively controlled on test days to avoid bias in determining responsiveness.

P-005 - FIRST PREGNANT PKU PATIENT TREATED IN THE NBS/PKU REFERENCE CENTER IN RIO GRANDE DO SUL, BRAZIL: CASE REPORT

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INTRODUCTION: Neuro-psychiatric effects are found in patients with Phenylketonuria (PKU), untreated or insufficiently treated, due to elevated phenylalanine (PHE). Similarly, high PHE concentration in pregnant PKU women exerts a teratogenic effect on growing and developing fetuses which leads to maternal phenylketonuria syndrome (MPKU syndrome). In Brazil, nationwide PKU's NBS started in 2001: the majority of teenagers/young adults patients, when classically pregnancy are unplanned and patients are often non-adherent. **OBJECTIVE:** Report the first case of a PKU pregnant patient in the NBS/PKURCRS. **CASE REPORT:** Patient diagnosed with PKU on NBS (PHE: first test 6mg/dl – 4d life; second test 8,9mg/dl – 12d life; third test 10,6mg/dl – 16d life). Treatment began on 24thd. No genetic testing. Responsive to sapropterin test. Always presented as a mild PKU, no compliant to treatment = regularly PHE between 10-14 mg/dl. In March 2021 (19 y) unplanned pregnancy was diagnosed: partially out of diet and doubts about pregnancy age and PHE levels. Hospitalized, ultrasonography evaluation: 5 weeks pregnancy and PHE 16 mg/dl, started restricted PKU diet. 6th week started sapropterin (10mg/Kg/d). PHE levels were reduced to 2-4 mg/dl, but in the 8th week, a miscarriage occurred. She got depressed, left the strict diet, disappeared from PKU consultation service, but sapropterin was taken continuously. In June 2021, informed the PKU team she was pregnant again. Presented to consultation with 3 weeks pregnancy, PHE levels lower (between 6-10mg/dl), using sapropterin, and ready to re-start strict diet. Presented herself to clinical-nutritional evaluation 2x/m, and pre-natal care 1x/m. PHE levels were planned to be sent every week (sometimes lab samples were only taken at hospital visits), and her plasma PHE was maintained at 2-10mg/dl (we tried to elevate sapropterin to 20mg/kg/d - government pharmacy did not accept). Ultrasonography revealed normal fetal development. Currently, 32nd week, fetal development 75th-90th centile, femur length and head circumference 50th centile**. CONCLUSIONS:** In our country, MPKU is a recent aspect of PKU care, and few centers have real expertise. Essential points should be: sexual education and planning since early teenager years; continuous efforts to maintain treatment compliance and possibility to use sapropterin in responsive girls since the beginning of puberty.

P-006 - MATERNAL PKU UNCOVERED AFTER TRUE POSITIVE NEWBORN SCREENING OF THE SECOND CHILD.

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INTRODUCTION: Newborn screening (NBS) programs of phenylketonuria (PKU) have been successfully implemented in many countries for more than 50 years. Late diagnosis of PKU still occurs and is an emergent phenomenon. In Europe, immigration from countries with no NBS programs is the cause of the late diagnosis of PKU. In Uruguay, the national NBS for PKU began in 2007 with MS-MS technology. In our country, there are women of child-bearing age born before NBS that do not know that they are affected by PKU. Their pregnancies could result in damage to the fetus expressed as intrauterine growth retardation, microcephaly, congenital malformations, dysmorphic facial features. **OBJECTIVE:** We present the case of a family of a true positive PKU newborn whose mother, who had been born before the NBS program, is affected by PKU. **CASE REPORT:** Female, a product of the second normal pregnancy and delivery of nonconsanguineous parents. Born at 35 weeks. Normal anthropometry and Apgar test. She was admitted at 8 days of life because of omphalitis. No evident dysmorphic features, normal cardiac and brain ultrasound. The mother has a mild intellectual disability. Noticeable difficulties in caring for the baby during her hospitalization led us to analyze the dried blood spot sample from the umbilical cord. After the high phenylalanine (Phe) result on this sample, the mother was studied confirming the diagnosis of PKU. Breastfeeding was suspended and the patient's Phe decreased. The mother refused

to start a diet and formula in order to maintain breastfeeding. It was quite difficult for her to manage with a combination of the special and standard formulas. It has been difficult to sustain Phe levels between 120-360 mmol/L. Familial mutations were identified, the father and older brother are carriers. This boy is 2 years of age and has microcephaly, failure to thrive and developmental delay. **CONCLUSION:** The offspring of PKU mothers untreated during pregnancy are affected by characteristic embryopathy related to the level of phenylalanine. In order to avoid similar cases like the one in this report, we have to educate our medical community, pediatricians and adults, emphasizing the importance of assaying the blood level to all females with mental retardation, no matter the age.

P-007 - UPDATE IN THE CHARACTERIZATION OF PHENYLALANINE HYDROXYLASE GENE MUTATIONS IN CHILEAN PKU PATIENTS

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INTRODUCTION: Phenylketonuria (PKU, OMIM 261600) is an autosomal recessive disease, caused by mutations in the Phenylalanine Hydroxylase PAH gene situated in chromosome 12q22-q24.2. To date, 1282 mutations have been described. The genotype is one of the main factors that determine the phenotype of this disease. **OBJECTIVE:** Update the characterization of PKU genotype and phenotype seen in Chilean PKU patients. **METHODS:** We studied the PAH gene by sequencing techniques to identify pathogenic mutations in 113 PKU subjects in Chile and Spain. We classified the genotype according to allelic phenotype values (APVs) and Genotypic Phenotype Values (GPVs). **RESULTS:** We identified 34 different mutations, 104 had biallelic pathogenic mutations while 9 had only one pathogenic mutation identified. Exon 7 included many mutations (23.5%), and 44% of mutations were missense, followed by splice ESS. The three most frequent mutations were c.1162G>A, c.1066-11G>A, and c.442-?_509+?del, all with classic AVP. 40 subjects out of 113 had GVPs = 0. Most subjects (>80%) had the classic GVP. Additionally, 4 patients with PTS, one with GCH1 and 3 with DNAJC12 mutations were identified. Classic PKU had mean phenylalanine (Phe) plasma levels at diagnosis at 19.5±9.3 mg/dL, 11.9 ± 4.9 mg/dL for milds and 11.6 ± 6.8 mg/dL for MHPs. For classic subjects mean Phe plasma levels during the last year were 5.59 ± 2.95 mg/dL, and 3.78 ± 1.08 mg/dL for MHP. Phe daily intake was 456 mg/d for classics PKUs, 497 mg/d for Mild, and 1049 mg/d for MHP subjects. Medical food intake was 1.44 gr/kg/d for classics, 1.69 gr/kg/d for Mild and 1 gr/kg/d for MHP group. **CONCLUSIONS:** The most frequent mutations in our Chilean patients were classic PKUs, which establish a characteristic phenotype with higher levels and lower Phe intakes compared to Mild and MHP forms. Therefore, in most cases, it is possible to predict phenotype by detecting the genotype and adjusting the patient's medical and nutritional management.

P-008 - PHENYLKETONURIA IN PERU: A DECADE OF FOLLOW-UP

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INTRODUCTION: Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency of phenylalanine hydroxylase leading to increased serum phenylalanine. It is detected by neonatal screening, which allows it to be treated early and avoid its fatal consequences. The Social Health Insurance of Peru, Essalud, which covers 30% of the population, has been screening since 2011. There are no previous studies in the country that describe the symptoms and follow-up of the treatment of children with phenylketonuria. **OBJECTIVE:** To describe the clinical characteristics and treatment followup of patients with PKU in a reference hospital in Peru. **MATERIAL AND METHODS:** Retrospective longitudinal study, includes patients treated at Rebagliati Hospital of Lima between 2011 and 2021. The study has the approval of the Pediatric Nutrition Unit of the hospital. **RESULTS:** Thirteen patients were included, nine (69.2%) with biochemical or genetic confirmation, and four (30.8%) without confirmation, followed up with fluorometric testing. The median age at diagnosis was 19 days, with an interquartile range (IQR) (2 - 44), two (15.4%) with late diagnosis, nine (69.2%) women, and twelve (92.8%) classic

PKU. At diagnosis, all eutrophic, two (15.4%) with autism spectrum disorder and one (7.7%) with delayed psychomotor development (DPD). Nutritional treatment included a phenylalanine-free formula, protein restriction, and mineral supplements. Twelve (92.3%) started nutritional treatment, with a median age of starting of 30 days (IQR 27.5-60). Five (41.7%) started treatment at diagnosis, and seven with a median delay of 20 days (IQR 12-23). Nine (75%) continue in treatment to date, with a median age of 68.5 months (IQR 44-103). During follow-up, one patient presented hypercalciuria. At the end of the follow-up, eight (88.8%) presented adequate psychomotor development, with median phenylalanine of less than 6 mg/ml, all of them eutrophic. IQ was not evaluated. One was admitted with delayed psychomotor development due to previous poor treatment and two (22%) had poor adherence to treatment**. CONCLUSIONS:** It is the first clinical-therapeutic follow-up study of phenylketonuria in a reference hospital in Peru.

P-009 - ANALYSIS OF FOOD FREQUENCY IN PHENYLKETONURIC PATIENTS SEEN AT A PKU REFERENCE CENTER SERVICE IN PORTO ALEGRE, RS, BRAZIL

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INTRODUCTION: Phenylketonuria (PKU), an inborn error of metabolism identified by Newborn Screening (NBS), causes an increase in serum phenylalanine (PHE) levels, when not properly treated. The management consists of a diet free of foods with high PHE content, associated with supplementation with metabolic formula (PHE-free amino acid formula) in order to ensure dietary protein intake. The relevance of the nutritional approach in the management of this condition emphasizes the need for studies investigating aspects related to the dietary profile. **OBJECTIVE:** To investigate factors related to treatment compliance based on an analysis of the food frequency of phenylketonuric patients seen at the NBSRC-PKU of the Hospital Materno Infantil Presidente Vargas (HMIPV). **MATERIALS AND METHODS:** Cross-sectional study that consisted of applying an electronic questionnaire (link forwarded to patients and guardians was generated by Google Forms). The survey contained thirty-one objective questions, and was subdivided into three domains, 19 questions focused on the analysis of food frequency. **RESULTS:** 59/133 (total group) respondents: 78% of responses were generated by parents or guardians. The least prevalent age group was children under two years old (8.5%). A frequent consumption (five times a week or more) of fresh/minimally processed foods was observed, representing 55.9% of the consumption of vegetables, 40.7% of fruits, and 30.5% of tubers. The same response was also obtained for the consumption of white or brown rice, portrayed by 55.9%. The intake of special foods with low PHE content like preparations containing manioc flour or tapioca (both Brazilian non-expensive products) was presented in 45.8% and 44.1%. Consumption of industrialized fruit juice, reported drinking it rarely, while the consumption of natural juice the prevalent frequency was five times a week or more (25.4%). The answer "never" was also frequent regarding the intake of conventional cereals (88.1%), milk and or dairy products (86.4%), eggs (96.6%), legumes 91.5%, (oilseeds) 94.9% and meat, seafood or sausages 93.2%**. CONCLUSION:** Dietetic habits involve multiple other aspects but the analysis of food frequency of our patients enables the reestablishment of behaviors and strategies to promote increased adherence to diet therapy.

P-010 - PREVALENCE OF OBESITY AND METABOLIC CONTROL OF PHENYLKETONURIC ADULTS IN THE FEDERAL DISTRICT IN THE COVID-19 PANDEMIC.

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INTRODUCTION: Some studies highlight the decline in metabolic control in adults and an increased risk of obesity, particularly in women with phenylketonuria(PKU). The main goal of PKU treatment is to achieve normal neurocognitive development, with adequate serum phenylalanine (PHE) levels and nutritional status. The COVID-19 pandemic, which required social distancing measures, may negatively affect access to multidisciplinary follow-up and control exams. **OBJECTIVE:** To characterize metabolic control, assess the adequacy of the number of consultations and the presence of obesity in phenylketonuric adults during two years of COVID-19 pandemics. **METHODS:** Cross-sectional study with data obtained from January/2020 to October/2021. PHE levels of 360umol/L at the frequency of 4 annual exams/consultations were considered adequate, criteria for overweight (BMI ≥25 kg/m2) and obesity (BMI ≥30 kg/m2) in adults were used. Descriptive data analysis was performed using Microsoft Excel 16.34. **RESULTS:** 15 (8F/7M) adults had an average

PHE: 565.5±243.1 umol/L, 33.3% (5/15) had adequate levels. 33.3% (5/15) performed the PHE dosage at the recommended frequency. The mean number of MSMS exams and consultations was 8±4. The mean BMI was 26.1±4.9 kg/m2. 66.66% (10/15) of the sample is obese or overweight. Patients over 30 years of age (n = 6/15), diagnosed and treated late, had a mean PHE of 601.1±307.4 umol/L, of which only 33% (n=2/6) had an adequate mean PHE, differing of the total sample, however, the BMI showed a higher increase 28.5±4.9 kg/m2**. CONCLUSION:** Most of the sample showed inadequate metabolic control and a high prevalence of overweight and obesity. This result corroborates international data that report greater difficulty in adhering to long-term dietary treatment in adults, results that may have been exacerbated by the COVID-19 pandemic, with the need to intensify care for transition to adulthood in Phenylketonuria.

P-011 - HEALTH TECHNOLOGIES: APPLICATION TO CONSULT THE QUANTITY OF PHENYLALANINE IN BRAZILIAN FOOD.

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INTRODUCTION: Food composition tables are essential to provide information on nutrient intake, prescription and follow-up of diets. In Brazil, the food composition table of the Brazilian Health Regulatory Agency (TCFA/ANVISA) has data to check the phenylalanine (Phe) content in foods, but there are no mobile applications to consult these data. **OBJECTIVE:** To develop a mobile application that facilitates the consultation of information about TCFA/ANVISA. **MATERIALS AND METHODS:** The study was approved by the Local Research Ethics Committee (Protocol: 19-0208). The application was developed by 1 medical geneticist, 4 metabolic dietitians, 1 nutrition student, 1 programmer and 1 PKU representative. A responsive website was developed as a pilot test. Upon completion of the prototype, the System Usability Scale will be used to measure the performance of the application. **RESULTS:** Monthly team meetings were held between January and July/2021 to collect requirements and initiate the development of the website and application. The functionalities chosen for the application were: 1)screen to browse nutritional information of foods (carbohydrates, proteins, lipids and Phe content) grouped by categories; 2)Phe Calculator: Allows the user to add foods, calculate daily Phe intake and compare it with the prescribed Phe; 3)Reports of Phe intake according to the Phe calculator registries; and 4)field for user feedback. **CONCLUSION:** The application is in an advanced stage and is expected to be made available to the public in the first semester of 2022, being a pioneer in Brazil for this purpose.

P-012 - DEVELOPMENT OF AN EDUCATIVE MATERIAL TO PROMOTE SELF-CARE OF CHILDREN AND TEENAGERS WITH PHENYLKETONURIA.

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INTRODUCTION: Phenylketonuria (PKU) is the most frequent of inborn errors of amino acids metabolism worldwide, and its main treatment is the nutritional restriction of phenylalanine (Phe), which is supplemented using a medical formula throughout life. Due to the difficulties for adherence to therapy, the biochemical follow-up by dried blood spot Phe determination must be periodical and permanent. Patients must be trained to get the best disease control and to avoid long-term neurological complications. To that end, the development of educative materials is an essential task to promote selfcare, especially in children and teenagers. **METHODS:** An animated short film was performed in After Effects® with plugin Duik-Bassel v2 and Photoshop®, Adobe Creative Cloud®. The storyboard was designed by metabolic specialist staff. The screenplay and characters were manually designed. A liveaction of the auto-sampling process was incorporated into the film. **RESULTS AND DISCUSSION:** A fourminute cartoon animated short film, named "Sanita Zanahoria adventures" was obtained. Spanish was the language of the characters and English subtitles were included. The importance of the correct autosampling, including drying, handling and shipping of Guthrie card to the laboratory for Phe determination was highlighted. **CONCLUSION:** The development of educative material for strengthening the skills of patients and promoting their self-care is important. The evaluation of the utility of the material by presenting it to patients and their families is ongoing.

P-013 - IMPACT OF THE COVID-19 PANDEMIC ON THE BIOCHEMICAL FOLLOW-UP OF PATIENTS WITH HPA/PKU IN A NATIONAL REFERENCE CENTER

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INTRODUCTION: Covid-19 pandemic has affected all health systems, and it has been a challenge for the medical care of patients with chronic diseases, such as phenylketonuria (PKU), that requires a permanent clinical and biochemical follow-up by the periodic determination of amino acids concentration from dried blood spots (DBS), which are necessary for diet adjustments. **OBJECTIVE:** To compare the number of samples and the blood phenylalanine (Phe) and tyrosine (Tyr) concentrations in two periods; first, before the pandemic, and second, during the pandemic in a national specialized metabolic reference center. **MATERIALS AND METHODS:** Retrospective analysis of the number of samples received in a metabolic center, and the Phe and Tyr blood concentrations, in two periods, first from May 2018 to February 2020, and second, from March 2020 to December 2021. Statistical differences were investigated among the number of samples and between Phe and Tyr values in the studied periods. **RESULTS:** Before the pandemic, DBS from 68 patients was received for follow-up. During the pandemic, only 34/68 patients sent samples. From those 34 patients, 438 samples were received. A significant decrease in the number of samples sent to our center was observed during the pandemic compared with the previous period ($p < 0.0001$) since 316 of them were received before the pandemic and 122 were received during the pandemic. Furthermore, Phe concentration was significantly increased in the DBS during the pandemic period compared with the period before the pandemic ($p < 0.018$), since the mean blood Phe concentration was 297 µM before the pandemic and 381 µM during the pandemic. Tyrosine levels remained without any significant change. **CONCLUSION:** The COVID-19 pandemic had a deleterious impact on the follow-up of HPA/PKU patients in our center, observed as a significant decrease in the number of samples. Moreover, the most concerning fact were the elevation in Phe blood levels of patients during the pandemic, which would be related to several factors such as difficulties to send samples, and reduced family care of the HPA/PKU patients due to a major concern in the COVID-19 infection, and its economic and social consequences for the families.

P-014 - EFFECTS OF THE SARS-COV-2 PANDEMIC ON NUTRITION AND METABOLIC CONTROL IN CHILEAN PATIENTS WITH PHENYLKETONURIA.

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BACKGROUND: Since 1992 Chile has had a Newborn Screening Program for Phenylketonuria (PKU). The PKU treatment protocol in Chile consists of a continuous follow-up and education by the clinical team and the intake of the protein substitute without Phe subsidized for life by the Chilean government. In March 2020, a pandemic by SARS-Cov-2 virus was declared, changing important health policies and imposing lockdowns and social distance. To maintain the follow-up, we adopted a telemedicine service and continue with metabolic control(metabC) by dry blood spot filter paper. **AIM:** Evaluate the impact of the SARS-Cov-2 pandemic in metabC and nutritional status in Chilean PKU subjects. **METHODS:** Longitudinal study compared 3 times: Pre-pandemic (P1) April to September 2019; first-pandemic time (P2) April to September 2020, considered a focus group of the analysis; and second-pandemic time (P3) April to September 2021. Paired T-test was used to compare P2 with P1 and P3 independently. The values were represented in median (min-max), average (±SD) and percentages. Statistical significance $p<0.05$. **RESULTS:** In P2 we had 157 effective counseling by telemedicine. Of them, 92% we could obtain real weight and height, and 94% kept sending the sample for metabC of which 52% correspond to subjects between 4 and 14 years old. The median of samples sent in P2 was 4 samples (1-26), where the 1 to 3-year-old-group was maintained according to the expected with a median of 10 samples (2-26). Regarding the Phe concentration (PheC), the average in P2 was 312 umol/L(±228), where subjects between 1 to 14 years old stayed within the expected metabC. Comparing the situation of these subjects in P1, both the mean of the samples and the PheC were higher ($p <0.05$). And the situation in P3, the number of samples was a lower but not significant difference ($p=0.07$) and the PheC increased significantly (127 subjects; 4.74±2.6 vs 5.25±3.4; $p=0.03$). In relation to the nutritional status of this sample, in P2 the overweight/obesity reached 48%; comparing the situation in P1, this percentage was lower (41%), while in P3 had a marked increased (52%)**. CONCLUSION:** A beneficial impact on PheC was observed during the lockdown, the opposite was observed with overweight/obesity in PKU subjects.

P-015 - DIFFERENCES IN THE METABOLIC PROFILE OF TYROSINEMIC TYPE-1 PATIENTS UNDER MEDIUM AND LONG-TERM TREATMENT WITH NITISINONE.

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Tyrosinemia type-1 (HT-1) is an inborn error of metabolism caused by a defect in the tyrosine degradation pathway and characterized by the accumulation of the toxic metabolite, succinylacetone (SA). Treatment of HT-1 patients is based on nitisinone (NTBC) administration and tyrosine- and phenylalanine-restricted diet. Monitoring of biochemical, nutritional, and clinical parameters in patients has been carried out quarterly in our center since 1998. Recently, we have proposed for our cohort of HT-1 patients a therapeutic range of NTBC associated with the concentration of NTBC in blood and the optimal levels of biochemical and hepatic parameters. Since our patient's cohort is highly diverse in terms of age at diagnosis, and time to NTBC exposure (<1 year to >20 years), we aimed to explore the effects of medium and long-term exposure to NTBC over metabolic parameters in HT-1 patients. We retrospectively analyzed the following parameters: NTBC levels, SA, liver biomarkers, amino acids levels, and acylcarnitine profile in 43 samples from fifteen Tyr-1 patients in a one-year follow-up. The age range of patients was from 1 to 24 years, and the range of NTBC time treatment was from 6 months to 24 years. Data were analyzed as independent samples and multivariate analysis was performed by associating each laboratory parameter with time of NTBC exposure or with three different intervals of NTBC treatment period (<5 years; 5-10 years; >10 years). We found a positive and significant correlation (Spearman analysis) between the time of NTBC exposure with: acylcarnitines (C3: 0.6526, $p<0.0001$ and C16: 0.7228 $p<0.0001$), plasmatic tyrosine concentration (0.5374, $p>0.0001$) and citrulline (0,5841, $p<0.0001$). Otherwise, negative correlation was found with alfa-fetoprotein (-0.4042, $p<0.0027$) and aspartate aminotransferase (-0.6729, $p<0.0001$). In conclusion, differences could be found in the metabolic profile of HT-1 patients under long-term treatment with NTBC compared to HT-1 patients' medium term-NTBC exposure. Further studies are required to evaluate the role of metabolites well associated with the time of NTBC exposure in HT-1 patients and their possible implications in the longterm complications of the disease.

P-016 - A MACHINE-LEARNING APPROACH TO DEFINE -THROUGH CLINICAL AND BIOCHEMICAL BIOMARKERS- SUBTYPES OF TYROSINEMIA TYPE-1 PATIENTS UNDER ACTIVE FOLLOW-UP

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Hereditary tyrosinemia type-1 (HT-1) is an autosomal recessive inborn error of metabolism caused by the deficiency in the enzyme fumarylacetoacetate hydrolase (FAH), leading to hepato-renal complications. Early diagnosis is crucial to promptly initiate treatment that combines administration of 2-(2-nitro-4-trifluoromethyl benzoyl)-1,3-cyclohexanedione (NTBC) and tyrosine/phenylalanine restricted diet. In Chile, newborn screening does not include HT-1 and patients are clinically diagnosed in later stages. Therefore, patients might present sudden hepatic failure or hepatocarcinoma, in spite of their adherence to treatment. Our patients are clinically diverse and it has not been entirely determined which factors contribute to more or less extent to the prognosis of disease severity. The aim of the present study was to identify subpopulations of HT-1 patients in active follow-up by using a machine-learning (ML) approach based on biochemical and clinical features. Our approach considered synthetic data augmentation to achieve well-defined subpopulations. We collected 6-time points of retrospective clinical, dietary and biochemical data from the quarterly follow-up from our patients (n=19). Biochemical data comprised 16 parameters, including NTBC in blood, Succinylacetone (SA) in urine, amino acids, alpha-fetoprotein and liver biomarkers. Then we labeled patients as adherent when NTBS > 15 µmol/L in DBS, SA < 0.5 mmol/mol creatinine and Tyrosine < 600 µmol/L in plasma. Otherwise, the patient was labeled as non-adherent. Using this labeled data, we generated synthetic adherent and non-adherent patients via Generative Adversarial Networks (GANs), thus we ended up having a hybrid dataset (empirical data plus synthetic data). From this hybrid dataset, we identified subpopulations of patients via two-step dimensionality reduction; metabolite reduction followed by temporal reduction, in combination with semi-supervised clustering techniques. In conclusion, this is a pilot ML-based study applied for HT-1 patient adherence classification. By data augmentation through data synthesis, we were able to identify subgroups of HT-1 patients according to follow-up adherence criteria. Future studies integrating laboratory and

clinical data from multiple centers will allow us to develop predictive models for disease severity and to anticipate liver complications.

P-017 - CLINICAL, BIOCHEMICAL AND MOLECULAR FEATURES OF TYROSINEMIA TYPE I PATIENTS DIAGNOSED AND FOLLOWED AT HOSPITAL JUAN P GARRAHAN, ARGENTINA

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INTRODUCTION: Hereditary tyrosinemia type 1(HT1) is a rare inborn error of tyrosine metabolism which can be a fatal disorder without treatment. Early treatment by nitisinone (NTBC) and diet is essential to prevent acute liver failure, renal dysfunction, liver cirrhosis, hepatocellular carcinoma (HCC) and improves survival. Current data indicates that HT1 patients treated with NTBC are at risk of presenting developmental delay and impaired cognitive functioning. **OBJECTIVES:** The aim of this study is to characterize clinical, biochemical and molecular findings in 13 Argentinean HT1 patients and describe the appearance of complications. **PATIENTS AND METHODS:** Data of 13 patients from one center in Argentina was collected retrospectively including diagnosis, biochemical parameters, therapy and followup from January 1990 to November 2021. **RESULTS:** Eight patients had a history of dead siblings. The median age at symptoms was 6 months (4 days-36 m), the median age at diagnosis was 8.5 months (13 days-45 m). Clinical features at diagnosis included: liver (7), renal tubular dysfunction (4), acute liver failure (6), hepatic nodules (9), cardiomyopathy (2) growth retardation (4) and rickets (3). Media values of alpha-fetoprotein were 341341,45 ng/ml (14253-1499489) and normalized within the first year of therapy (except in 4 patients). Two were born before NTBC became available and died from HCC. Median time of NTBC treatment was 91,5 months(31-225m) and mean delayed NTBC treatment was 1,1 months(0-2m). A significant correlation was found between tyrosine and phenylalanine levels ($r=0.474$; $P < 0.001$). Tyrosine levels increased with age($r =0.471$;$p<0.001$). Three NTBC treated patients underwent liver transplants because of HCC suspicion at 17, 4 and 1,8 years of life. One of them had renal involvement later. Neurocognitive testing (WISC-IV) was performed in 6 NTBC treated children and one liver transplant. IQ values ranged from mild-normal (63-99) and 3 exhibited learning difficulties. Neither plasma tyrosine nor phenylalanine level was correlated with IQ indices. A significant correlation was found between IQ and NTBC use ($r=-0.927$; $p = 0.024$)**. CONCLUSIONS:** Treatment with NTBC has improved the survival rate of HT1. Treatment with NTBC after 2 months of life is associated with cirrhosis and/or HCC. At longterm follow-up, most patients showed cognitive impairment. Prospective studies are required to characterize neurocognitive outcomes. This highlights the importance of regular cognitive assessments.

P-018 - TYROSINEMIA TYPE 1: REPORT OF THE THIRD CASE CONFIRMED IN PERU

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INTRODUCTION: Tyrosinemia type 1 (HT1) is an inborn error of tyrosine catabolism caused by the defective activity of fumarylacetoacetate hydrolase with progressive liver disease, renal tubular dysfunction and peripheral neuropathy. The estimated birth incidence is 1: 100,000 worldwide. treatment with oral nitisinone has notably improved prognosis and life expectancy. **OBJECTIVE:** This report presents the third biochemically and molecularly confirmed case of HT1 successfully treated in our hospital. **MATERIAL AND METHODS:** We present and describe the clinical and biochemical findings of a new case of HT1 managed at Rebagliati Hospital of Lima, Peru. **RESULTS:** 2- year- old male, was the second child born to healthy non-consanguineous parents., Born by cesarean section due to acute fetal distress, birth weight 2250 gr. Good psychomotor development with no significant pathological or family history. From the age of 18 months abdominal distension, failure to thrive and intermittent febrile episodes were noticed. Was admitted with 10 days of nausea and vomiting. Abdominal ultrasound performed revealed cirrhosis, nodules of liver regeneration and nephromegaly. Laboratory investigations documented high alpha-fetoprotein levels: 27,025 ng/ml (NV<30ng/ml), altered coagulation and liver profile, elevated plasma tyrosine, methionine and succinylacetone. 4-OH-phenylactic, 4-OH-phenylacetic, 4-

OH-phenylpyruvate, and succinylacetone (9mmol succinyl acetone/mol creatinine) were markedly increased in urine. A genetic panel for metabolic diseases was carried out, the pathogenic variant c.1062 + 2TG was detected in the (FAH) gene in homozygosity, which confirmed the diagnosis of HT1. Treatment was started with oral nitisinone at a dose of 1mg/kg once a day, a protein-restricted diet and phenylalanine and tyrosine-free formula. A rapid improvement was observed in his general condition, coagulation profile and in the level of alpha-fetoprotein and succinylacetone at 2 months of follow-up. Currently, he continues on treatment with favorable evolution**. CONCLUSIONS:** This is the third patient with HT1 with biochemically and molecularly confirmation successfully treated at our hospital.

P-019 - CLINICAL EVOLUTION OF A COHORT TYROSINEMIA TYPE 1 PATIENTS IN CHILE: OUTCOME FROM 25 YEARS IN FOLLOW UP PROGRAM AT A NATIONAL REFERENCE CENTER

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INTRODUCTION: Tyrosinemia Type 1 (HT-1) is a rare autosomal recessive inherited inborn error of metabolism in the tyrosine catabolic pathway due to deficiency of the enzyme fumarylacetoacetate hydrolase. Without treatment, 90% of patients develop hepatic carcinoma. NBS is available for this disease in Chile but has yet not been implemented on the entire population. **OBJECTIVE:** To describe the clinical evolution of a cohort of Chilean patients in active follow-up in a national reference center, INTA University of Chile since 1996.**METHODOLOGY:** Retrospective review of clinical records from 1996 to 2022. **RESULTS:** a total of 23 patients has been diagnosed with HT-1 in this period, currently 20 patients are in our active follow-up program, 2 patients had died: one was prior to transplantation, and the other one was because of complications after transplantation, both of them before the year 2000. All patients have been managed according to the Chilean protocol with NTBC and tyrosine-phenylalanine restricted diet since 1996. The Median time in follow-up =10, 4 years. Median age at diagnosis = 16,15 months. Mean exposure time to NTBC = 10 ,8 years. Mean tyrosine plasma levels = 534,73 umol/L and mean NTBC plasma levels = 52,51umol/L. All of them were diagnosed symptomatically except one (familiar case). The most frequent clinical presentation was hepatomegaly with or without rickets 15/20 and acute hepatic failure 7/20. Only 2/20 patients in the active follow-up program developed a hepatic carcinoma despite good metabolic control, both were successfully liver transplanted**. CONCLUSION:** This cohort of patients in Chile demonstrates an overall good clinical outcome as treatment prevents the development of serious complications like hepatic carcinoma, changing drastically the survivability of treated patients. This fact reinforces the idea that this treatable metabolic condition must be included in newborn screening programs, especially in developing countries. In Chile, access to NTBC treatment is guaranteed for this group of patients by law 20.850 since 2015. Also, it is necessary to standardize protocols according to published international consensus, consolidate a multidisciplinary team for an optimal followup program and achieve a favorable long-term outcome.

P-020 – NUTRITIONAL STATUS IN TYROSINEMIA TYPE 1 CHILEAN SUBJECTS

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INTRODUCTION: Tyrosinemia type 1 (HT1) is an autosomal recessive inherited metabolic disease (OMIM 276700) caused by fumarylacetoacetate hydrolase (FAH) deficiency in the liver and kidney. Without diagnosis and treatment, patients develop liver failure, hepatocellular carcinoma, porphyria-like neurological episodes and renal tubulopathy. Treatment of HT1 consists of the use of NTBC (2-(2 nitro-4-3 trifluoro-methylbenzoyl)-1, 3-cyclohexanedione) to block succinylacetone (SA) synthesis and dietary restriction of phenylalanine (Phe) and tyrosine (Tyr) with the prescription of protein substitute free of Phe and Tyr; in addition to a strict multidisciplinary follow-up. **OBJECTIVE:** describe the nutritional status of Chilean subjects with HT1. **METHODS:** We conducted a descriptive cross-sectional statistical analysis of the 18 Chilean patients, who maintained the Chilean treatment protocol in 2021. **RESULTS:** 12/18 are female subjects. The mean age was 11.9±6.2 years. Around 61% complied with the follow-up program in 2021, which consists of biochemical tests, NTBC doses, medical and dietitian appointments. Tyr plasma levels were 385±118 umol/L (reference value (rv): 200 – 600 umol/L) and Phe 42.5±13.2 umol/L (rv: 20 – 80 umol/L), both

in therapeutic range. NTBC doses were 0.9±0.2 mg/kg/d, maintained SA excretion in urine below 0.5mmol/mol of creatinine. Only 16 of them had weight and height in 2021, all had a normal height (z-score = -0.3±0.8), and 44% present overweight/obesity. The dietary data was: mean Phe+Tyr intake 763±307(269-1899) mg/d, daily total protein 61.3±20.2 gr/d (1.7±0.5gr/kg/d). The protein substitute represents around 90% of the daily protein intake (1.5±0.2gr/kg/d) and just 28% need L-Phe supplement to improve Phe plasma concentration (270-1200 mg/d). Regarding micronutrients, 89% maintain their calcium, iron and zinc supplementation. **CONCLUSIONS:** HT1 cohort accomplished with the follow-up program, achieving the nutritional goals determined in the protocol. Most patients had a normal nutritional status, Tyr and Phe plasma concentrations within range; and SA undetectable excretion. This decreases the possibility of HT1 long-term complications.

P-021 - TYROSINEMIA TYPE III: REPORT OF A MEXICAN CASE AND IMPORTANCE OF THE STUDY OF SIBLINGS.

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INTRODUCTION: Tyrosinemia type III or hawkinsinuria is an inborn error of tyrosine metabolism characterized by mild hypertyrosinemia and increased urinary excretion of 4-hydroxyphenyl-pyruvate, 4-hydroxyphenyl-lactate, and 4-hydroxyphenyl-acetate. This rare disorder (1: 1,000,000 NB) is poorly studied in Mexico. The objective of this report is to present a family with tyrosinemia type III.**CASE REPORT:** Male patient, term product of GII, PII, non-consanguineous parents, inbred population, birth weight 3,385 g, height 50 cm, Apgar 9/9. The first newborn screening (NBS) showed high tyrosine 897 µM (normal 26-115), with normal succinylacetone. A second screening test showed persistently high tyrosine 683.76 µM and normal succinylacetone. He had an antecedent of neonatal jaundice that did not require treatment. Medical evaluation, at 2 months 28 days of age, showed slightly hepatomegaly and indirect hyperbilirubinemia 13.53 mg/dl (0.6-10.5) and nephrolithiasis. The molecular test showed a pathogenic variant in HPO gene c.61T>C or p.(Ser21Pro), in the homozygous state. He started with free tyrosine and phenylalanine formula, which provided 1.65 g/kg/day of protein, tyrosine requirements were given with breast milk on demand, after each formula intake. With this diet, his blood tyrosine levels decreased to 285 µM. Sibling: Term male, 1 year 10 months old. Product of Gl, Pl, birth weight 3,380 g, height 51 cm, Apgar 9/9. Normal newborn screening, without tyrosine determination. As part of the familiar study in our center, a metabolic screening was performed, showing hypertyrosinemia of 1068 µM. Complications such as abnormal neurodevelopmental skills were found, especially in the language and behavioral areas. He started treatment at 22 months of age with a low tyrosine and phenylalanine diet (total protein intake 1.87 g/kg/day). With this diet, his blood tyrosine levels decreased to 184 µM**. CONCLUSION:** Differential diagnosis of hypertyrosinemia observed in the NBS is essential to establish adequate treatment, and early treatment must be established to prevent complications. The integral study of the family is required to detect affected siblings and should be done.

P-022 - MAPLE SYRUP URINE DISEASE (MSUD) ASSOCIATED WITH CLIFAHDD SYNDROME: A CASE REPORT

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INTRODUCTION: MSUD is an autosomal recessive aminoacidopathy, due to a defect in the branchedchain alpha-keto acid dehydrogenase enzymatic complex and accumulation of valine, isoleucine and leucine (VIL). The classic neonatal form must be diagnosed and treated early to avoid neurological sequelae or death. In Chile, it is not included in the neonatal screening program. Cases are diagnosed by metabolic decompensation or a family history of MSUD. CLIFAHDD is a syndrome that associates limb and facial contractures, hypotonia, and psychomotor development delay. Epilepsy has also been described. It´s inherited as an autosomal dominant trait and explained by a de novo mutation of the NALCN gene, which encodes for a sodium channel. It can cause death before the end of the first year of life. **OBJECTIVE:** To present the case of a newborn with both pathologies, which made the diagnosis of MSUD difficult. **METHODOLOGY:** Review of the medical records of the centers that treated the patient. **CASE REPORT:** Female newborn, first child, non-consanguineous parents, prenatal diagnosis of polyhydramnios and severe growth restriction. Cesarean delivery 37 weeks, Apgar 5-8, weight 1765 g. Examination: Dysmorphic facies, distal arthrogryposis in 4 limbs. She presented epileptic seizures since the first day of

life. Since day 9, she presented episodes of apnea, increment of epileptic seizures, and coma, requiring mechanical ventilation. Laboratory: Metabolic acidosis with an increased anion gap, normal lactate, mild hyperammonemia, and moderate ketosis. On day 17, an amino acid profile with increased VIL was informed. Brain magnetic resonance image showed diffuse involvement of supra- and infratentorial myelin. Specific treatment for MSUD was started on day 17. She had multiple infections and progressive multisystemic deterioration, dying at week 10. Postmortem exome results confirmed MSUD and CLIFAHDD syndrome**. CONCLUSIONS:** Our case shows that a dysmorphic genetic syndrome and an inborn error of metabolism can coexist. In this case, the high suspicion of a genetic syndrome made early diagnosis of MSUD difficult. In turn, the catastrophic evolution of the patient was most likely influenced by the poor prognosis of CLIFAHDD syndrome.

P-023 - MAPLE SYRUP URINE DISEASE (MSUD): EARLY NUTRITIONAL MANAGEMENT OF SIBLINGS DIAGNOSED AND TREATED FROM BIRTH

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INTRODUCTION: Classic severe and neonatal MSUD leads to impaired cognitive function presenting neurological symptoms in the first days of life. Treatment consists of dietary restriction of branched-chain amino acids: leucine, valine and isoleucine (LVI) as well as close monitoring of plasma amino acid (AA) levels. **OBJECTIVE:** To describe the nutritional management of two newborn siblings of patients with MSUD from the neonatal period to the present. Subjects/methods: Two families with newborn siblings of patients with MSUD had scheduled their deliveries and were treated from birth in the Neonatology Unit. Feeding regimens, dietary intakes (calories/protein/LVI), and specific biochemical parameters (AA) were described and analyzed from medical records from birth to hospital discharge to the present. **RESULTS:** Both infants started treatment with a high glucose intravenous line (IV) during the first 24h of life. On the 2nd day, they started enteral feeding by providing 0.5g/kg of intact protein. Plasmatic leucine and alloisoleucine levels increased 3 times over normal values providing evidence to diagnose. Protein restriction and LVI-free formula were indicated according to their nutritional requirements and SERN/GMDI guidelines. Protein and LVI intakes were titrated through close metabolic monitoring according to biochemical values and adjusted to weight gain. Case 1 (discharged from hospital on the 16thday): 110 kcal/kg; 2.9 g total protein/kg; 0.7g intact protein/ kg; 78 mg of leucine/kg and Case 2 (discharged on day 24): 138 kcal/kg; Total 3g protein/kg; 0.7g intact protein/kg; 70 mg of leucine/kg. Currently, both patients (8 and 4 years old) have adequate development, growth and good metabolic control, with good adherence to dietary treatment, without metabolic decompensations. Case 1: 2400 kcal/day; 45g Total protein/day; 8g intact protein/day; 370mg leucine/day and Case 2: 2500 kcal/day; 38g total protein/day; 7.8g intact protein /day; 310mg leucine/day. Both of them consume the total intake orally, exceeding the daily amounts of energy according to their requirements and dietary prescriptions indicated**. CONCLUSION:** The immediate and early postnatal medical-nutritional treatment of newborn siblings in families with MSUD is essential during the first hours of life. The subsequent close follow-up and monitoring by a metabolic team allow us to improve the prognosis of this disease later in life.

P-024 - NUTRITIONAL ASSESSMENT PRE AND POST-LIVER TRANSPLANT IN PATIENTS WITH INBORN ERRORS OF METABOLISM: MAPLE SYRUP URINE DISEASE AND TYROSINEMIA TYPE 1

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INTRODUCTION: Some metabolic disorders cause progressive liver injury, eventually leading to cirrhosis and liver failure. Liver transplantation (LT) is the treatment of choice when other therapeutic options are not adequate or do not yet prevent metabolic decompensation. **OBJECTIVES:** To evaluate the nutritional evolution of 10 patients who had LT at the Hospital de Clínicas de Porto Alegre, Brazil. **METHODOLOGY:** Retrospective study with convenience sampling. Data were collected from the medical records such as weight, height, body mass index, routine biochemical tests and, food intake and metabolic formula. **RESULTS:** From 2008 to 2021, 10 patients were included, with age at diagnosis between 15 days to 10 years, 4 TT1 and 6 MSUD, with ages at LT ranging from 11 months to 12 years, 7/10 received LT from a deceased donor. The indication for LT was hepatocellular carcinoma (n=3), cirrhosis (n=1) and frequent metabolic decompensation (n=6). The z-score mean pre and post-LT were: height/age - 1.33 ± 0.85 and -1.33 ± 0.88 (p=0.959); weight/age 0.53 ± 1.73 and 0.07 ± 1.34 (p=0.314);

weight/height 0.82 ± 2.24 and 0.96 ± 1.84 (p=0.515). 6/10 patients maintained their nutritional status (NS) after LT (overweight n=3, obesity n=1; risk for overweight n=2). 2 patients showed improvement in NS: 1 coming out of malnutrition for overweight risk and 1 underweight for normal weight; and 2 patients had a worsening in NS: 1 risk of overweight and being classified as overweight and 1 being classified as malnutrition. There was no significant difference in protein status biomarkers, which remained in the normal range pre and post-LT (lysine p=0.093, methionine p=0.074 and albumin p=0.646). Before LT all patients used metabolic formula (MF), after surgery, it was suspended and the diet was allowed according to age. Some patients (MSUD=5, TT1=1) maintained food selectivity and had to maintain the use of tube feeding**. CONCLUSION:** LT is an alternative for patients with IEM, however, most patients showed no change in their NS or improvement in biochemical tests. The multidisciplinary team is important after LT considering the difficulty these patients have to introduce an unrestricted diet.

P-025 - NEONATAL NONKETOTIC HYPERGLYCINEMIA. FIRST MEXICAN REPORT; HOMOZYGOUS MUTATION IN THE GENE *GLDC*, C.2219C>G (P.C740G)

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INTRODUCTION: Nonketotic hyperglycinemia (NKH) is an autosomal recessive disease, four associated genes are known: GLDC, AMT, GCSH, and GCSL. It affects the mitochondrial system of glycine cleavage. **OBJECTIVES:** Describes the clinical presentation of an NKH patient and the management in our institution. **MATERIAL AND METHODS:** A case report results, Female patient of 3 months old, from Mexico. Parents without medical history relevance. Normal delivery, without complications; At 2 days old, she had hypoactivity, a "weak" cry, absence of suction reflex and cyanosis, MRI with hypoplasia of the corpus callosum, she started seizures at 30 days old. We received her at the National Medical Center "20 de Noviembre", she had apnea episodes, the video EEG with substitute base rhythm by a pattern of attenuation and outbreak of slow waves, she needed PICU management, levels of glycine were 1600 mmol/l. Clinical presentation was compatible with NKH, genome sequence confirmed it, with a homozygous mutation in the GLDC gene, c.2219C>G (p.Pro740Arg), she was treated with dextromethorphan and sodium benzoate. She had a good evolution and was discharged from the hospital**. DISCUSSION:** The NKH has a low prevalence, in our country, it doesn´t exist in any prevalence studies. Affected patients have a normal examination at birth, the clinical symptoms appear on the first 24 hours of life with lethargy and/or seizures. Once the first symptoms have begun, the patients have no spontaneous, motor, and sensory response. When hypotonia and apnea episodes appear, they have high morbimortality. Dextromethorphan is used to NMDA antagonist and this has shown beneficial effects in neurological manifestations, like our patient. Sodium benzoate binds glycine to form a hippurate and be excreted in the urine. Diazepam is a competitive inhibitor of the binding sites of glycine NMDA receptors. In this patient, the presence of the homozygous mutation in the GLDC gene was classified as class 3. Pathogenic variants in this gene are associated with NKH, also known as glycine encephalopathy.

P-026 - ORNITHINE-TRANSCARBAMYLASE DEFICIENCY IN FEMALE PATIENTS. A CASE REPORT.

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INTRODUCTION: The ornithine transcarbamylase (OTC) deficiency is an inborn error of metabolism grouped in the urea cycle diseases with X-linked inheritance. It is caused by the partial or total deficiency of the enzyme coded by the OTC gene. Traditionally, it courses with seizures and hepatic failure in male patients, but several female carriers of the OTC gene mutation have been reported to have these clinical outcomes leading to severe phenotypes. **OBJECTIVES:** We report a female patient with an ornithinetranscarbamylase deficiency with a severe clinical presentation and discuss the clinical outcomes and molecular findings. **MATERIALS AND METHODS:** Retrospective medical record review of a female patient diagnosed with OTC. **RESULTS:** We report a female that initiated at the age of 6 months with seizures, altered liver function test and coagulopathy with posterior developmental delay. At the age of 11 months, it is admitted with somnolence, hypotonia and seizures. Laboratory tests revealed high liver function tests, metabolic alkalosis and hyperammonemia. Metabolic disease is suspected. Brain MRI showed cortical hyperintense lesions that involved gray matter in both hemispheres with no white matter involved and loss of volume in the corpus callosum. Liver biopsy revealed hepatocytes'

inflammation with nuclear inclusions. Using a next-generation sequencing panel, a likely pathogenic variant in the OTC gene was detected (c.207del) that leads to a frameshift mutation that produces the following change p.(Gly71Glufs*12) in a heterozygote state**. CONCLUSION:** In patients where ornithine-transcarbamylase deficiency is suspected, molecular characterization es useful due to the variable expressiveness of the variants associated with severe phenotypes, especially in female carriers.

P-027 - HYPERAMMONEMIA SECONDARY TO ORNITHINE TRANSCARBAMYLASE DEFICIENCY DUE TO SYNONYM PATHOGENIC VARIANT IN OTC GEN: A CASE REPORT

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INTRODUCTION AND OBJECTIVES: Hyperammonemia due to Ornithine Transcarbamylase (OTC) deficiency (MIM 311250), an X-linked metabolic disorder, is one of the most common disorders of the urea cycle, and therefore, of the metabolism of nitrogen compounds. We picture the medical history of a pediatric patient with a pathogenic synonymous variant in the OTC gene. **METHODS:** Clinical case report of a Colombian patient with hyperammonemia due to OTC deficiency and review of the medical literature. Prior informed consent. **RESULTS:** 3-year-old male patient from Antioquia, Colombia, with recurrent explosive vomiting from 8 months old, after the introduction of animal protein in the diet, within the family history, presents a maternal first cousin with unspecified urea cycle disorder and a second-degree maternal cousin with intolerance to animal protein. An amino acid metabolism disorder was suspected, therefore a blood ammonium level was requested, with evidence of initial hyperammonemia of 271 mmol / L. Therefore, it was decided to perform a multigenic panel study for metabolic diseases, identifying a variant in the OTC gene (c.867G> A; p. (Lys289 =)), classified as pathogenic. The patient was diagnosed with hyperammonemia due to OTC deficiency, because of a synonymous variant in the OTC gene. Treatment with a restricted animal protein diet, rich in vegetables, dairy, and eggs, associated with an ammonium chelator (sodium phenylbutyrate) and arginine supplementation with multidisciplinary follow-up; with good tolerance, adequate control of ammonium levels, reduction of symptoms**. CONCLUSIONS:** Urea cycle disorders usually present in the early stages of life, being more of a milder clinical presentation the later the onset. In the previous case, a patient with a mild clinical picture, a family history of urea cycle disorder, and hyperammonemia is presented. In pediatric patients, given that OTC deficiency is not included in the neonatal screening for metabolic disorders, it is necessary to strictly monitor the neurological and behavioral development of the patients, since adequate and early management can imply a significant improvement in outcomes.

P-028 – CLINICAL AND METABOLIC PROFILE OF A MOLECULAR CONFIRMED MEXICAN PATIENT WITH GLYCINE N-METHYL TRANSFERASE: CASE REPORT

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INTRODUCTION: Glycine N-Methyl transferase deficiency (GNMTD) is an autosomal recessive condition of methionine metabolism. Few biochemical and clinical manifestations had been reported in the literature. **OBJECTIVE:** To report a patient with two variants of uncertain significance in GNMT and describe the clinical and metabolic profile. **MATERIALS AND METHODS:** The patient was diagnosed and evaluated in our center. Clinical and biochemical data of a 3-year follow-up were analyzed. The diagnostic genetic test included sequence analysis and deletion/duplication was performed. (INVITAE®). **RESULTS:** Mexican female patient with low weight for gestational age referred for a heart murmur, she was diagnosed with membranous pulmonary atresia with entire interventricular septum which was surgically resolved when she was 5 days of age. Routine newborn screening was performed, showing elevation of C3, C3/C16, C5OH + C4DC and alanine, homocysteine levels; subsequent samples remain with a slightly persistent elevation of C3. The urine organic acid profile evidenced high methylmalonic and methyl citric acids. Vitamin B12 and folates were normal, ammonium levels were slightly elevated. Due to the metabolic profile, she was initially considered as a cobalamin defect and treated with

carnitine, folates, betaine and vitamin B 12. No dietary restrictions were made. At age three a molecular analysis was performed showing two variants of uncertain significance, c.617C>T (p.Thr206Ile) heterozygous, and gain of entire coding sequence (copy number = 3) in GNMT. We searched for genomic variants in ClinGen Dosage Sensitivity Curation Page and other databases (Clinvar, Franklin, Varsome, gnomAD, 1000genome and HGM) and no pathogenic classification of the two variants reported in the patient were found**. DISCUSSION:** Despite the diagnosis of GNMTD, this patient did not show any of described symptoms reported in the literature, but she had a mild homocysteine elevation and elevation of methylmalonic acid in the urine that can be explained because of the cyanotic cardiopathy. We propose to extend the molecular study to her parents to better classify these variants according to the ACMG&G criteria and measure vitamin B 12 levels in the mother. A careful follow-up should be performed in case of a newly diagnosed patient that includes molecular analysis.

P-029 - THE RELATIONSHIP BETWEEN SHORT-CHAIN FATTY ACIDS AND GUT MICROBIOTA PROFILE IN CLASSICAL HOMOCYSTINURIA PATIENTS

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BACKGROUND: Classical Homocystinuria (HCU; CBS deficiency) is a rare genetic disease causing an excess of methionine (Met) and homocysteine (tHcy) levels. Treatment may consist of a Met-restricted diet, metabolic formula, betaine, and vitamin supplementation (B6, B9, and B12). Short-chain fatty acids (SCFAs) are the main products of gut microbiota from the fermentation of dietary fiber. **AIM:** To evaluate the SCFAs profile and its relationship with gut microbiota profile of HCU patients on treatment. **METHODS:** Cross-sectional and observational study with convenience sampling. Stool samples were collected from 6 patients from HCPA and 6 age and sex-matched controls. SCFAs quantification (acetic, formic, lactic, propionic, and succinic acids) were performed by HPLC-UV (Shimadzu Prominence UFLC). Numerical variables were analyzed by the Mann-Whitney U test. **RESULTS:** The median age of patients was 25.5 years (IRQ: 15.2-32.2) and 5 were male. None were pyridoxine responsive. The median levels in patients of Met were 287.1µmol/L (IQR: 40.0-460.1) and tHcy was 80.0µmol/L (IQR: 45.5-97.8). Ongoing treatment were: diet (n=6), metabolic formula (n=3), betaine (n=4), B6 (n=5), B9 (n=6) and B12 supplementation (n=5). There is no difference in dietary fiber intake between groups (p=0.7). The concentration of propionic acid in patients was the only SCFA that showed a difference (p=0.01) between patients (18.7µmol/L, IQR: 11.9-25.5) and controls (46.5µmol/L, IQR: 39.8-70.1). Patients showed a decrease in the abundance of some bacterial genera that are known as propionic acid producers as Alistipes (HCU: 8.2%; Control: 12.2%), Roseburia (HCU: 2.0%; Control: 3.2%), Blautia (HCU: 0.1%; Control: 0.6%), Odoribacter (HCU: <0.1%; Control: 0.7%)**. CONCLUSION:** This is the first study to quantify SCFAs in HCU patients on treatment. We previously described the presence of 2 operational taxonomic units (OTUs) in the analysis of microbial biomarkers referring to the genus Alistipes (effect size: -1.107 and -1.138; $p<0.05$). The possible relationship between the low abundance of other genera with the decrease in the propionic acid levels should be taken into account as some species of these genera have already been related to the diet and intake of B vitamins. Further studies are needed to understand the role of propionic acid in HCU patients.

P-030 - MOLECULAR BASIS OF CLASSICAL HOMOCYSTINURIA IN BRAZIL: REPORT OF 52 PATIENTS AND 5 NOVEL MUTATIONS

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INTRODUCTION: Classical homocystinuria (HCU; CβS deficiency) is caused by a variant in CBS gene. Our group has to lead a multicentric effort to characterize the genetic profile of HCU in Brazil, and the results of the genetic profile of 35 patients were already published (Poloni et al., 2017). **AIM:** To present an update of molecular diagnosis of HCU Brazilian patients including previously published data of Poloni et al.,

2017. **MATERIALS AND METHODS:** In addition to the 35 patients already published, we included 17 new patients with diagnoses of HCU based on clinical and biochemical features. In total, 52 patients were included (41 families). Genomic DNA was extracted from whole blood using the commercially available Easy-DNA™ gDNA Purification Kit (Invitrogen). Exons 1-14 and 16 and the exon/intron junctions of the CBS gene were amplified by conventional PCR. Missense mutations not previously described in the literature were analyzed in silico in the PolyPhen2 and SIFT software. Novel mutations were classified according to ACMG guidelines. **RESULTS:** Consanguinity was reported in 17 families (41.4%) and 17.3% of patients were pyridoxine responsive. Families were from the following regions of Brazil: South (n=15), Southeast (n=14), Northeast (n=11) and Midwest (n=1). Most prevalent mutations were: p.Ile278Thr (16.4%), p.Trp323Ter (14.9%) and c.828+1G>A (10.4%). All families (6) with the p.Trp323Ter variant were from the same geographic region (Bahia). Fourteen novel mutations were found, being five unpublished: c.1598T>G, c.1051G>C, c.1052G>A, c.386A>G and c. 862_866delGCAGA. These variants were predicted to be pathogenic by in silico analysis. According to ACMG, evidence of pathogenicity of all novel variants is "supporting". In one patient, only one mutated allele was identified**. CONCLUSIONS:** These results corroborate our previous findings, showing a very particular genetic profile of HCU in Brazil, were p.Ile278Thr, p.Trp323Ter and c.828+1G>A variants account for nearly half of mutated alleles. The high prevalence of the Saudi p.Trp323Ter variant might be associated with a founder effect.

P-031 - ALKAPTONURIA: CLINICAL CASE AND NEW MUTATION REPORT

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CASE REPORT: We report a 13-year old female with a history of 3 years of severe arthralgia in the hands, associated with morning stiffness and mild swelling. Physical examination showed normal, except, hyperlaxity and pain 7-8/10 on palpation in the Achilles tendon. We make an initial diagnosis of juvenile arthritis. A low limbs MRI showed significant tenosynovitis. Studies for other autoimmune diseases were extended with negative results. The initial urinary spot protein was 203.84 mg/dl but was not consistent with proteinuria seen in the 24-hour sample which was < 150 mg/day. Renal ultrasound and echocardiogram were normal. Due to persistent proteinuria, a renal biopsy was performed. Histopathology of the kidney biopsy describes mesangial proliferation without endocapillary proliferation or segmental sclerosis. Later, dark urine is observed. The family was re-interrogated: she had a personal and family history of dark urine. The grandfather has had dark sweating and black earwax. With these new findings, homogentisic acid (HGA) in urine by HPLC was performed reporting 6400.0 mg/24h (normal value < 10 mg/24 hours). The exome sequencing by NGS of the HGD gene showed a new variant not seen previously: homozygous c.164_166 del (thr55del). With these exams, the diagnosis of alkaptonuria was confirmed. The Alkaptonuria is rare organic aciduria that occurs in 1 in 1,000,000 live newborns involving a deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (HA), an intermediate in the degradative pathway of tyrosine. Over time, age and a lower resistance of the tissues cause articular degenerative changes and extra-articular signs such as thickening of the cardiac valves**. CONCLUSIONS:** a family and personal history of dark urine and arthritis are sufficient criteria to suspect alkaptonuria. Moreover, HGA has been reported to interfere with common methods for urinary protein. With inconsistent data between 24-hour proteinuria and isolated sample proteinuria, alkaptonuria must be ruled out. An acute clinical suspicion, a good medical interrogatory, and a careful interpretation of urinary biochemistry can lead to timely diagnosis of children with alkaptonuria to avoid unnecessary procedures and treatments and eventually improve the prognosis of this disease.

P-032 - A CASE OF GYRATE ATROPHY OF CHOROID AND RETINA

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INTRODUCTION: Gyrate atrophy of the choroid and retina is an autosomal recessive disorder due to mutations of the OAT gene encoding ornithine-delta-aminotransferase enzyme (OAT). It is associated with progressive retinal deterioration and blindness. It is extremely rare, the estimated incidence is

1: 1.500.000 live births. OAT is mainly involved in ornithine catabolism. The biomarker of the disease is hyperornithinemia. It is essentially an ophthalmological disorder, but extraocular manifestations have been reported. Typically onset is in late childhood with night blindness and myopia that evolve to blindness at 40–60 years of age. The treatment with an arginine-restricted diet (precursor of ornithine in food), or the administration of a pharmacological dosage of pyridoxine, a precursor of the OAT coenzyme, pyridoxal phosphate, decreases hyperornithinemia. OAT deficient patients are usually distinguished in pyridoxine-responsive and non-responsive variants. Some studies support the efficacy of such treatments in slowing disease progression. **OBJECTIVE:** To present our first case of an extremely rare metabolic disorder: OAT deficiency. **CASE REPORT:** 7-year-old, male patient, a product of the first normal pregnancy of a non-consanguineous couple. Normal growth and development. At age 4, a decrease in visual acuity was noticed. Ophthalmologic assessment evidenced myopia and astigmatism. Visual acuity impairment progressed. On ophthalmological examination at 6 years of age, sharply demarcated circular areas of chorioretinal atrophy were evident. The optical coherence tomography showed intraretinal cysts in superficial layers of the macula. No cognitive impairment or other signs or symptoms were evident. Fasting plasma amino acids revealed isolated elevation of ornithine: 854 µmol/l (N 22-97). A trial with pyridoxine was carried out for 6 weeks with no change in natural protein intake but there was no significant decrease of plasma ornithine: 796 µmol/l. The addition of a limited natural protein diet resulted in a plasma ornithine level of: 467 µmol/l. Molecular genetic analysis was performed**. CONCLUSIONS:** Classical OAT deficiency is essentially a progressive and disabling ophthalmological disorder affecting the quality of life of the patients. The ophthalmologist has an important responsibility for an early diagnosis since pyridoxine therapy and/or arginine restriction diet, have proven to slow progression in most cases.

P-033 - REPORT OF MUTATION IN THE PHOSPHORYLASE KINASE (*PHKA2*) GENE IN A FAMILY OF CARTAGENA DE INDIAS, COLOMBIA

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INTRODUCTION: The glycogen storage disease (GSD) type IX is a rare disease of variable clinical severity that mainly affects the liver tissue. Individuals with hepatic phosphorylase b-kinase (PHK) deficiency due to mutation in the PHKA2 gene (GSD IXa) may present hepatomegaly with elevated serum transaminases, ketotic hypoglycemia, hyperlipidemia, and poor growth with considerable variation in clinical severity. **OBJECTIVE:** To identify and describe the different clinical manifestations of a family with the same type of mutation in the PHKA2 gene (GSD IXa), which represent the first cases described in Colombia. **MATERIALS AND METHODS:** Four members of the same family were studied (mother, two brothers and a sister on the mother's part), from the city of Cartagena, who according to the symptoms, findings to the physical, clinical and biochemical examinations performed in the Biochemistry Laboratory of the University of Cartagena, had high suspicion that they had some glycogenosis, In addition, genetic studies were carried out at the Center for the Diagnosis of Molecular Diseases (CEDEM) in Madrid-Spain, through massive sequencing analysis, bioinformatic analysis, bioinformatic analysis of mutations and confirmation by sequencing of Sanger. **RESULTS:** We present the cases of a family, who according to the symptomatology, clinical, biochemical, and genetic tests carried out, get to diagnose and confirm that they suffer from GDSIXa with mutation c.919-2A> G in heterozygosity for the mother and daughter, and in hemizygosity for the two siblings of thePHKA2 gene, the which represents a new variant of this gene**. CONCLUSIONS:** type IX GSD, due to glycogen phosphorylase kinase (PHK) deficiency, accounts for 25% of cases, the most common being the PHKA2 subtype (GSDIXa; MIM: 306000) with recessive inheritance linked to the X chromosome; the development of the so-called next-generation sequencing technologies (NGS), such as those used in this study, is currently the method of choice to confirm the diagnosis of GSD, avoiding the use of a test invasive as the liver biopsy.

P-034 - BONE STATUS IN 10 CHILEAN PATIENTS WITH GLUT 1 DEFICIENCY (GLUT1D) TREATED WITH KETOGENIC DIET

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BACKGROUND: Ketogenic diet (KD) has been used as a first-line treatment in patients with GLUT1D. Earlier studies describe a progressive loss of bone mineral content in patients with refractory epilepsy subjected to multiple AED, but usually nonambulatory. In long-term follow-up studies, approximately 20% of children treated with KD (≥ 6 years) experience an increased incidence of bone fractures. Considering GLUT 1D patients use KD as a life-long therapy, monitoring bone health is important as part of comprehensive follow-up management. **OBJECTIVE:** characterize bone status in 10 patients with GLUT1D treated with KD. **METHODOLOGY:** Cross-sectional study. Dual-energy X-ray absorptiometry (DEXA) was used for assessing bone mineral density (BMD). **RESULTS:** The medical records of 10 patients (6 males) were reviewed. Four patients were on classic KD (3: 1), and 7 patients were on a MAD diet with ketogenic ratios between 2-2.5: 1. All patients had normal ambulation. DEXA was used for assessing bone status. Whole-body bone mineral density z score (BMDz) was measured: group 1 had 5 patients with normal values and group 2 had BMDz between -1 and -2.5 SD. One of these patients had a fracture after a high-altitude fall, but none had fractures of clinical significance. Patients in group1 had been on KD between 1m and 20y (x: 5.2y, M: 1y) and those in group 2 between 4m and 5y (x: 1.7y, M 1y). All patients complied with calcium RDA at the time of DEXA (x: 1181 mg/d, M 1150). Eight patients had 25-OH-vitamin D values measured (x: 46.5, M: 40 ng/ml), only 1 patient in group 2 had insufficient levels. Statistical analysis (Wilcox Test), shows no significant difference between both groups in terms of time on KD and BMDz, and in terms of vitamin D levels and abnormal DEXA values (p=0.59)**. CONCLUSION:** In this GLUT1D Chilean cohort, patients with long-term KD had conserved BMD, and patients with altered BMDz scores had no clinically significant consequences due to this alteration. Factors that potentially contribute to this outcome are adequate calcium supplementation and vitamin D sufficiency, as well as ambulation which was a probable protective factor.

P-035 - GLUCOSE TRANSPORTER 1 DEFICIENCY: A BRAZILIAN COHORT STUDY OF AN TREATABLE INBORN ERROR OF METABOLISM

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INTRODUCTION: The Glucose Transporter type 1 (GLUT1) Deficiency Syndrome is a genetic condition, of autosomal dominant inheritance, and corresponds to a spectrum of signs and symptoms, which include seizures, neuropsychomotor development delay, intellectual disability, of movement, dysarthria and postnatal microcephaly. The presence and severity of symptoms are variable. Symptomatic treatment consists of the ketogenic diet, which allows the supply of energy to the brain through sustained and continuous ketosis. **OBJECTIVES:** To present the experience of the Medical Genetics Service of a University Hospital in the clinical follow-up of patients with GLUT1 Deficiency Syndrome who were treated with a ketogenic diet. **MATERIAL AND METHODS:** This is a retrospective case series study. Retrospective patient data were reviewed and genotypic and phenotypic characteristics were described. **RESULTS:** Four patients, three male, and one female, aged between three years and seven months and 35 years were included in the study. All had delayed neuropsychomotor development and ataxia. Three patients had a history of seizures. All undergo treatment with a ketogenic diet. The oldest patient at diagnosis was 30 years old and the youngest was three years old. The age of diet initiation also ranged from three years to 30 years. Two patients had seizures at the time of initiation of the ketogenic diet and after initiation, they achieved seizure control. The most commonly reported side effects were nausea, constipation, and restlessness. There was an improvement in the symptoms of ataxia and motor delay in all patients. **DISCUSSION AND CONCLUSION:** In the GLUT1 deficiency syndrome, glucose transport in the brain is deficient, causing an energy deficit and justifying the neurological manifestations. Symptoms often improve substantially when a ketogenic diet is started early. In this sense, the diagnosis of this condition can directly impact the clinical prognosis of affected patients.

P-036 - FEEDING DIFFICULTIES IN CHILDREN WITH HEPATIC GLYCOGEN STORAGE DISEASES IDENTIFIED BY A VALIDATED SCREENING TOOL IN BRAZILIAN-PORTUGUESE

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INTRODUCTION: Hepatic glycogen storage diseases (GSD) are inborn errors of metabolism that result in a defect in glycogen synthesis or degradation, predominantly affecting the liver and muscles. The treatment is basically nutritional with strict diet guidelines and regular use of raw cornstarch. To date, no study has evaluated the degree of feeding difficulty in hepatic GSD and/or its correlation with parental stress. **OBJECTIVE:** This study aims to investigate the presence and severity of feeding difficulties through a validated scale for the Portuguese language in children with GSD and the presence of parental stress using the Parental Stress Scale. **MATERIALS AND METHODS:** Twenty-nine individuals (parents and/or caregivers of individuals with GSD) participated in the study, responsible for children aged from 6 mo. to<7yo. The presence and severity of feeding difficulties in children with GSD were evaluated through the Brazilian Infant Feeding Scale (EBAI) and the presence of parental stress was evaluated using the Parental Stress Scale (EEPa), through the use of a standardized form with application of consent form applied in 2020. **RESULTS:** The patients under their care were predominantly male (19/10), had a mean age of 47.75 months, with a mean age at GSD diagnosis 8.39 months. Diagnosis of GSD type Ia (15) and Ib (5) was the most reported, followed by type III (2), VI (1), IX (2) and unknown type (4). In this sample, 22/29 (76.0%) had feeding problems, classified as mild (24.0%), moderate (24.0%) and severe (28.0%). The EBAI score was significantly higher among female patients and among patients who did not have meals with families. One parent/caregiver had high parental stress. No statistical significance was observed when comparing feeding difficulties and parental stress. **CONCLUSIONS AND DISCUSSION:** This study corroborated the findings of feeding difficulties in groups at risk and showed the prevalence and degree of feeding problems in this population. Although the scales were not related, quantifying parental stress enabled to verify the impact of the diagnosis on the quality of life from the caregiver's perspective. More studies in this field are warranted aiming for better treatment of GSD.

P-037 - CHARACTERIZATION OF THE POPULATION WITH GLYCOGEN STORAGE DISEASES IN CHILE AND THE IMPACT OF THE GENETIC STUDY ON THE DEFINITIVE DIAGNOSIS OF THE DISEASE

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INTRODUCTION: Glycogen storage diseases (GDS) are a group of low-frequency pathologies, derived from the alteration of glycogen metabolism, which leads to its being stored in different organs, producing different clinical manifestations. Liver-compromised GSDs are classified into types I, III, IV, VI, and IX, depending on the different enzymes affected. They are clinically characterized by hypoglycemia and hepatomegaly as cardinal symptoms. The diagnostic suspicion is based on the present clinical manifestations and the results of the laboratory tests, but the definitive diagnosis requires a genetic study. **OBJECTIVE:** To characterize phenotypically and genotypically the patients affected by GSD with hepatic compromise in clinical follow-up at the Institute of Nutrition and Food Technology (INTA). **METHODOLOGY:** In a retrospective cross-sectional study, clinical records of 15 patients (13 boys, 2 girls) from INTA were reviewed to obtain data on the genetic study and biochemical tests. **RESULTS:** Average age before the suspicion of a GSD was 13 months and the average age of diagnostic confirmation was 39 months. 12/15 had a liver biopsy compatible with GSD prior to taking a sample for the genetic test. 13 performed a molecular study, 8/13 the suspicion of the type of GSD prior to the examination does not coincide with the final diagnosis. Of the 13 patients, 8 were GSD type III, 2 GSD type Ib, 2 GSD type IXa and 1 GSD VI. Of the 14 mutations identified in the patients, 6 were homozygous, 2 hemizygous, 3 heterozygous and 2 could not be determined. Of the 8 patients with GSD type III: 3 had the c.3216_3217delGA mutation and 2 patients had the c.3216_3217del (p.Glu1072Aspfs*36) mutation. 100% of the patients presented hypoglycemia, hepatomegaly and hypertriglyceridemia, and 13/15 presented elevation of transaminases**. CONCLUSION:** It is the first pediatric report in Chile to include mutations associated with GSDs, together with the clinical and biochemical characterization of patients. This allowed access to the genetic study of mutations to the patients studied. This diagnostic accuracy makes it possible to optimize treatment, helping to improve their metabolic stability and probably their long-term prognosis, together with their quality of life.

P-038 - CLINICAL CHANGES IN PEDIATRIC PATIENTS WITH TYPE IIIA GLYCOGENOSIS WITH A HIGH DIET PROTEIN

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OBJECTIVES AND STUDY: Describe the clinical changes in patients with GSD IIIa after a high protein diet. Quasi-experimental study, before and after. **METHODS:** A complete medical history was made, with points of main interest: clinical symptoms of mild hypoglycemia (drowsiness, diaphoresis, nausea) or severe (seizures), presence of cardiac or muscular affections, liver size, and portal hypertension data. The nutritional intervention was for 12 months and consisted of 3 points: 1) High protein diet, at least 3 g/kg/day, supplementary powder supplement (>2g/kg/day), 2) Restriction of fructose, sucrose, and lactose, 3) Raw cornstarch doses 0.5 – 1 g/kg every 4-6 hours. **RESULTS:** 12 patients were included, with a median age of 98.3 months. Before intervention height for age median z score -2.63, after -2.57. Liver size before 4.23 after 3.44, no data of splenomegaly or portal hypertension were found. Before the intervention, 9 patients reported exercise intolerance, after 5. Before 10 patients didn't perform physical activity after only 4 patients didn't. 5 patients increased the intensity of physical activity. No cardiac alterations were found. 6 patients reported hypoglycemia before, only 1 patient reported after the intervention. Median of AST 469 U/L before and 329.5 U/L after. ALT before 425 U/L after 401 U/L and median of ALT reduced from 425 U/L to 401 U/L. All patients persisted with high CK. No differences were found in the lipid profile**. CONCLUSION:** This is the first quasi-experimental study focused on a high diet protein in GSD IIIa and the clinical changes. A good dietetic intervention without simple sugars restrictions like fructose, sucrose, and lactose plus a diet high in protein and raw cornstarch can improve exercise intolerance which leads to an increase in physical activity. It also leads to reduced liver size and better control of glucose levels in patients with type GSD type IIIa. The changes in the lipid profile can be explained by the energy demands for the changes in physical activity, as well as the maximum fasting time of the patients, 6 hours, no ketone bodies were made in this study that helps to support this theory.

P-039 - GLYCOGEN STORAGE DISEASE TYPE IV-A: A CASE SERIES

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INTRODUCION: Glycogen storage disease type IV (GSD IV, OMIM #232500) is an ultra-rare autosomal recessive disease caused by variants in the GBE1 gene, which encodes for the glycogen branching enzyme (GBE). GSD IV accounts for approximately 3% of all GSD. The phenotype of GSD IV ranges from neonatal death to mild adult-onset disease with variable hepatic, muscular, neurologic, dermatologic, and cardiac involvement. There is a paucity of literature on clinical and dietary management in GSD IV and liver transplantation (LT) is described to correct the primary hepatic enzyme defect. **OBJECTIVES:** Describe four cases of patients with GSD IV with different ages of onset and outcomes. **MATERIALS AND METHODS:** Case series study with longitudinal follow-up. **RESULTS:** Patient #1 is a male child who was admitted to the Rare Diseases Reference Center at the Hospital de Clínicas de Porto Alegre (HCPA), Brazil, with the chief complaints of hepatosplenomegaly, failure to thrive, and elevated liver enzymes starting at the age of 5 months. The diagnosis of GSD IV was established by genetic analysis at the age of 2 years. Before LT at the age of 2 empirical treatment with corn starch (CS) and high protein therapy was performed with subjective improvement in his overall disposition and liver size. Liver samples revealed hepatocytes with intracellular hydropic degeneration and cytoplasmic inclusions compatible with the phenotype. Patients #2 and #3 were siblings, Patient #2 is a female patient with onset of symptoms at the age of 3 months with bloody diarrhea, abdominal distention, and splenomegaly. Her molecular diagnosis was confirmed at 6 months of age. There was no attempt to treat with CS. She is currently waiting for LT. Patient #3 began to be investigated after one year of age and already presented with hepatosplenomegaly and a previous diagnosis of histiocytosis. He passed away at the age of 1.5 years without molecular confirmation. Patient #4 is a 30-month-old female patient who has already undergone liver transplantation. The treatment with cornstarch was attempted before transplantation with no improvement noticed. No patient presented with hypoglycemia**. CONCLUSION:** GSD IV is a rare condition that must be included in the differential diagnosis of hepatosplenomegaly even in the absence of hypoglycemia. Dietary treatment is being better understood for the treatment of GSDIV alongside the LT.

P-040 - BETAKETOTHIOLASE DEFICIENCY: REPORT OF THE FIRST CONFIRMED CASE IN PERU

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INTRODUCTION: Beta-ketothiolase deficiency is organic aciduria that affects the metabolism of ketone bodies and the catabolism of isoleucine. Enzyme deficiency is caused by mutations in the ACAT 1 gene that is involved in ketolysis. Beta-ketothiolase deficiency leads to excess ketone bodies due to poor utilization. Patients develop recurrent episodes of ketoacidosis with periods of well-being between episodes. Ketoacidosis crisis can compromise consciousness and threaten life. **OBJECTIVE:** We present the first biochemically and molecularly confirmed case of beta-ketothiolase deficiency in Peru. **MATERIALS AND METHODS:** We describe the clinical and biochemical findings of an infant who came to the Rebagliati hospital (Lima, Perú) with severe metabolic acidosis. **RESULTS:** Male patient, the first child of unrelated parents born by cesarean section due to preeclampsia, weighed 3,7 kg at birth. Good psychomotor development without a history of disease until the onset of the disease. At 7 months of age, he presented fever, coryza for 2 days and vomiting lethargy for 1 day. When he went to emergency service he was with tachypnea and blood gas confirmed metabolic acidosis (PH 6.8, bicarbonate of 2.2mmol/L, anion gap >20mmol/L) urine ketones 3+ with euglycemic. Herpesvirus encephalitis was suspected by a positive antigenic test and managed appropriately. He also received bicarbonate infusion and invasive respiratory support due to impaired consciousness. Persistent ketosis with elevated anion gap and euglycemia raised suspicion of a ketone body utilization disorder. The analysis of organic acids in urine revealed a massive presence of tiglylglycine and 3OH-butyric, acetoacetic, 2-methyl-3-OH-butyric and 2-methylacetoacetic acids. A genetic panel for metabolic diseases was carried out, 3 variants of uncertain significance were detected in the ACAT 1 gene in heterozygosity (c.464G>T/c.497G>A/ c.135_136delinsGC), none have been previously described. Family segregation studies will be carried out to reclassify the variants. Shortly after discharge from the hospital, he was readmitted for a new episode of ketoacidosis triggered by poor nutritional management. On the moderate protein-restricted diet, this infant is doing well at follow-up. **CONCLUSIONS:** Betaketothiolase deficiency is a rare, often underrecognized disorder. This case highlights the need for clinical suspicion when we face a child with severe metabolic acidosis.

P-041 - VERY-LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY WITH LETHAL CARDIOMYOPATHY IN TWO NEONATES

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INTRODUCTION: Mitochondrial fatty acid oxidation disorders (FAODs) are caused by defects in βoxidation enzymes, including very long-chain acyl-CoA dehydrogenase (VLCAD), trifunctional protein (TFP), carnitine palmitoyltransferase-2 (CPT2), carnitine-acylcarnitine translocase (CACT) and others. VLCAD deficiency is generally classified into three phenotypes based on onset time. The presentation of these disorders is variable but common findings include hypoketotic hypoglycemia, liver disease and associated mortality and morbidity due to cardiomyopathy. Neonatal cardiomyopathies due to mitochondrial oxidative phosphorylation defects are severe conditions that can be either isolated or included in a multi-organ disease. Cardiomyopathy is more often hypertrophic than dilated. Pathophysiological mechanisms are complex, going beyond ATP deficiency of the high-energy-consuming neonatal myocardium. Birth is a key metabolic period when the myocardium switches ATP production from anaerobic glycolysis to mitochondrial fatty acid oxidation and OXPHOS. Heart-specificity of the defect may be related to the specific localization of the defect, to the high myocardium dependency on OXPHOS, and/or to interaction between the primary genetic alteration and other factors such as modifier genes. Here, we report on two patients with hypertrophic cardiomyopathy and arrhythmias due to FAO disorders. **CASES REPORT:** Patient 1, is the first child of non-consanguineous parents, who in the newborn period began with hypoglycemia and cardiac arrest. At 3 months of age, he developed hypertrophic cardiomyopathy with arrhythmia and cardiac tamponade. Basic biochemical tests, as well as plasma acylcarnitines analysis by gas chromatography-mass spectrometry (GC- MS), were performed. Patient 2, is the first child of non-consanguineous parents, who in the first month of

life began with hypoglycemia. Afterward, hyperammonemia, hepatomegaly with hepatocellular dysfunction, steatohepatitis and hypertrophic cardiomyopathy and myopathy were detected secondary to an SVR infection. Basic biochemical tests, as well as acylcarnitines analysis by GC-MS, were performed. Both initial biochemical tests showed hypoketotic hypoglycemia. The echocardiography, hypertrophic cardiomyopathy. Plasma acylcarnitine analysis demonstrated a significant elevation in C14: 1, C14: 2, C14, and C12: 1 in both patients. Genetic analysis of both patients showed a homozygous splicing mutation in the ACADVL gene**. CONCLUSION:** The description of these two cases confirmed the presence of hypertrophic cardiomyopathy and arrhythmias due to FAO disorders. Taking into account the absence of newborn screening in our country, FAO disorders should always be considered in these scenarios.

P-042 - MENKES DISEASE: BETWEEN SUSPICION AND DISTRACTORS.

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INTRODUCTION: Menkes disease (MD) is an X-linked, serious and rare disorder of copper metabolism. It is caused by pathogenic variants of the ATP7A gene that encodes for an ATP-ase transmembrane copper transporter protein. The clinical features include characteristic connective tissue disturbances and progressive neurodegeneration with a fatal outcome generally within the third year of life. **OBJECTIVE:** We report the case of two patients with MD who were initially diagnosed as symptomatic epileptic seizures of a viral etiology. **MATERIALS AND METHODS:** Medical report of patients evaluated in the Laboratory of Neurochemistry Dr. N.A. Chamoles in 2021. **RESULTS:** A 6-months-old male patient with a history of psychomotor delay, presented focal seizures and febrile epileptic status associated with altered consciousness and vomits, interpreted as viral encephalitis in the context of symptomatic SARS2 Covid-19 infection. His family history revealed a 3-year-old brother with progressive epileptic encephalopathy of uncertain etiology that presented at 4-months-old, a similar episode assumed to be Herpes simplex virus (HSV) encephalitis. Both children shared pathological images on brain MRI and their physical examination showed hypotonia, generalized increase in subcutaneous fat, sparse and lusterless scalp hair, pale skin and micrognathia. Low serum levels of copper and ceruloplasmin and the molecular tests confirmed MD**. DISCUSSION:** Viral encephalitis is a common cause of seizures in childhood. In the younger boy, seizures were interpreted as a COVID-19 complication. Several neurological complications associated with COVID-19 have been reported, including encephalitis and seizures. The second case was interpreted as secondary to HSV encephalitis, the most common cause of viral encephalitis. This fact shows that, sometimes, the most frequent condition can conceal the true etiology of the symptoms. MD is a rare disease; however, we must include it in the differential diagnosis of epilepsy in children under 6 months, especially if psychomotor delay and connective tissue disorders are associated. Despite current treatment, the prognosis continues to be somber. Thereby, an early diagnosis based on the acknowledgment of the disease results is important at the time of genetic counseling.

P-043 - AUTISM SPECTRUM DISORDER FEATURES IN PATIENTS WITH INBORN ERRORS OF METABOLISM: TWO NORTHEAST BRAZILIAN EXAMPLES

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INTRODUCTION: Features of Autism Spectrum Disorder (ASD) can be present in many Inborn Errors of Metabolism (IEM). Autistic symptoms can occur at the onset of metabolic diseases, are usually related to other symptoms such as neurological regression, seizures and are more frequent in consanguineous families, since most of them are autosomal recessive. **OBJECTIVE:** Report two patients previously diagnosed with isolated ASD who was lately diagnosed with IEM. **MATERIAL AND METHODS:** This is a descriptive study. Two patients previously diagnosed with ASD were evaluated and two different IEM were detected. **RESULTS:** Case1: male, a second child from an unrelated couple. He was first diagnosed with isolated ASD at the age of 2 years due to speech delay and hypotonia. An investigative protocol (including karyotype, Fragile X, Microarray and CNS MRI) had normal results. Since he had started with seizures, swallowing problems and increasing hypotonia, tandem mass spectrometry was performed and confirmed maple syrup urine disease (MSUD). He has been on an appropriate diet since and has improved. Case2: male, 2 years old, first child from an unrelated couple. He was first diagnosed with isolated ASD due to speech delay and hyperactivity. He developed progressive macrocephaly and recurrent ear infections. A 27-gene panel for lysosomal storage disorders was performed and

two pathogenic variants in SGSH gene were detected, c.1080del (p.Val361Serfs*52) and c.1276del (p.Asp426Thrfs*165). They were on opposite chromosomes, confirming thus the diagnosis of mucopolysaccharidosis type IIIA (MPS IIIA)**. CONCLUSION:** It is important to investigate IEM in patients diagnosed with autism. For this purpose, a detailed personal and family history and a complete physical examination are necessary; in order to search for specifically associated signs that may help the clinician in the decision to perform a metabolic workup. If a metabolic disease is diagnosed, treatment should focus on both ASD and IEM.

P-044 - EPIDEMIOLOGICAL PROFILE OF PATIENTS WITH INBORN ERRORS OF METABOLISM IN A NORTHEAST BRAZILIAN STATE

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INTRODUCTION: Inborn errors of metabolism (IEM) have a great impact on morbimortality and present better outcomes through early identification and treatment. **OBJECTIVES:** To determine the epidemiological profile of patients with IEM in Sergipe State. **MATERIAL AND METHODS:** A descriptive study was performed at the two Medical Genetics Centers from the Federal University of Sergipe, after Research Ethics Committee approval. Patients diagnosed with IEM from April 2018 to July 2021 were enrolled and the ones with metabolic disorders detected by newborn screening were excluded. **RESULTS:** 27 patients were diagnosed. 55,6% were females and parental consanguinity was found in 25,6%. The mean age of the studied group was 14 years, but at the onset of symptoms the mean age was 2.5 and at the diagnosis was 5. They have been listed into the following categories: 20 lysosomal storage disorders, 02 organic acidurias, 03 aminoacidopathies and 02 glycogen storage disorders. The diagnosis was performed through Next Generation Sequencing (NGS) in 26% of cases and 29,6% of patients were under specific therapy such as enzyme replacement therapy**. DISCUSSION:** Sergipe is the smallest State in Brazil and has only two Medical Genetics Centers. Therefore, our sample is quite representative. The few cases of disorders with the neonatal presentation may be related to early and undiagnosed deaths. The consanguinity rate found was similar to other Brazilian studies with IEM populations and reinforces consanguinity as an important risk factor. The delay in diagnosis may be due to the difficult access to specialized services, diagnostic exams, and the possible lack of knowledge about IEM from health caregivers. According to the literature, NGS is an effective and useful technology for the diagnosis of metabolic diseases, especially in complex or unsolved cases**. CONCLUSION:** Despite the limitations of this research, our results can serve as a warning about the panorama of patients with IEM in Sergipe and reinforce the need for public policies regarding diagnosis and management of IEM in Sergipe State.

P-045 - THE INBORN ERRORS OF METABOLISM CALL FREE SERVICE IN BRAZIL (SIEM): FOR MORE THAN 20 YEARS HELPING HEALTH PROFESSIONALS IN THE DIAGNOSIS AND MANAGEMENT OF METABOLIC GENETIC DISORDERS

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INTRODUCTION: SIEM (Inborn Errors of Metabolism Information Service) was founded in 2001 and the aim was to be a free tool, easy to access (telephone, e-mail and website) to support health professionals, assisting in the diagnosis and management of patients with suspected IEM. The genetic-metabolic conditions are, for most cases, serious pathologies, sometimes difficult to recognize, but with high potential for treatment. However, to the best care and a favorable outcome, the diagnosis must be as soon as possible. **OBJECTIVES:** report the SIEM data recorded from 2001 to 2022. **MATERIALS AND METHODS:** For each call, we have a standard protocol to collect clinical information and the results of the initial laboratory investigation. After 3 months of the first contact, we have run a follow-up of cases. Cross-sectional study using the EpiData database. **RESULTS:** 4,406 records, 69% from the south and southeast regions, 29% from the northeast, north, center-west of Brazil, in addition to 2% from LATAM. In 91% of the cases, the consultants sought support for diagnosis and initial management, 4%, assistance in management with an already established diagnosis. Initial contact was made by pediatricians/neonatologists (34%), neuropediatricians (20%), geneticists (26%) or other professionals (20%). Excluding requests for information, 9.8% of the cases confirmed IEM, 17.4% had a non-metabolic diagnosis, in 27% the investigation was incomplete, 32% are still under investigation and in 13.8% there was a loss of follow-up. Of the 410 cases diagnosed with IEM, amino acids and Organic academia in 41%, lysosomal diseases in 19%, energy metabolism in 12%, carbohydrates metabolism 12%, peroxisomal diseases in 5% and miscellaneous11%.

CONCLUSION: We believe SIEM to be an extremely important source of information about Inborn Errors of Metabolism in a country where such group of disorders is often unrecognized, aiding different medical specialists to better and more efficiently diagnose and treat patients, avoiding and limiting sequelae. The follow-up of the SIEM cases is important to mapping the national profile on IEM in our country and maybe can be a model for Latin America.

P-046 - DIAGNOSTIC YIELD OF WHOLE EXOME SEQUENCING IN A COHORT OF COLOMBIAN PATIENTS WITH CLINICAL SUSPICION OF INBORN ERRORS OF METABOLISM: CLINICAL AND GENETIC CHARACTERIZATION

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INTRODUCTION: Inborn errors of metabolism (IEM) are a diverse group of diseases characterized by heterogeneous clinical, biochemical, and genetic features. They share a great impact on patients' health and constitute a diagnostic challenge. Whole exome sequencing (WES) offers a cost-effective tool for the molecular diagnosis of these patients, but the diagnostic yield is variable within populations. **OBJECTIVE:** To identify the diagnostic yield of WES, and to describe the clinical and genetic features, in a group of Colombian patients with a suspicion of an IEM. **METHODS:** We performed a descriptive, crosssectional cohort study in a group of Colombian patients with a possible IEM for whom a WES was indicated between July 2019 and December 2021. WES including nuclear and mitochondrial genome was run and analyzed at Gencell Pharma. A descriptive clinical and genetic analysis of the sample was carried out. Cases were considered "diagnostic" when a pathogenic (P) or likely pathogenic (LP) variant was found in a gene explaining the patient's phenotype and accomplished the disease's inheritance pattern; "non-diagnostic" when only benign, likely benign or variants of unknown significance (VUS) were identified; and "undetermined" when two P or LP variants were found in a gene causing an autosomal recessive disease explaining patient's manifestations, but segregation analysis was not available to confirm whether they were in trans. Diagnostic yield was defined as the percentage of diagnostic over non-diagnostic and undetermined causes. **RESULTS:** Sixty-six cases from several regions in Colombia were included. Clinical indications for WES were mainly a suspicion of mitochondrial disease (56%), any EIM (10,6%), lysosomal/peroxisomal disease (9%) and mucopolysaccharidosis (6,1%). Neurological manifestations were predominant (48,8%), followed by muscular and ophthalmological (10,6% each). Abnormal biochemical analyses were reported in 27,2% of cases. We identified a P, LP variant or a VUS in a gene explaining the case's phenotype in 42,2% of patients. Diagnostic yield was 16,6%. Seven of the diagnostic cases had variants in a nuclear gene, whereas five had a mutation in the mitochondrial genome**.** **CONCLUSIONS:** WES is an efficient tool to diagnose IEM when both nuclear and mitochondrial genomes are analyzed, and a clinical assessment of the patient's individualized phenotype is performed.

P-047 - IDENTIFICATION OF VANILLACTIC AND VANILLYLMANDELIC ACIDS RATIO FROM RETROSPECTIVE ANALYSIS OF URINE ORGANIC ACIDS CHROMATOGRAMS IN A COLOMBIAN REFERENCE CENTER.

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INTRODUCTION: Aromatic L-amino acid decarboxylase deficiency (AADCD) is an ultra-rare inborn error of metabolism with about 140 patients reported worldwide. AADCD remains underdiagnosed in Colombia in part due to the lack of availability of diagnostic methods. Recently, the use of the urinary vanillactic/vanillylmandelic (VLA/VMA) ratio was reported as a diagnostic tool. These metabolites are detected by urinary organic acid (OA) analysis, which is commonly used in the diagnosis of organic acidurias. Therefore, we performed an exploratory analysis of the utility of VLA/VMA ratio in OA chromatograms to improve the local availability of a diagnostic tool that will facilitate and promote the diagnosis of AADCD patients in Colombia. **OBJECTIVES:** To evaluate the VLA/VMA ratio determination by urinary OA analysis as a diagnostic tool for AADCD in a Colombian diagnosis center. **METHODS:** Descriptive data analysis was performed on 1200 organic acid chromatograms. In addition, an exploratory data analysis was implemented to contrast the behavior of VLA/VMA ratio with

variables such as age, gender, and the profile of healthy versus high-risk population. **RESULTS:** Our data show that VLA is an unusual metabolite within the urinary organic acid profile compared to VMA. VLA/VMA ratio < 1 in individuals younger than eight years old can be considered normal. Additionally, VLA/VMA ratio tends to decrease with age and a tendency of higher VLA/VMA ratio was observed in females from a highrisk population. However, due to control population characteristics, we could not establish age-matched cut-off values**. CONCLUSION:** Besides VLA/VMA ratio values, our analyses suggest that isolated VLA presence (without VMA) could be of diagnostic value for AADCD. However, this must be confirmed in a wider sample and correlated to clinical information. Our preliminary results suggest that VLA/VMA ratio might be a useful test for initial approximation for AADCD. However, it should be confirmed with the determination of the specific biomarker.

P-048 - AMINO ACID ANALYSIS FOR DIAGNOSIS OF INBORN ERRORS OF METABOLISM. EXPERIENCE WITH HIGH-RISK POPULATION

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BACKGROUND: Aminoacidopathies are a group of more than 40 diseases characterized by the accumulation in biological fluids of the amino acid that is not being metabolized due to genetic defects that alter its metabolism or transport. High-performance liquid chromatography is considered the gold standard for the biochemical diagnosis of these entities. However, interpretation of amino acid profile may be hindered by the clinical condition of the patient, dietary habits, medication among others, especially when the diagnosis is considered by clinical suspicion rather than newborn screening. Here we present a four-year experience with amino acid quantification in a reference center for diagnosis of inborn errors of metabolism from Colombia. **METHODS:** Retrospective analysis of results from samples sent for amino acid analysis to the institute for the study of Inborn Errors of Metabolism from January 2017 to December 2020. **RESULTS:** 3875 samples were submitted for analysis among urine, plasma, leucocytes and CSF corresponding to 21%, 67%, 4% and 7%, respectively. The processed profile includes 43 metabolites including amino acids and amino derivatives. We observed abnormalities in 42% of urine samples characterized by unspecific alterations related to increased levels of OH-proline, 1-methylhistidine, B-aminoisobutyric acid, anserine and B-alanine; or alterations of several amino acids that are not metabolically related that corresponded in half of the cases to decreased amino acid levels. Less positive rate was observed in plasma (approximately 30%) although still, most samples present unspecific alterations with less than 5% of abnormal profiles allowing confirmation of an aminoacidopathy. Among unspecific profiles we observed differences in the kind of alterations observed depending of the age of the patient, thus below 3 months most alterations corresponded to an increase of several amino acids while over one year of age decreased levels of amino acids were most common. CSF and leukocytes samples showed few unspecific results mainly for CSF due to lack of plasma submission for confirmation of NKHG**. DISCUSSION:** Our results agree with the literature regarding the sensibility and specificity of amino acid analysis of different biological samples. Data presented highlights the importance of a deep understanding of analyzed populations, diet, pre-analytical sample condition, and the need for age-based approximations.

P-049 - COVID-19 INFECTION IN THE PEDIATRIC PATIENTS WITH INBORN ERRORS OF METABOLISM: REPORT OF 18 LATIN AMERICAN PATIENTS AFFECTED IN THE PRE-VACCINATION ERA

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INTRODUCTION: Up to now, little is known about the impact of COVID-19 infection on pediatric patients with inborn errors of metabolism (IEM). **OBJECTIVE:** To evaluate the impact of COVID-19 infection in a cohort of Latin

American pediatric patients with IEM or suspected of having IEM (pre-vaccination era). **METHODS:** Observational, cross-sectional study with convenience sampling strategy. Eighteen pediatric patients with IEM (n= 14) or suspected of having IEM (n= 4) were included [female=7, mean age at inclusion 6 ± 3.01 years (2–11)]. All patients had a confirmed diagnosis of COVID-19 before being vaccinated. **RESULTS:** Mitochondrial myopathy, Mucopolysaccharidosis IVA and Phenylketonuria were the most frequent IEM. Ten (55.5%) presented at least one comorbidity, of which seizures/epilepsy, asthma, and lung disease were the most common. Fourteen (77.8%) developed clinical manifestations: High fever (64.3%), cough and coryza (35.7% each) and breathing difficulties (28.6%). Ten patients sought medical assistance, mainly in hospitals/public clinics. Five individuals needed hospitalization and 2 required ICU [Mitochondrial myopathy (n=1, age 11), and one patient with no confirmed diagnosis of IEM (age 8)]. Eventually, the patient with mitochondrial myopathy passed away**. CONCLUSIONS:** Our data suggest pediatric patients with IEM (or suspected of having IEM) may present severe COVID-19 disease. Appropriate monitoring of these patients must be ensured, and priority groups must be considered in vaccination programs against COVID-19.

P-050 - EFFECTS OF THE SARS-COV-2 PANDEMIC ON PATIENTS WITH INBORN ERRORS OF METABOLISM. A LITERATURE REVIEW

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INTRODUCTION: Inborn errors of metabolism (IEM) are chronic diseases that require continuous followup and, in some cases, highly complex treatments. Pandemics have imposed several challenges for patients and health services. This work explores the published information related to the effects of the SARS-CoV-2 virus on health, treatment, medical care and lifestyle of IEM patients. **METHODS:** A literature review was made including publications made between 2020 and 2021, published in English or Spanish and available in google scholar, SciELO, ScienceDirect, NCBI, ELSEVIER®, Wiley Online Library. Publications found in indexed journals or web pages from health national institutions or specialized organizations were included (recommendations, letters to editor, comments, case reports, reviews and primary articles) that were freely available or accessible through our institutional search engine. **RESULTS:** 45 publications were analyzed observing mainly publications from Europe and USA, while publications from Latin America (Mexico and Brazil) accounted only for 6% of the total. A higher number of publications was observed in the second semester of 2021 (28 vs 17). The main topics addressed were medical care; treatment and outcome of patients with specific diseases which were reported by 57.7% of publications (n=26). In addition, 20% of publications (n=9) discuss hypothesis related to COVID19 impact on specific IEM (familial hypercholesterolemia, Glucose-6-phosphate dehydrogenase deficiency, Gaucher and Hartnup diseases); 15.5% were case reports (n=7); and 6.6% included recommendations for treatment/follow-up (N=3). In general, contrary to expectations, there is a positive outlook in terms of the disease course in the IEM population with around 20% of publications mentioning that there is no evidence of the higher frequency of complications or fatal outcomes in the IEM population, although specific entities raise some concerns (familial hypercholesterolemia and glucose-6-phosphate deficiency). In terms of medical care approximately 50% of publications report negative effects of pandemics on patients, the main disadvantages documented were related to followup and treatment accessibility/continuity**. CONCLUSIONS:** These results highlight the importance of analyzing and reporting the available evidence to provide information that contributes to the improvement of patient care and counseling based on specific realities and needs. Moreover, more information is needed about the situation in Latin America.

P-051 - IMPACT OF PANDEMICS IN BIOCHEMICAL DIAGNOSIS OF INBORN ERRORS OF METABOLISM. EXPERIENCE OF A COLOMBIAN REFERENCE CENTER

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INTRODUCTION: Pandemics has represented important changes in the lifestyle of people influencing all aspects of living including health care. Different authors have referred that pandemics lead to focus medical services on COVID attention and that patients from chronic pathologies presented delays in medical attention and controls. This work presents the experience of a reference center for the biochemical diagnosis of inborn errors of metabolism during the last two

years, in terms of processed samples and diagnosis established. **METHODS:** Retrospective analysis of data from 2020-2021 and comparison of the results obtained with the observed in the two years before the pandemics (2018-2019). **RESULTS:** In general the main change observed was in referrals, with a decrease of about 45% of processed samples in the period 2020-2021 (around 7.000) compared to 2018-2019 (around 13.000). In fact, the number of referrals was similar between 2020 and 2021. Regarding entities diagnosed, in general, the number of confirmed diagnoses were similar although changes were detected in terms of the specific pathologies, for instance in 2020 six cases of NKHG and one case of homocystinuria was confirmed compared to four and eight cases respectively, in the period 2018-2019**. CONCLUSIONS:** Restrictions and prevention measures applied during pandemics probably lead to changes in the profile of patients submitted to biochemical testing for inborn errors of metabolism. Although this experience constitutes an overview of a short period of time, it provides information that could be valuable for comparison with other centers and helps to understand the impact of pandemics in Latin America.

P-052 - EDUCATION AND DISSEMINATION OF IEM INFORMATION. A WEB-BASED PROPOSAL.

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INTRODUCTION: Inborn Errors of Metabolism (IEM) is a growing group of diseases that currently brings together about 1.500 metabolic disorders of genetic origin. Their study and diagnosis are usually carried out in specialized institutions like universities and research institutes. Ideally, the education and dissemination work of IEM must reach not only health professionals, and researchers, but also patients, families, policy-makers, and the general public. **OBJECTIVES:** Here we summarize the experience of the Institute for the Study of Inborn Errors of Metabolism (IEIM, Spanish acronym) at Pontificia Universidad Javeriana (Bogotá D.C., Colombia) during the last years to increase the awareness about IEM and provide educational tools for these disorders focused on non-experts' health personnel, patients, and relatives. **MATERIALS AND METHODS:** A retrospective compilation of multimedia tools and educational materialoriented towards specific pathologies or groups of pathologies such as games, infographics, and texts designed by the IEIM. **RESULTS:** During the last two years, six divulgation videos have been developed for lysosomal storage diseases, small-molecules disorders, GM2 gangliosidoses, Mucopolysaccharidosis Isovaleric acidemia, integrated management of IEM, and ammonia sample collection. These videos have about 3.000 views from different countries around the world, mainly from Latin America, North America, and Europe. Also, a game was developed as an educational tool for patients and families with IEM, a freely accessible protein intake list for the most common foods found in our country, and specialized nutritional educational material for medical professionals and nutritionists (four systematized lists and standardized measurement tools). All the material is available at https: //javeriana.edu.co/ieim, section "Oferta Académica y Contenido Educativo". In our experience, although initially, some resources were researcher´s initiatives, interaction with patients and health professionals allowed the identification of specific needs that enriched the kind and focus of the generated material. In this sense, it is important to note the active participation of advocacy groups during the design and dissemination of these materials**. CONCLUSIONS:** The designed material has allowed increasing the awareness, dissemination, and education of IEM, reaching the target community and allowing greater knowledge of these pathologies and therefore the continuous improvement of their care.

P-054 - CONGENITAL DISORDER GLYCOSYLATION IB: REPORT OF A MEXICAN PEDIATRIC CASE

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Male of 9 years old, non-consanguineous parents, the mother had Hodgkin's Lymphoma at age 15, treated with chemotherapy. Originating from Rio Verde San Luis Potosí Mexico. He was born at term by cesarean section with adequate weight and height but with congenital cleft lip and

palate defect treated surgically at 3 and 18 months of age. Normal psychomotor development. At 18 months presented events of loss of balance, associated with drowsiness and disorientation, in his first clinical check-up only left hepatic lobe liver enlargement was detected, without any other alteration. Hypoglycemia < 50 mg/dL was identified during these events and the symptomatology clearly disappears when food was offered. He also has intermittent diarrhea lasting 2 or 3 days, every 7-10 days. His first test found, mild anemia, lymphocytosis, hypoglycemia 41mg/dL High aminotransferases almost 20 times above the normal value, no cholestasis, normal albumin, globulins, prothrombin time, urea, creatinine, uric acid, electrolytes, lipid profile, ammonium and lactate. Cortisol, adrenocorticotrophic hormone, insulin and somatomedin C, were normal too, as well as expanded metabolic screening. Hepatitis A, B, C serologies were negative. All the studies for gastrointestinal infections were negative. **EVOLUTION:** 2y 6m starts nocturnal cornstarch, then this was increased to every 4 hours, to ensure a glucose supply of 5g/hour, but hypoglycemia persisted, although less frequently and asymptomatic. At 3y 6m liver biopsy showed abnormal ductal plate malformation consistent with congenital hepatic fibrosis, At 4y 8m splenomegaly as the first manifestation of portal hypertension was detected, and At 7y 7m old presented first variceal bleeding treated with sclerosis and then ligation. Aminotransferases gradually improved with normalization since 3y 7mo. At 5y 6m old the molecular sequencing study found 2 nonsense mutations for the MPI gene, one variant was c.305C>T, giving rise to p.Ser102Leu with a predicted change in the protein sequence, the second variant was c..1178G>C that translates to p.Gly393Ala establishing a definitive diagnosis of a glycosylation defect IB, so at 6y 3m old starts mannose treatment 1g/k / day fractioned into 5 doses with remission of hypoglycemia and diarrhea.

P-055 - REPORT OF TWO PATIENTS WITH CDG TYPE II WITH TRANSAMINITIS, HYPOTONIA AND MYOPATHY

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INTRODUCTION: Congenital disorders of glycosylation (CDG) are heterogeneous genetic defects in the glycoprotein and glycolipid glycan synthesis and attachment. At least 130 CDG are known A CDG subgroup are defects in the conserved oligomeric Golgi (COG) complex, an eight-protein vesicle involved in Golgi structure and function. **CASES REPORT:** Case 1: Male patient with a history of hypotonia, transaminitis and elevated protein kinase, consulted due to fatigue and muscle cramps. Muscle resonance with spectroscopy was performed, which showed inflammatory-type changes in all muscle groups, for which oral steroids were started with stabilization to date. This boy also developed an episode of non-infectious hepatitis, thrombocytopenia and now has hypothyroidism and hypogonadism. Given a polysymptomatic condition, the possibility of a DCG was considered; a diagnosis of congenital glycosylation defect IIg, COG1 gene was documented. c.2665dupC in homozygosity. Case 2: Female with a history of hypotonia, episodes of encephalopathy due to hyperammonemia associated with infectious conditions and disproportionate responses to infectious diseases, transaminitis and elevated protein kinase C, consulted the neurogenetics group. Electromyography was performed, with proximal and distal myopathic involvement. Hypogammaglobulinemia was documented. Due to the multiple manifestations and multisystem involvement, CDG was suspected. Molecular confirmation of congenital type IIG glycosylation defect due to a mutation in the homozygous COG 1 gene was made. c.2665dup/p. (Arg889Profs*12) frameshift**. DISCUSSION:** There are few data reported on CDG type II in the literature so far. The phenotypic heterogeneity of O-glycosylation disorders reflects the great diversity of O-glycan structures with high tissue specificity. For example, due to the substantial presence of O-glycans in mucincontaining proteins including glycosaminoglycans (GAGs) and epithelial surfaces, there is skeletal dysplasia or connective tissue disease. Affected patients may present with musculoskeletal, skin, and joint abnormalities. Today we report the case of children whose evolution has been characterized by hypotonia, transaminitis, developmental delay, skeletal dysplasia and progressive muscle inflammation similar to muscular dystrophies, who required treatment with steroids**. CONCLUSION:** In the presence of multiple systemic manifestations and having ruled out the most frequent known causes, the possibility of CDG should always be considered.

P-056 - BODY COMPOSITION OF MEXICAN PEDIATRIC PATIENTS WITH LYSOSOMAL ACID LIPASE DEFICIENCY.

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OBJECTIVES AND STUDY: To describe body composition (BC) measured by densitometry (DEXA) in pediatric patients with lysosomal acid lipase deficiency (D-LAL). Cross-sectional study.**MATERIALS AND METHODS:** DXA was performed, lean and fat mass indexes (LMI, FMI) were estimated, data were interpreted with reference parameters for the Mexican population. The anthropometric evaluation consist of weight, height, mid-upper arm circumference (MUAC) and tricipital skinfold (TSF) and arm fat area (AFA) and arm muscle area (AMA) were estimated. Data were interpreted with percentiles (p) and z scores with the CDC reference values. **RESULTS:** We included 10 patients with a confirmed molecular diagnosis of D-LAL, 5 females and 5 males, median age 14 years (6y-18y). At the time of evaluation, all patients had at least two years of replacement therapy with sebelipase alfa. Five patients with short stature were identified. By BMI, 1 patient was identified as overweight and 1 with malnutrition. With MUAC 3 patients with malnutrition were identified. When estimating the arm muscle area, 1 patient below p5 was identified, in contrast, the LMI by DXA identified 7 patients below < p.5. It was observed that TSF, AFA and FMI by DXA within the same percentile intervals, identifying 2 patients with FMI above the p90 by DXA, while by anthropometry one of them**. CONCLUSION:** This study is the first to describe the body composition of pediatric patients with D-LAL measured by DXA compared to anthropometric assessment. Sarcopenia in chronic liver disease patients has been underestimated; this work shows how patients identified through BMI as normal can have a significant decrease in muscle mass and that the MUAC measurement is not always sufficient to identify this depletion. Finally, to complete the diagnosis of sarcopenia it would be necessary to extend its study with strategies for the evaluation of muscle strength in pediatric patients.

P-057 - NEPHROPATIC CYSTINOSIS IN THE DOMINICAN REPUBLIC: CASE REPORT.

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INTRODUCTION: Cystinosis is a rare autosomal recessive lysosomal storage disorder characterized by excessive accumulation of cystine within the lysosome, it is caused by mutations in the lysosomal cystine transporter, cystinosis (CTNS). The CTNSgene consists of 12 exons and encodes for an integral lysosomal membrane protein with seven transmembrane domains. A majority of cystinotic patients are of European descent, and only a few cases have been reported from other ethnic groups. **CASE REPORT:** nephropathic cystinosis in two Dominican male brothers at the time of the referral they were 11 and 2 years, both presenting chronic kidney disease, with a history of failure to thrive, rickets and impaired renal function. They were no consanguinity and no family history of chronic kidney disease. They have a history of vomiting, polyuria, polydipsia, failure to thrive and rickets, on examination, the height and weight were both below the 5th percentile of the CDC growth chart, the older was on peritoneal dialysis, the biochemical investigations revealed: metabolic acidosis normal anion gap, hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia and hypothyroidism, Low vitamin D, urinalysis revealed traces of protein and glucose; the urine pH varied between 6 -7, high serum creatinine levels, renal ultrasound with no nephrocalcinosis. On the basis of the clinical, biochemical, and radiological findings the diagnosis of Fanconi's syndrome, so they were referred to the ophthalmologist for evaluation presenting photophobia and crystals in the cornea, crystals were demonstrated by light microscopy, confirming the diagnosis of Cystinosis. **DISCUSSION:** typical clinical presentation of Fanconi's syndrome in these patients made of think of Cystinosis as one of the differential diagnoses, confirming the diagnosis by slit-lamp examination of the cornea and conjunctiva. Despite the clinical manifestations and severity of illness, both patients can be classified as having nephropathic cystinosis; These are the first two cases reported in the Dominican Republic, we are having limitations accessing to a genetic test or specific treatment for the disease.

P-058 - NEURONAL CEROID LIPOFUSCINOSIS: AN EPIDEMIOLOGICAL APPROACH IN LATIN AMERICA

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INTRODUCTION: Neuronal Ceroid Lipofuscinosis (NCL) comprises 13 hereditary neurodegenerative pathologies of

very low frequency. They affect individuals of all ages in various regions of the world. Advances are taking place after the encouraging expectations of enzyme replacement therapy (ERT) for CLN2 disease since 2017. Other therapeutic approaches are under development for the different types. A specific research program was established at the National University Cordoba, with the participation of the National Council for Scientific and Technical Research of the Argentine Republic (CONICET) and current headquarters in the Metabolic Diseases Section of the Children's Hospital of the Cordoba Province. Multidisciplinary studies in the Latin America (LA) region have not yet been evaluated. The objective of this work is to survey and qualitatively evaluate the casuistry in the region. **METHODOLOGY:** a meta-analysis of multidisciplinary evidence from 1995 onwards with qualitative weighting. Biostatistical evaluation of the casuistry. **RESULTS:** 29 publications originating in the region were evaluated. The prevalence of each type of NCL is analyzed by period. The number of families and individuals of each type per country is summarised up. Study methods, clinical evolution, morphological data, biochemical data, CNS images, genomic aspects, and references to other clinical details are surveyed. The NCL types, the genetic variants for each type, and the number and type of alleles are analyzed. Epidemiology calculations are finally made. **DISCUSSION AND CONCLUSIONS:** The prevalent type in the region is CLN2, followed by CLN3. The presence of compound heterozygotes in all NCL types is highlighted, probably due to the ethnic heterogeneity of the LA population. The founder effect of some DNA variants is verified and the prevalence in different locations is compared. The less prevalent types may still be underdiagnosed. The evolution of the diagnostic odyssey by period is verified. There would be a statistical deviation of the data due to the approval of the ERT for CLN2, which has led to an increased interest of the medical community for the early description of this pathology. The data from Argentina also appear oversized due to the existence of a reference center since the 1990s.

P-059 - AN UNUSUAL DIAGNOSIS: 2 CASES OF SALLA DISEASE

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INTRODUCTION: Salla Disease (SD) is a sialic acid storage disease caused by an autosomal recessive mutation in the SLC17A5 gene that varies in presentation, ranging from mild to severe forms. There exist less than 200 cases reported. **OBJECTIVES:** To share the experience with two different presentations of Salla Disease and amplify the number of physicians' differential diagnoses. **CASE REPORT:** Patient 1 is a 4-year-old female who was brought to the office at 8-months with right-sided weakness and spasticity. She was born at 38 weeks, weighed 3.29 kilograms (kg) and had a normal newborn screening. A Magnetic Resonance Imaging (MRI) was performed, showing marked hypomyelination and thin corpus callosum. She is stable and is currently on physical and occupational therapies. The patient is in the 25th and 10th percentile for weight and height, respectively. Patient 2 is a 7-year-old male who was brought at age 3 because of motor delay. With no relevant family history, born to term and weighed 3.63 kg. He had evident strabismus, the discrepancy in the finger to nose test, intention tremor and hypotonia. An MRI was ordered, exhibiting hypoplasia of the corpus callosum and deepening of the cerebellar folia**. DISCUSSION:** Infants affected by SD can have no signs of it at birth and develop them in the first year of life, which was the case of the two patients presented. Signs and symptoms include hypotonia, ataxia, motor delay and even regression of acquired abilities. SD occurs in both males and females equally. Diagnosis is made through imaging studies, genetic testing, and urinary sialic acid. In addition to the MRIs done to the patients in this paper, exome sequencing was ordered, and both patients had a mutation of the *SLC17A5* gene. There is no specific treatment, the management is based on symptoms. Life-threatening complications related to SD can happen.

P-060 - APTAMER EVALUATION WITH AFFINITY FOR BLOOD-BRAIN BARRIER RECEPTORS CONJUGATED TO THE ENZYME ALPHA-N-ACETYLGLUCOSAMINIDASE

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Mucopolysaccharidosis IIIB is an autosomal recessive lysosomal storage disease caused by deficiency of α-N-acetylglucosaminidase (NAGLU), producing accumulation of heparan sulfate (HS) within the lysosome. In patients, central nervous system impairment predominates in addition to abnormalities in peripheral organs and tissues. At present, there is no therapy approved for this disease. Enzyme replacement therapy has been proposed as a model of therapy which allows the reduction of the substrate accumulated. The recombinant NAGLU enzyme has been produced in our laboratory using the yeast Komagataella phaffii. Reduction in

the lysosomal mass of MPSIIB patients was evidenced in addition to a cell uptake. Since the major problem associated with this disease is the crossing through the blood-brain barrier, this work proposes the use of aptamers, nucleic acids capable of recognizing specific targets, as a strategy for such crossing. Potential aptamer candidates to cross the blood-brain barrier were TfRA4, GL21.T, and RNV-L17. Docking studies were performed to evaluate the changes in the protein affinity for the substrates HS and 4-methylumbelliferyl-2-acetamide-2-desoxy-alpha-Dglucopyranoside. These results predicted differences in the interaction of amino acids surrounding the active site, resulting in minimal differences in the enzyme-substrate affinity. Later, it was predicted the interaction of conjugated aptamers with their receptors, suggesting that NAGLU conjugation may impair the receptor-aptamer interaction. NAGLU was produced in the laboratory at a 400 mL scale and then conjugated to TFRA4. At the end of the conjugation process, the specific activity was 0.36U/mg. Verification of the conjugation was done by spectrophotometry where the conjugated 260/280 ratio was 1.19; while the negative control of conjugation was 1.16, values that did not allow to conclude on whether the conjugation was successful or not. These results serve as a baseline for future experiments where the appropriate conjugation conditions have been proposed that lead to the protein being unaffected.

P-061 - PRENATAL DIAGNOSIS OF LYSOSOMAL STORAGE DISORDERS BY THE ANALYSIS OF AMNIOTIC FLUID SUPERNATANT USING MASS SPECTROMETRY: EXPERIENCE IN MUCOPOLYSACCHARIDOSIS VI AND METACHROMATIC LEUKODYSTROPHY

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Lysosomal storage disorders (LSDs), including Mucopolysaccharidosis type VI (MPS VI) and Metachromatic Leukodystrophy (MLD), are progressive and multisystem conditions usually leading to severe manifestations. A challenging aspect associated with this context is the time at diagnosis since better outcomes are observed in patients who start treatment before irreversible damage has occurred. The development of new analytical tools is helping to improve the diagnostic processes. Prenatal diagnosis in high-risk pregnancies is frequently requested, but the need for studies in cultured amniocytes usually delays the result, generating uncertainty and anxiety. Here, we describe two independent cases involving prenatal diagnosis of fetuses with MPS VI and MLD, using the analysis of amniotic fluid supernatant by UPLC-MS/MS. In these cases, both amniocenteses were performed at 19 weeks of gestation and the cells were grown to perform enzyme assays and molecular genetics studies in material obtained from cultured amniocytes. In the case of MPS VI, disease-specific oligosaccharides were quantified in the AF supernatant by UPLC-MS/MS, and increased levels of the oligosaccharides HNAc (1S) and HNAc (2S) were found elevated in the supernatant of AF. These abnormal results in AF were later confirmed by the finding of deficient activity of ARSB and by molecular analysis of the *ARSB* gene in cultured amniocytes. In the case of MLD, C16: 0 sulfatides were quantified by UPLC/MS/MS in the supernatant of amniotic fluid, showing levels significantly elevated in comparison to age-matched controls (5-fold increase). This abnormal result was later supported by the deficiency of ARSA activity in fetal cells, as well as by molecular analysis of the *ARSA* gene, which revealed a pathogenic variant in homozygosity, confirming the diagnosis of MLD. These cases highlight the potential of MS/MS for the fast identification of LSDs in the amniotic fluid supernatant, providing an early indication of the fetal status, which is critical when dealing with prenatal diagnosis.

P-062 - CASE REPORT: VARIANT OF UNCERTAIN SIGNIFICANCE CONFUSING THE OUTCOME OF NEWBORN SCREENING

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INTRODUCTION: Type I mucopolysaccharidosis is an autosomal recessive disease, caused by the accumulation of partially degraded mucopolysaccharides due to deficiency of the lysosomal enzyme alpha-L-iduronidase. It is one of the diseases that can be diagnosed by neonatal expanded screening, allowing early approach and treatment. **OBJECTIVES:** Describe a clinical case of a newborn with a Variant of Uncertain Significance (VUS) confusing the interpretation and outcome of newborn screening. **MATERIAL AND METHODS:** This is a descriptive study of a patient that attended the Reference Service in Neonatal Screening of Amazonas using local data. **RESULTS:** Clinical case description of a newborn submitted to neonatal expanded screening, with the first qualitative test presenting decreased alpha-Liduronidase. The quantitative test showed the enzyme at a lower limit than the reference, but not a "disease" limit. In the molecular study were identified variants described as NM_000203.5 (*IDUA*): c.{920C>T (;) p.Ser307Phe (;) Pro357Leu}, both of uncertain significance (VUS) in the *IDUA* gene. The proband's father had a molecular study result presenting NM_000203.5 (*IDUA*): c1070C>T;p(Pro357Leu). Her mother had NM_000203.5 (*IDUA*): c920C>T;p.Ser307Phe. Parents were both born in Amazonas, with negative family history and this result brought stress to the family during the investigation, which made them seek genetic testing for confirmation. Newborn screening (NBS) methods and therapeutic options have become increasingly available for mucopolysaccharidoses, and there is clear evidence that early intervention significantly improves the outcome. A significant problem that is encountered in the followup of infants with abnormal NBS and VUS on molecular analysis results relates to those who cannot be positively identified as either affected or unaffected. Long-term follow-up of these infants, and of those detected with late-onset disorders, will be essential to document the true risks and benefits of NBS**. DISCUSSION***:* The expansion of neonatal screening must be a challenge and confusions like this must be addressed. Clinical cases like this allow patients with similar results to having conduct taken quickly and optimally, reassuring the family and providing genetic counseling.

P-063 - GENOME EDITING IN MUCOPOLYSACCHARIDOSIS FIBROBLASTS USING CRISPR-CAS9

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Mucopolysaccharidosis IVA (MPS IVA; Morquio A, OMIM 253000) is a monogenic recessive lysosomal storage disease (LSD) caused by mutations in the gene encoding for N-acetyl-galactosamine-6-sulfate sulfatase (*GALNS*). The absence of an active enzyme causes a progressive accumulation of the glycosaminoglycans (GAGs) keratan sulfate (KS) and chondroitin-6-sulfate (C6S) mainly in the bone, cartilage, and connective tissue. GAGs build-up leads to skeletal dysplasia, organomegaly, respiratory problems and heart valve disease among other symptoms. Currently, there are two different strategies as treatment options for MPS IVA with clinical approval: Enzymatic replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). Although these strategies have proved promissory results, they still lack effectiveness, especially in reaching bone tissue. Also, ERT does not offer a longterm solution and in the case of HSCT, there is a considerable risk associated with this procedure. Gene therapy offers a potential long-term solution for genetic diseases. Here we explored the potential of the CRISPR/Cas9 system in a gene therapy scenario for MPS IVA targeting the AAVS1 locus for insertion of a functional copy of the (*GALNS*) gene under the expression of a CMV promoter. MPS IVA fibroblast was treated with CRISPR/Cas9 system and GALNS donor vector. We confirmed the gene editing in the AAVS1 locus, as well as the reduction in lysosomal mass and the increase in the intracellular GALNS activity after 30 days post-treatment with CRISPR/Cas9 system and GALNS donor vector. This study shows the first evidence about the use of CRISPR/Cas9 on MPS IVA and will shed light in the design of a novel therapeutic strategy for this disorder.

P-064 - HIGH-RISK POPULATION SCREENING BY DIFFERENTIAL DIAGNOSIS FOR MUCOPOLYSACCHARIDOSES (MPSS)

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Mucopolysaccharidoses (MPSs) are a group of chronic, progressive lysosomal storage diseases (LSDs) with multi-system impairments. These disorders are caused by an enzyme deficiency resulting in the inability to break down glycosaminoglycans (GAGs; formerly called mucopolysaccharides) and their accumulation in arteries, eyes, skeleton, joints, skin, ears and/or teeth. Glycosaminoglycans can also accumulate in the respiratory system, spleen, liver, central nervous system, bone marrow, and blood. Depending on which of the eleven known enzymes are affected as well as

the level of enzyme activity, different clinical manifestations are described varying from mild to severe forms with potentially early death. Differential diagnosis by phenotype is very challenging or sometimes not possible. To overcome limitations, our medical laboratory has developed, validated, and accredited a novel diagnostic panel for differential diagnosis of MPSs utilizing a single Dried Blood Spot (DBS). Our assay includes testing for MPS I (α-L-Iduronidase), MPS II (Iduronate-2-sulfatase), MPS IIIB (N-α-Acetylglucosaminidase), MPS IVA (NAcetylgalactosamine-6-sulfate-sulfatase), MPS VI (Arylsulfatase B), MPS VII (ß-Glucuronidase). Here we are presenting data from high-risk population screening of over 10,000samples from over 57 countries. In total, over 500 MPSs positive patients were confirmed within the tested cohort and a retrospective data analysis was performed based on origin and type of MPS. The highest incidences were observed for MPS I, MPS VI, and MPS IVA with significant differences linked to the sample origin. In general, for Europe and Africa, a similar distribution of the investigated MPSs was observed, compared to the Middle East with a divergent distribution of MPS I, MPS IVA, and MPS VI. The presented data underlines the benefit of a fast and reliable diagnostic workflow for MPS suspected individuals and can be considered as a highly efficient strategy for national newborn screening programs in the near future.

P-065 - HURLER'S SYNDROME: A CASE REPORT

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INTRODUCTION: Mucopolysaccharidosis is a group of metabolic disorders caused by the deficiency or complete absence of certain lysosomal enzymes responsible for the breakdown of mucopolysaccharides, causing an accumulation of glycosaminoglycans throughout the body. Mucopolysaccharidosis type I (MPS I), also called Hurler syndrome, is an autosomal recessive lysosomal storage disorder resulting from deficiency of the enzyme α-L-iduronidase. The objective of this report is to present the clinical findings and diagnosis in a pediatric patient with Hurler syndrome. **CASE PRESENTATION:** We studied the case of a 16-month-old female with no history of similar cases in their previous generations. The diagnosis of Hurler syndrome was considered based on clinical and radiological characteristics including coarse facial features, enlarged head circumference, depressed nasal bridge, corneal clouding, macroglossia, gingival hypertrophy, skeletal dysplasia, hepatosplenomegaly, umbilical hernia, and psychomotor retardation. Echocardiographic evaluation indicates asymmetric hypertrophic cardiomyopathy and dilated aortic root. **RESULTS:** Genomic DNA from the patient was used to amplify all 14 coding exons of the *IDUA* gene (chromosome 4p16.3). Specifically, this essay showed a homozygous mutation in exon 9 where a nucleotide change occurred from Guanine1205 to Adenosine, producing an amino acid change to tryptophan 402. In a quantitative way, a total deficit (0 nmol/ml) was found (normal range 2.02 -16.1), leading to confirming the diagnosis of Hurler syndrome**. CONCLUSION:** We intend to raise awareness about the clinical manifestations of the disease, thus can help diagnose type I mucopolysaccharidosis, even in countries with limited access to diagnostic tools such as genomic DNA testing. It's been demonstrated that enzyme replacement can improve patients' survival; therefore early diagnosis is an important matter to address to the scientific community.

P-066 - COMPLEX REARRANGEMENT IN THE IDS GENE IN PERUVIAN TWINS WITH MUCOPOLYSACCHARIDOSIS TYPE II

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INTRODUCTION: Mucopolysaccharidosis type II (MPS II) or Hunter Syndrome is inherited in an X-linked recessive manner. The biochemical cause is a deficiency in the activity of the lysosomal enzyme iduronate-2-sulfatase (I2S), resulting in a progressive accumulation of glycosaminoglycans (GAGs). In most patients the symptoms are severe and they die at an early age. Until now, more than 600 variants have been described, the majority (49%) of which are missense/nonsense variants, and only 3% are complex rearrangements, these are homologous intrachromosomal recombinations between *IDS* and its pseudogene *IDSP1*. **OBJECTIVE:** Report a complex rearrangement in MPS II in Peruvian twins. **METHODS:** The patient was referred to our institution for suspicion of a short and stiff neck due to intubation difficulty for inguinal hernia surgery. Urine GAGs analysis was performed (qualitative) and the approach to determine MPS II, through sponsorship, including NGS, PCR-based method and iduronate sulfatase activity. **RESULTS:** 3-year-old male patients referred to genetic service for overgrowth, short neck. Patients product of the first twin

gestation, born at term by cesarean section with weight and height appropriate to their age, both with inguinal hernia. Psychomotor development up to one year of age was appropriate, then both begin with regression of development. Physical examination showed in both a large Mongolian spot, with coarse facial features, wide and short neck, umbilical hernia, inguinal operation scar with small hands with claw brachydactyly. Both have hearing loss. Mother denies consanguinity. Urine GAGs analysis was altered. A complex rearrangement of *IDS* was detected between intron 3 and intron 7 of *IDS* and the *IDSP1* pseudogene in hemizygous. In addition, iduronate sulfatase activity is pathologically decreased**. CONCLUSIONS:** We report a complex rearrangement of *IDS* in Peruvian twins with MPS II. It is important to consider the identification of *IDS/IDSP1* recombinations in the molecular analysis for early diagnosis, comprehensive management and genetic counseling to the family.

P-067 - FIBROBLAST FROM PATIENTS WITH MUCOPOLYSACCHARIDOSES IIIB AND IVA EXHIBIT AN ALTERED EPIGENETIC PROFILE

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INTRODUCTION: Mucopolysaccharidoses (MPS) are monogenic diseases, but heterogeneity in phenotypes, disease progress, and patient's response to therapy highlights the lack of absolute association between genotype and phenotype. In this vein, a role for epigenetic regulation in inborn errors of metabolism (EIMs) has been proposed. Recent studies have reported that increased DNA methylation is related to mutations in the genes coding for the enzyme iduronate 2-sulfatase and *NPC1* altered in Hunter syndrome (MPS II) and Niemann-Pick disease type C (NPC), respectively. Furthermore, peripheral blood cells from patients with Gaucher disease and fibroblast from patients with NPC disease show increased histone deacetylases (HDACs) expression and histone hypoacetylation. Significantly, HDAC inhibitors (HDACi) such as suberoylanilide hydroxamic acid (SAHA) o LBH-589 (panobinostat) improved enzymatic activity. However, to date, no reports have described epigenetic changes for MPS IIIB or IVA or whether HDACs could reverse such putative changes. The objective of this work was to compare the levels of histone acetylation (H3K14ac) and histone methylation (H3K9me3) in skin fibroblast from patients with MPS IIIB (GM02931 and GM01426) and MPS IVA (GM01361, GM01259, and 0598) and a non-affected person (GM00613). Also, the potential of the HDACi Trichostatin A (TSA) to reverse epigenetic changes was tested. Analysis of confocal imagines of fibroblast nuclei after immunofluorescence was performed using Cell profiler software. **RESULTS:** It was observed increased signal of total acH3K14 in MPS IIIB and IVA fibroblast and increased H3K9me3 in IVA fibroblast; the distribution of this epigenetics mark in the cell's nuclei was also altered. Significantly, treatment with 10 nM TSA partially restores the H3K9me3 level in IVA fibroblast. These results highlight the role of epigenetics in the development of MPS IIIB and IVA and the potential of HDACs for disease treatment.

P-068 - IN VITRO EVALUATION OF HYDROLYTIC ACTIVITY OF TWO RECOMBINANT NACETYLGLUCOSAMINIDASES AS POTENTIAL THERAPEUTIC TOOLS FOR MUCOPOLYSACCHARIDOSIS IIIB

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INTRODUCTION: Deficiency of the enzyme α-N-acetylglucosaminidase (NAGLU; E.C. 3.2.1.50) leads to the accumulation of the glycosaminoglycan (GAG) heparan sulfate in the cellular lysosomes of different organs, generating the neurodegenerative disease mucopolysaccharidosis III-B (MPS IIIB). Although recently there is no approved treatment for this disease, enzyme replacement therapy (ERT) has represented an alternative. Mammalian cells have been mainly used as hosts for the expression of recombinant human NAGLU (rhNAGLU); however, methylotrophic yeasts as Komagataella phaffii have been currently used for its expression. Although there are differences in glycosylation patterns between yeast and human proteins, it has been demonstrated that this does not affect the properties and normal rhNAGLU activity in patient cell lines. However, because such differences could contribute to the generation of adverse reactions once administered, K. phaffii was modified in the glycosylation pathway in order to obtain rhNAGLU with a humanized glycosylation pattern. **OBJECTIVE:** In this study two rhNAGLU obtained from Komagataella phaffii strains, one native and other carrying a deletion in the *OCH1* gene, were used to evaluate their ability to be uptaken by MPS IIIB cells and hydrolyze the accumulated glycosaminoglycans. **MATERIALS AND METHODS:** Production of rhNAGLU

was carried out by induction of the AOX1 promoter by methanol, in both native and deleted strains of K. phaffii. Enzyme activity was measured by fluorescence in crude extracts and was used as stimuli for MPS III-B fibroblasts. Cellular uptake and total glycosaminoglycans quantitation were followed through intracellular activity measurement and 1,9-dimethylmethylene blue technique respectively. **RESULTS:** The rhNAGLU production at 100 mL scale in K. phaffii deleted (NRRLY-11430/ΔOCH1), was 1.8-fold higher than obtained with the native strain (GS115). In in vitro assays, both proteins were endocyted showing intracellular activity values of up to 52.08 U/mg for rhNAGLU from K. phaffii NRRLY-11430/ΔOCH1 and 38.3 U/mg for K. phaffii GS115 in MPS III-B cells. Finally, a significant decrease in total glycosaminoglycans was observed after 6 hours of incubation with the stimuli, indicating lysosomal activity in rhNAGLU-treated cells**. CONCLUSIONS:** These results showed the potential of both strains as alternative platforms to produce recombinant NAGLU as therapeutic tools for the development of an ERT to MPS IIIB.

P-069 - DISEASE PROGRESSION IN SANFILIPPO TYPE B: CASE SERIES OF BRAZILIAN PATIENTS

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INTRODUCTION: Mucopolysaccharidosis type III B (MPS IIIB, Sanfilippo syndrome type B) is caused by deficiency of alpha-N-acetylglucosaminidase, leading to storage of heparan sulfate oligosaccharides. The disease is characterized by intellectual disability and hyperactivity, but other somatic features (hepatosplenomegaly, joint contractures, cardiovascular abnormalities) are also present. **OBJECTIVE:** A retrospective study of Sanfilippo Syndrome type B in patients followed up by the MPS Brazil Network. **METHODS:** Patients' charts were reviewed for biochemical findings, medical history, clinical manifestations and assessments. Any available results of the following investigations were also recorded: electroencephalography (EEG); electrocardiography (ECG); echocardiography; hearing assessment by pure-tone audiometry; tympanometry; physical exam; polysomnography, as well as other information relevant to the course of the disease, including surgical procedures and use of medication. **RESULTS:** Here we studied retrospective data from twenty-two MPS IIIB patients from Brazil, aiming to evaluate disease progression. Mean age at diagnosis was 6.2 years. Speech delay was one of the first symptoms to be identified, around 2-3 years of age. Behavioral alterations include hyperactivity and aggressiveness, starting around age four. By the end of the first decade, patients lost acquired abilities such as speech and the ability to walk. Furthermore, respiratory, cardiovascular and articular abnormalities were found in more than 50% of the patients, along with organomegaly. The most common cause of death was due to respiratory problems. **CONCLUSION:** The disease progression was characterized in multiple systems, and hopefully these data will help design appropriate clinical trials.

P-070 - CASE REPORT OF TYPE IV MUCOPOLYSACCHARIDOSIS DIAGNOSED AND TREATED DURING COVID-19 PANDEMIC

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INTRODUCTION: Mucopolysaccharidosis type IV is a lysosomal storage disease, characterized by skeletal dysplasia which not only leads to difficulty in walking and in daily activities but also to growth arrest around 8 years of age and potential neurological complications secondary to bone deformities. Early diagnosis and treatment with enzyme replacement are important for good results and reduction of disease complications. **OBJECTIVES:** Describe a clinical case of a patient with type IV mucopolysaccharidosis, diagnosed during COVID-19 pandemic. **MATERIAL AND**

METHODS: This is a descriptive study of a patient that attended the medical genetics outpatient clinic using local data. **RESULTS:** LMS, 5 years old, second daughter of a consanguineous couple, from the interior of Amazonas. Skeletal dysplasia is seen from the first months of life, initially "pectus carinatum". She sought medical care at the medical genetics outpatient clinic at the age of 4 with significant short stature and skeletal dysplasia. Due to the difficulty of transporting samples, it opted for initial diagnosis by performing a molecular panel for skeletal dysplasias. Identified pathogenic variant in homozygosity in the *GALNS* gene, ch16: 88,832,099 C>A that promotes the substitution of the amino acid glycine in codon 301 by cysteine (pGly.301Cys). Her older brother was investigated with urinary glycosaminoglycan measurements presenting normal results. Treatment with enzyme replacement was initiated and in the first infusions, the patient presented a reaction with cough, chest pain and vomiting. Desensitization with enzyme dilution and antihistamine was performed before infusion with good response. Currently, the patient makes the infusion in her municipality in the interior of Amazonas, many miles away from the infusion center, after nurses and families are trained**. DISCUSSION:** This is an important case for reflections on diagnosis and treatment during the COVID-19 pandemic and treatment in remote areas, such as the interior of Amazonas. In addition, the training of health professionals for infusion and management of reactions allows the treatment to be carried out in their municipalities, reducing expenses and avoiding exposure in situations of public calamity.

P-071 - CLINICAL, BIOCHEMICAL, AND MOLECULAR ANALYSIS OF AN ADULT PATIENT WITH SEVERE PHENOTYPE OF MUCOPOLYSACCHARIDOSIS TYPE IVA WITH A NEW HETEROZYGOUS VARIANT C.1481T>C (P.M494T) IN *GALNS*

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INTRODUCTION: Mucopolysaccharidosis type IVA/Morquio A syndrome (MPS IVA) is an autosomal recessive disorder caused by biallelic variants in the *GALNS* gene encoding the enzyme Nacetylgalactosamine-6-sulfatase (GALNS). Patients with MPS IVA present a wide range of clinical phenotypes, from the classic/severe to the non-classical/attenuated forms. Molecular analysis of *GALNS* by sequencing analysis/targeted next-generation-sequencing (TNGS) and/or quantitative-PCR (qPCR), identified the two allelic variants in about 95% of these patients. Although, the second variant, is not identified in the remaining 5%. **OBJECTIVE:** To describe the clinical, biochemical and molecular findings of an adult patient with the severe phenotype of MPS IVA. **MATERIAL AND METHODS:** A 49-year-old female patient was adopted from her birth for an unrelated family. Clinical evaluation: weight/height (perc<3), coarse facies, enamel alterations, short neck, cervical hyperlordosis, hepatomegaly, joint hyperlaxity, ulnar deviation and genu valgum. Multidisciplinary evaluation, enzymatic determination and *GALNS* analysis by TNGS/qPCR (Centogene©) were performed. Also, an MPS panel with seven enzymes related to MPS/EP-MPS (Ultragenyx©) and the Comprehensive Panel of Lysosomal Storage Disorders with 48 genes related to LSD/P-NGS-LSD (Invitae©) were carried out with informed consent. It was not possible to carry out the urinary test. **RESULTS:** The patient showed corneal opacity, sensory hearing loss, normal heart and dysostosis multiplex. Enzyme determinations were (0.5 and <0.03 µmol/1/h) (references >2.0 and >0.39 µmol/1/h) and the rest of EP-MPS were normal. TNGS/qPCR study revealed a heterozygous SNV: *GALNS* (NM_00132354): c.1499T>C (p.M500T). P-NGS-LSD detected only one heterozygous SNV: *GALNS* (NM_000512.4): c.1481T>C (p.M494T). (The differences are explained by the version of the reference sequence used). Analyzes in the different databases (eg Franklin/VarSome) revealed that c.1481T>C (p.M494T) is a pathogenic variant. Other disorders with clinical and/or enzymatic findings similar to MPS IVA (eg MPS IVB, Multiple sulfatase deficiency), were ruled out with the results of EP-MPS and/or P-NGS-LSD. The clinical, radiological and biochemical characteristics in our patient confirmed the diagnosis of MPS IVA. We will perform WGS/mRNA analysis to identify the second allelic variant**. CONCLUSIONS:** This is the first report of a Mexican patient in her 5th decade of life with a severe phenotype of MPS IVA, carrier of a new heterozygous pathogenic variant in *GALNS*.

P-072 - FACIAL DYSMORPHOLOGIES IN MUCOPOLYSACCHARIDOSIS TYPE IVA: EXPLORING THE ANCESTRY COMPONENT IN A COLOMBIAN POPULATION

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BACKGROUND: Mucopolysaccharidosis type IVA (MPSIVA) produces an accumulation of glycosaminoglycans that lead to progressive facial dysmorphology and characteristic facial phenotype with recognizable facial patterns. However, the ancestry heterogeneity, genotype, and the use of enzymatic replacement therapy (ERT) might disrupt the facial phenotype. The use of DeepGestalt technology in particularly Face2Gene app has become more popular and has permeated and changed the decision-making in clinical practice. **OBJECTIVES:** We aim to identify how ancestry inference in diagnosis validity and precision in a heterogeneous ancestry population. **MATERIALS AND METHODS:** We performed a phenotypic study on a cohort of 11 patients harboring causative variants on *GALNS* gene in order to evaluate Face2Gene validity and precision on populations with different ancestry backgrounds. The cohort was added to the clinical interface of Face2Gene by adding frontal 2D photos. Clinical analysis using similarity assessment according to gelstats and heatmap were used to study precision and validity according to race, ERT, and genotype. Validity and precision through age were evaluated in three patients at different time points. Multiple unpaired t-tests to determine significant difference between groups was used. **RESULTS:** Based on the frontal 2D image of patients, a diagnostic of MPSIVA with the top five predictive syndromes for 45.4% of our cases and none listed as a first prediction. A statistically significant difference in validity was observed between black and Hispanic groups (2.6 vs 5.6 gelstats, p=0.0031), respectively, and Hispanic and brown significant differences in validity and precision (5.6 and 3.33 gelstats), respectively (p=0.0005). Additionally, a difference in gelstats similarity index on precision was observed between MPSIVA treated and non-treated with ERT (1.3 vs 4.8, p=0.01). The age of patients seems to affect the prediction accuracy and precision, whereas our results indicate from average of (0 and 86.6%) validity and precision at a younger age to (26.6% and 93.3%) at an older age, respectively**. CONCLUSION:** Overall, we concluded that computer-assisted diagnosis analysis using deep machine learning could have an ancestry bias or racial disparity, which might affect the clinical diagnosis. On the other hand, age and use of ERT might influence precision and diagnosis validity.

P-073 - CLINICAL, BIOCHEMICAL AND MOLECULAR CHARACTERIZATION OF MUCOPOLYSACCHARIDOSIS TYPE VI PATIENTS AT DR. ROBERT REID CABRAL CHILDREN´S HOSPITAL, DOMINICAN REPUBLIC

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INTRODUCTION: Mucopolysaccharidosis type VI (MPS IV) is a lysosomal storage disease due to deficiency of arylsulfatase B (ASB), which leads to the accumulation of glycosaminoglycans (dermatan sulfate) in connective tissue. It is transmitted in an autosomal recessive manner and has variability in its clinical expression. **OBJECTIVE:** Show the existence of this pathology in the Dr. Robert Reid Cabral Children's Hospital, due to its higher frequency in relation to other MPS; being its initial evaluation late, as well as its diagnosis, with a limited therapeutic approach. **MATERIAL AND METHODS:** Description of the clinical characteristics of the patients, who, due to their phenotype, underwent multisystemic evaluations, qualitative quantification of mucopolysaccharides in urine, enzymatic activity and molecular analysis. **RESULTS:** We present 13 patients (7 males and 6 females). At the time of diagnosis, the ages were between 1 and 5 years old, except for two patients, an 11-year-old and a 5-month-old, with an average of 4 years. One hundred percent of the patients presented: short stature, macrocranium, coarse facial features, dysostosis multiplex and hernias. Central nervous system abnormalities 12/13, of which 4 had hydrocephalus. Corneal opacity 12/13, hearing deficit 10/13. Cardiovascular abnormalities 9/13 (aortic mitral valve disease, mitral tricuspid, 1/9 right axis deviation). The semi-quantitative test for glycosaminoglycans (Berry Spot Test) was positive in 9/13. The results of the enzymatic activity of ASB were decreased in 13/13 (0.95 to 3.3 Umol/l/h). The molecular analyzes corresponded to pathogenic variants for the ASB gene: c.971G >T(p.324 Gly Val), homozygous (5/10); c.914delC(THr 305Fs), homozygous (2/10); c.899-2A > T, homozygous (2/10); c.971G > T(p.324Gly Val) and c.1299dup(p.Arg434F*) double heterozygous (1/10). One of these patients received enzyme replacement therapy in the United States, and three of them in the Dominican Republic for 11 months in 2020**. CONCLUSIONS:** The clinical approach guides the performance of complementary tests that allows establishing differential diagnoses of other MPS, multidisciplinary intervention, therapeutic approach and genetic counseling

P-074 - MUCOPOLYSACCHARIDOSIS TYPE VII: CLINICAL AND BIOCHEMICAL FOLLOW-

UP OF AN ARGENTINIAN PATIENT RECEIVING ENZYME REPLACEMENT THERAPY

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INTRODUCTION: Mucopolysaccharidosis type VII (MPS VII) is an ultra-rare lysosomal storage disease due to beta-glucuronidase (bGUS) deficiency. Clinical variability is described from classical phenotype with non-immune hydrops fetalis, skeletal dysplasia and mental retardation to milder forms with fewer symptoms. **OBJECTIVE:** Describe 3 years clinical and biochemical follow-up of a MPS VII 15 years old (yo) patient receiving enzyme replacement therapy (ERT). **MATERIALS AND METHODS:** A retrospective medical record analysis from 2019 to 2022 of an MPS VII mild-form patient was performed. Clinical data like: onset age, diagnosis age, family history, signs and symptoms of the disease, X-ray images, respiratory functional assay, cardiovascular and abdominal images, IQ test as biochemical tests bGUS enzyme activity, urine glycosaminoglycans (GAGS) and GUS gene sequencing were analyzed. **RESULTS:** We collected information from a 15yo patient born from a non-consanguineous couple with unremarkable family history. First symptoms started at 3 months old with bilateral inguinal hernia surgery, he associated phonetic spelling deficit at 6yo and conductive hypoacusis at 11yo. His first genetical consultation was at 12yo when MPS disease was diagnosed because of deficient bGUS enzyme activity, elevated chondroitin and heparan sulfate urinary GAGS and 2 variants of unknown significance (VUS) in GUS gene. His baseline exams detected a minimal pelvis and spine X-ray compromise, minimal hepatomegaly, normal low IQ test and normal spirometry. In July 2019 he started 4mg/k alfa-vestronidase treatment every other week with acceptable tolerance and adherence. Follow-up assessment showed normalized hepatic measurement, stable IQ test as respiratory and cardiovascular tests, GAGS normalized and better outcome in daily life activities were referred**. CONCLUSIONS:** We consider that although MPS VII is an ultra-rare disease, it's very important to reach an early diagnosis as it´s a treatable condition that generates improvement or stabilization of some signs and symptoms as shown on the monitoring of our patient.

P-075 - POMPE DISEASE IN A FEMALE INFANT WITH CARDIOMYOPATHY. A CASE REPORT.

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INTRODUCTION: Pompe Disease is a lysosomal storage disease caused by a deficiency in an enzyme known as acid alpha-glucosidase active in lysosomes where glycogen is broken into glucose. The enzyme deficiency is produced by mutations on the GAA gene and it is inherited as an autosomal recessive condition. The classic form has an infantile-onset characterized by hypotonia, myopathy, hepatomegaly and cardiac involvement. **OBJECTIVES:** We report a female patient with Pompe Disease suspected because of heart failure and hypertrophic cardiomyopathy. **MATERIALS AND METHODS:** Retrospective medical record review of a female patient diagnosed with Pompe Disease. **RESULTS:** We report a female patient a one-year-old patient which was evaluated for cyanosis around the mouth and mild respiratory distress. An echocardiogram was performed and revealed an ejection fraction of 20% associated with left ventricle hypertrophy with low cardiac. Contractibility. In the physical examination, the following features were relevant: a notorious hypotony with global developmental delay including poor neck holding and with deglutition disorder; a liver enlargement 4 centimeters below the right costal border, macroglossia, mild edema in lower extremities and global hyporeflexia. Electromyography was performed reporting myotonic discharges in needle study on deltoid and lateral vastus muscles. Laboratory tests were positive with high levels of CPK and liver enzymes. Pompe disease was suspected so an enzymatic activity test of acid alpha-glucosidase enzyme was performed resulting in positive. The patient passed away a few days after diagnosis, so parents were studied using next-generation sequencing tests in order to provide genetic counseling. In both parents, a pathogenic single nucleotide variant (c.2560C>T) in the exon 18 of the GAA gene was found in a heterozygous state leading to a nonsense mutation. (p.Arg854*)**. CONCLUSION:** In patients with cardiomyopathy, developmental delay features and hepatomegaly, Pompe disease should be suspected. Enzymatic activity and molecular characterization should be done in order to establish a diagnosis and provide adequate genetic counseling to families of patients.

P-076 - INFANTIL ONSET POMPE DISEASE AT DR. ROBERT REID CABRAL HOSPITAL, SANTO DOMINGO, DOMINICAN REPUBLIC

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INTRODUCTION: Infantile Onset Pompe disease (IOPD) is a lysosomal glycogenosis due to deficiency of acid maltase enzyme with multisystemic involvement manifested mainly by hypotonia, hypertrophic cardiomyopathy, respiratory problems, and hepatomegaly. Early enzyme replacement therapy (ERT) with recombinant human rhGAA improves symptoms, survival, and quality of life; many children treated with rhGAA develop antibodies, making therapy difficult, requiring immunosuppression. The immune response is due to the lack of the enzyme defined as cross-reactive immune status (CRIM). CRIM- have a complete absence and greater risk than CRIM+ and maybe more immune sensitive to ERT, due to previous exposure to the enzyme, however, 1/3 of CRIM+ can develop a high level of antibodies handle with personalized management strategies. **OBJECTIVE:** Show experience with immunosuppression and ERT in one of our patients. **MATERIAL AND METHODS:** Diagnostic, clinical and therapeutic description. **CASE REPORT:** Male, 4 months old. Parents' first-born, low socioeconomic status and teenager mother. Admitted for respiratory distress. Physical examination shows generalized hypotonia, macroglossia, hepatomegaly 4cms below the coastal ridge. Creatinine phosphokinase at 1,195 (normal range 55-170). EKG, chest X-ray and ECHO showed evidence of hypertrophic cardiomyopathy. Pompe disease suspected and confirmed by decreased activity of the enzyme, pathological molecular study (p. Arg854Xhomozygosity) and CRIM -. Before diagnosis and immunogenicity condition, immunosuppression and ERT, started under the Duke University scheme and informed consent with rhGAA, rituximab, methotrexate, and immunoglobulin with hematological, biochemical and immunological monitoring. Treatment can be applied for 8 weeks with tolerance and slight cardiovascular improvement, motor and liver involution, despite continuous respiratory infectious processes. The patient died from aspiration. **DISCUSSION AND CONCLUSION:** Of the five patients with IOPD in our center, only in this case we could implement ERT with immunosuppression, others arrived in serious condition. The experience allowed us to see the effectiveness of ERT with immunosuppression in CRIMs. Early diagnostic and therapeutic approaches have a positive impact on the survival and progression of the disease.

P-077 - IDENTIFICATION OF CLINICAL MANIFESTATIONS IN COLOMBIAN PATIENTS WITH GAUCHER DISEASE

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INTRODUCTION: Gaucher disease (GD) is the most common inherited lysosomal storage disease caused by the inherited deficiency of the lysosomal enzyme β-glucocerebrosidase, which leads to the accumulation of its normal substrate, glucocerebroside, in tissue macrophages with damage to hematological, visceral and bone systems. Severity and coexistence of different symptoms are highly variable in GD. the timely identification of signs and symptoms allow a better approach to the disease, avoiding morbidity and mortality **OBJECTIVE:** To identify the most frequent clinical manifestations in Colombian patients with Gaucher disease. **METHODOLOGY:** A review of the medical history of 19 patients with a molecular diagnosis of Gaucher disease was performed **RESULTS:** The patients included in the study presented hepatomegaly (52,6 %), splenomegaly (73,6%), anemia (57,8%), and thrombocytopenia (42,1%) with or without any bone abnormality. The review of the clinical history of each patient, allowed to find specifically that: Patient 3 presented a report of hepatosplenomegaly and grade III hepatic steatosis; In addition, a limitation of gait was confirmed, associated with left hemiparesis, retractions in general and appearance of bone necrosis. Patients 4,5,6 and 7 are part of the same family group, with a family history of anemia and bone necrosis. Patients 5 and 7 presented decreased enzyme activity values, without any associated symptoms. Patient 4 was diagnosed with bicytopenia, perivascular dermatitis, erythema nodosum in the lower limbs and severe dilatation of the blood vessels of the lower limbs. Patient 17 presented symptoms consisting of severe anemia after the age of 60, the enzymatic tests presented very low concentration values, for which the diagnosis was made. The pelvis MRI report of patient 19 revealed hyperintensities over the upper shaft of the right femur along with changes in pelvic floor muscles. Only two patients did not receive ERT at the time of the study due to technical difficulties of the health service**. CONCLUSION:** Research, diagnosis, and treatment of GD in Colombia hold great

potential given the number of studies done for this disorder. Knowledge about this disease opens an opportunity to develop novel treatments, improve existing ones, and to strengthen the basic and clinical research of GD in our country.

P-078 - USE OF GENE INTERACTION NETWORKS TO UNDERSTAND THE PHENOTYPIC HETEROGENEITY OF GAUCHER DISEASE

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INTRODUCTION: Gaucher disease (GD) is a lysosomal storage disease caused by the defective activity of the acid lysosomal enzyme B Glucocerebrosidase, encoded by the *GBA* gene, leading to an accumulation of glucosylceramide in organs and tissues. It is important to know in-depth the effect of Gene interactions of the *GBA* gene with particles and proteins on the development of the disease, its progression, prognosis, and response to treatment. ***OBJECTIVE:*** Build gene interaction networks associated with the *GBA* gene. **METHODOLOGY:** A construction of genomic interaction networks was carried out for the *GBA* gene. By using the bioinformatics software STITCH 5 and GeneMANIA. Each interaction network was built relating it to associated proteins and small molecules, considering only evidence found from experiments, process databases biological, molecular function, pathway, or domain of the protein that was altered and co-expression with provided confidence levels of more than 0.900. **RESULTS:** Physical interactions, co-expression, prediction of associations, and genetic interactions between the *GBA* gene, the *PSAP*genes, *SCARB2*, *NEDD4*, *HYOU1*, *RPS6KA3* and *LAMP2*, the transcription factors. All the associated genes were activated in functions associated with vacuolar locations, instructions regarding the lysosomal and vacuolar lumen, vacuolar membranes, and lysosomal; In addition, a relationship was found with target drugs that alter or promote the functioning of the *GBA* gene and have been used at some point for the treatment of GD, proposing new understandings for the management of the disease through the impact of the *GBA* gene and associated genes. The activator of βglucocerebrosidase, saposin C, encoded by the gene prosaposin (*PSAP*) is an established activator for the hydrolysis of glucosylceramide by GCase in lysosomes; conditions in PSAP cause alterations in GBA activity leading to typical signs such as hepatosplenomegaly and neurological involvement, related to type 2 of the EG**. CONCLUSION:** it's possible to construct models that indicate activation or inactivation of genes and help to understand how genes interact with *GBA*, being an essential step to impact the knowledge of heterogeneity phenotypic of this disease, bringing us closer to precision medicine.

P-079 - GAUCHER DISEASE TYPE III – DIAGNOSTIC CHALLENGES IN A PEDIATRIC PATIENT IN PORT-AU-PRINCE, HAITI

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INTRODUCTION: Gaucher Disease (GD) is a rare autosomal recessive genetic disorder, caused by mutations in the *GBA* gene located on chromosome 1q21.31, which is characterized by the deficiency of the glucocerebrosidase enzyme. Organ damage results from the accumulation of glucocerebroside lipids throughout the body especially in the bone marrow, spleen and liver. **OBJECTIVE:** Describe the challenges associated with the diagnosis of Gaucher disease in Haiti. **MATERIALS AND METHODS:** We present the clinical presentation and testing done to confirm Gaucher Disease in a child from Haiti. **CASE REPORT:** A three-year-old girl was seen at our center with a history of chronic anemia, abdominal pain and distension, progressive hepatosplenomegaly since the first year of life. She had been seen at multiple health centers with no definitive diagnosis. Sickle cell disease had been ruled out. There was no other significant past medical history, except for maternal toxoplasmosis treated during this pregnancy. Physical examination was notable for convergent strabismus and significant abdominal distention due to hepatosplenomegaly in an otherwise normal child. She was referred to the Dominican Republic for further diagnostic evaluation. Gaucher disease type III was diagnosed based on decreased enzyme activity levels and confirmation of homozygous c.1448T< C mutation in the *GBA* gene. Ophthalmologic examination showed bilateral sixth nerve palsy with convergent strabismus. The fundus was normal, with no central neurological damage. CBC showed hypochromic microcytic anemia with thrombocytopenia (123,000/mm3). Abdominal MRI

confirmed hepatosplenomegaly (liver - 2,580.75 cm3, spleen 2,961.62 cm3) with no ischemia nor venous dilatation. The pancreas, adrenal glands and kidneys were normal. The chest X-ray was normal. There were no hip or long bone lesions, no Erlenmeyer flask deformities, fractures, or evidence of avascular necrosis, osteopenia, infarction, or bone marrow infiltration. The patient is currently stable and being evaluated for enzyme replacement therapy**. CONCLUSION:** This case highlights the diagnostic challenges of inborn errors of metabolism and the need for a high index of suspicion in a child presenting with the classic form of anemia, thrombocytopenia, and hepatosplenomegaly.

P-080 - COGNITIVE AND ADAPTIVE PROFILES IN PATIENTS WITH GAUCHER DISEASE TYPE 3 AT DR. ROBERT REID CABRAL CHILDREN´S HOSPITAL, DOMINICAN REPUBLIC

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INTRODUCTION: Gaucher disease, due to deficiency of the lysosomal enzyme glucocerebrosidase, accumulates glucosylceramide in the cells of the monocyte-macrophage system. It is classified as nonneuronopathic type 1 (>90%) and neuronopathic type 2 and 3 (<5%). Type 1 primarily affects bone marrow, liver, spleen, and bone. Type 2 is subdivided into perinatal-lethal/non-lethal forms. Type 3 has different phenotypes that are sub-classified as 3a, 3b, 3c and Norrbottnian. They present early type I symptoms and late neurological involvement, such as: gaze palsy, seizures, ataxia, spasticity, dementia, learning, language and intellectual disabilities, processing deficit, visual-spatial relationship difficulties, and perceptual organization impairment. Some have high verbal IQ scores. **OBJECTIVE:** Show intellectual and adaptive skills through standardized tests and intervention possibilities. **MATERIAL AND METHODS:** Assessment with the Wechsler Intelligence Scale (WISC-IV) for children, which evaluates verbal comprehension, perceptual organization, working memory, and processing speed, and with the Adaptive Behavior Assessment System (ABAS-II) for children that measure conceptual, social and practical skills. **CASES REPORT:** (1) Female, 16 y/o. At diagnosis 1.4 years. L444p/L444p mutation. Intelligence quotient (IQ) and general adaptive development 55 (very low). Disruptive behavior, social limitation, learning disabilities in concepts and reading-writing. (2) Male, 11 y/o. At diagnosis 1.2 years. L444p/L444p mutation. Bilateral strabismus and focal epilepsy. IQ 54 (very low) and general adaptive development 75 (borderline). Disruptive behavior. Difficulties in reading and writing. Good socialization. (3) Female, 9 years old. At diagnosis 1.7 years. Mutation C.14448T>C. IQ 66 (very low) and general adaptive development 89 (low average). Difficulty in learning concepts. Good socialization. All received enzyme replacement therapy with Imiglucerase from an early age with adequate dosage and adherence. **DISCUSSION AND CONCLUSION:** In the Dominican Republic, 3 out of 12 patients have Gaucher disease type 3 (25%). They have below-average intellectual and adaptive functioning with a better prognosis in the patient with c.1448T>C mutation. Highlights in some strengths in memory, social and verbal skills with weaknesses in fluid reasoning and processing speed. Limited psycho-pedagogical support at home and at school, making its prognosis difficult. We need more studies on neuronal pathophysiology, phenotypic overlap, and cognitive/adaptive aspects in GD3.

P-081 - TGF-B1 AND CASPASE-3 ARE INVOLVED IN FABRY NEPHROPATHY

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INTRODUCTION: The kidney is one of the main target organs in Fabry disease, a lysosomal X-linked disorder. Renal involvement is characterized by proteinuria and progressive chronic kidney disease. Pathogenic mechanisms were not fully described. Lysosomal Gb3 deposition occurs followed by complex pathological pathways resulting in renal sclerosis/fibrosis. TGF-β1 is an important cytokine involved in kidney fibrosis and can also mediate apoptosis. Our previous results showed positive staining for TGF-β1 in tubular epithelial cells in biopsies from Fabry patients. The apoptotic marker active-caspase-3 was also observed in tubular cells. **AIMS:** To quantify TGF-β1 and active caspase-3 expression by tubular cells in kidney biopsies from Fabry naïve patients and non-Fabry individuals, and to analyze possible correlations among these markers and clinical or histopathological parameters. **METHODS:** Fifteen renal biopsies from naïve Fabry patients and 5 from non-Fabry

individuals were included. Immunofluorescence staining for TGF-β1 and active-caspase-3 was performed. Fluorescence intensities were quantified using Image-J software. These markers were compared among patients according to sex, age, classical or late-onset Fabry disease, interstitial fibrosis and infiltration scores, proteinuria and glomerular filtration rate. The procedures followed were approved by the Ethical Committee of Framingham (La Plata, Argentina). **RESULTS:** TGF-β1 tubular expression was increased in Fabry classic patient´ specimens as compared to late-onset ones. Levels were independent of age or sex. Active-caspase-3 expression presented a similar tendency although without statistical difference. There was no correlation between TGF-β1 and active-caspase-3 levels. Caspase-3 was elevated in patients presenting inflammatory infiltration. This marker was also shown to correlate with proteinuria and glomerular filtration rate. No correlations were observed for TGF-β1 and histological/clinical parameters**. CONCLUSIONS:** TGF-β1 is highly expressed by tubular cells in kidney biopsies from Fabry naïve patients. TGF-β1 expression is higher in the classic variant of the disease showing that this cytokine plays a key role in the pathogenesis. However, it showed no correlation with active-caspase-3. The apoptotic marker showed to correlate with proteinuria (positively) and glomerular filtration rate (negatively), suggesting that tubular cell death is a clear component of Fabry nephropathy and it could be secondary to the increment in proteinuria levels rather than a direct effect of TGF-β1.

P-082 - IS IT A FABRY DISEASE OR A SARCOMERIC HYPERTROPHIC CARDIOMYOPATHY A POSSIBLE PITFALL IN DIAGNOSIS?

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INTRODUCTION: Fabry disease (FD) is a rare disorder that is considered a phenocopy of hypertrophic cardiomyopathy (HCM), the most common genetic cardiovascular disease related to sarcomere damage. Approximately 40%–60% of patients with HCM have at least one sarcomere gene altered. Of those individuals with positive genetic testing, most disease-causing variants occur in myosin heavy chain (MYH7) and myosin binding protein C (*MYBPC3*), identified in 70% of these cases. **OBJECTIVE:** To report a case of HCM due to a pathogenic variant in the *MYBPC3* gene previously misdiagnosed as FD. **METHOD:** This is a descriptive study. The patient was tested for FD and had *GLA* gene sequenced through Next Generation Sequencing and lyso-Gb3 quantified through Liquid Chromatography-Mass Spectrometry. Other family members were also screened through the same methods but the males also had the alfa-galactosidase activity (α-GAL) measured through fluorimetry. Then, all of them were investigated through a 168 gene panel related to HCM. **RESULTS:** R.M.O.A, a female, 45 years old, was diagnosed with HCM at age of 38 and has been using an implantable cardioverter-defibrillator (ICD) since then. Beyond the cardiac symptoms, she also referred acroparesthesias, hypohidrosis and hearing loss. Her younger sister also had fibromyalgia. FD was thus suspected and a "pathogenic" variant p.(Arg118Cys) in *GLA* gene was detected in both patient and her sister. Other first degrees relatives were tested, including the patient's two sons who both had the p.(Arg118Cys) variant with normal levels of lyso-Gb3 and α-GAL. A 168 gene panel for HCM was performed in the patient and the pathogenic variant (p.Arg495Gln) was found in the *MYBPC3* gene**. CONCLUSION:** The variant p.(Arg118Cys) has been reported in multiple individuals affected with mild, atypical or late-onset FD. Some studies have called the pathogenicity of this variant into question because it has been observed as homozygous in three related females who do not have Fabry disease, and in individuals who do not have evidence of storage on renal biopsy. Genetic counseling was offered and the family will be followed up for both conditions.

P-083 - INFECTION-INDUCED HEMOLYTIC UREMIC SYNDROME IN A GIRL WITH FABRY DISEASE

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INTRODUCTION: Hemolytic Uremic Syndrome (HUS) is a condition characterized by the occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. The most common mechanism of HUS in children involves protein synthesis inhibition caused by Shiga-toxin-producing Escherichia coli in sensitive cells expressing globotriaosylceramide (Gb3), a substrate accumulated in patients with Fabry Disease (FD). **OBJECTIVE:** To report a case of infection-induced HUS in a girl with FD. **METHODS:** A chart review. **RESULTS:** A 7 months old female was referred to the hospital due to a history of bloody diarrhea and fever. She is the daughter of a male with classical FD (GLA mutation G328R). Laboratory results were remarkable for the

presence of anemia (hemoglobin 5.2 g/dL), with raised hemolysis markers (LDH 5258 U/L), thrombocytopenia (37.000) and kidney failure (creatinine 2.66 g/dL). Stool culture was negative for Shigella and Salmonella. She was treated with blood transfusion, peritoneal dialysis and antibiotics and discharged after 23 days. In a 10 year follow-up period, she developed hypertension, a known long-term complication of infection-associated HUS. Her eGFR (Counahan-Barratt formula) is in the 85-105 mL/min/1.73m2 range in the last four measurements. Her last lyso-Gb3 level is 6 nmol/L (normal range for females 0.91-3.86). As there is no clear major organ damage attributable to FD until now, she remains on clinical and laboratory surveillance, without receiving enzyme replacement therapy**. DISCUSSION:** Previously, it was demonstrated that mouse models of FD, in spite of the high expression of Gb3, are less susceptible to the damage induced by Shigatoxin 2 (Stx2) when compared to wild-type mice. Furthermore, treatment with enzyme replacement therapy reduced that protection. To the best of our knowledge, there is no report of a male with FD developing infection-induced HUS. Nevertheless, our case demonstrates that at least females with FD are still susceptible to developing this condition. As new treatments for HUS targeting sphingolipid metabolism are emerging, we expect that new insights into the relationships between HUS and FD pathophysiology will be gained.

P-084 - DIAGNOSTIC STRATEGY FOR SUSPECTED CASES OF FABRY DISEASE

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Fabry disease (FD) is a progressive, X-linked inherited lysosomal storage disorder caused by genetic variants in the α-Galactosidase A gene (*GLA*). Partial or complete deficiency of the enzyme αGalactosidase A (α-Gal A) results in a progressive accumulation of lipids with terminal α-Galactosyl residues, primarily globotriaosylceramides (Gb3, GL-3) and its deacylated derivative Lyso-GL-3 (LysoGb3) and leads to organ damage. Early diagnosis is vital to prevent clinical complications. We would like to present data from over 65,000 tested cases (males and females) suspicious of FD where both α-Gal A activity together with Lyso-GL-3 levels were measured, followed by confirmatory genetic testing for over 7,000 cases. The aim was to demonstrate the benefit of adding Lyso-GL-3 to primary diagnostic screening to avoid unnecessary genetic testing. The results have shown that determination of the enzyme activity combined with the concentration of Lyso-GL-3 (Lyso-Gb3) in Dried Blood Spots (DBS), substantially improved the diagnostic detection of FD in females compared to using enzyme activity alone. In addition, data from validation of innovative self-sampling devices for patient sample collection show correlation to DBS results, and it could be utilized for at-home sample collection to significantly improve patient care during current covid-19 time restrictions.

P-085 - GLOBOTRIAOSYLSPHINGOSINE (LYSO-GB3) DETERMINATION IN CLASSIC AND LATE ONSET FABRY PATIENTS

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INTRODUCTION: Fabry disease (FD) (OMIM#301500) is an X-linked disease, resulting from the deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal A) [1,2]. The enzymatic defect causes the progressive accumulation of globotriaosylceramide (Gb3) and its derivative globotriaosylsphingosine (LysoGb3). Both males and females suffer from Fabry disease, and two major phenotypes of Fabry disease, classic and later-onset variants are observed. Recently, elevated serum levels of LysoGb3 were found in a group of Fabry patients. However the utility of LysoGb3 for screening, severity or treatment follow-up is still controversial, and more data is needed. **AIMS:** To determine LysoGb3 concentrations in Fabry patients and normal controls, as well as in patients with benign or unknown significance variants on *GLA* gene. **METHODS:** Informed consent for collecting clinical data and blood samples for biobanking was obtained from all patients. We recruited 205 adult patients, including normal controls, Fabry patients and patients with benign or unknown significance variants on *GLA* gene. Fabry patients were divided into 4 groups: late-onset females (n=11), classic females (n=21), late-onset males (n=10), classic males (n=21). 142 patients were on a specific treatment. LysoGb3 concentration was assayed in dried blood spots by HPLC-Tandem mass spectrometry. Comparisons between the study groups were performed using the t-test. **RESULTS:** LysoGb3 values were higher in 4 groups of Fabry patients as compared to normal controls. Overlap was found between late-onset patients and normal controls, with a rate of false negatives of 10 and 54% for males and females respectively. 20% of individuals with unknown significance variants displayed high values. Most of the patients on ERT have LysoGb3 not different from the naïve Fabry patients**. CONCLUSIONS:**

LysoGb3 assay as a screening test has a sensitivity of 89%. The specificity of this assay was 98%, so a value above a cut-off needs confirmation by gold standard methods. Using LysoGb3 as a possible biomarker for follow-up of therapy did not show a good response among late-onset and females. LysoGb3 levels among classic males on ERT were lower than that of naïve patients, but no normalization was observed in any of the cases.

P-086 - THE IMPORTANCE OF USING SEVERAL BIOMARKERS WHEN INVESTIGATING LSDS WITH OVERLAPPING PHENOTYPES: REPORT OF A CASE OF GM1 GANGLIOSIDOSIS IDENTIFIED AS AN INCIDENTAL FINDING

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Gangliosidosis GM1 (MIM#230500) is an autosomal lysosomal storage disorder, caused by the accumulation of GM1 ganglioside in lysosomes and consequent damage to neurons in the brain and the spinal cord. Type I Gangliosidosis (infantile form) is the most severe type, showing rapid psychomotor deterioration initiating within 6 months of birth, with neurodegeneration, hepatosplenomegaly, facial dysmorphism, skeletal irregularities, and early death. Niemann-Pick type C (NPC) is also a storage disorder related to disturbances in cholesterol trafficking. It has an autosomal recessive inheritance as well, causing somatic manifestations and progressive neurodegeneration. The symptoms of the patients appear between 2 and 4 years, and they progressively develop neurologic abnormalities, beginning with ataxia and seizures. The *GLB1* gene is located at position 3p22.3, spanning 62.5kb and comprising 16 exons. This gene encodes b-Galactosidase, a lysosomal enzyme that hydrolyses the terminal betagalactose from ganglioside substrate. A patient with severe neurodevelopmental delay, facial dysmorphism, hepatosplenomegaly was sent to us for investigation of NPC, through the NPC Brazil Network. The objective was to measure chitotriosidase activity by fluorimetry and to quantify lysosphingomyelin-509 through ultra-high performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS), in a dried blood spot (DBS). As the results of the analysis did not suggest a diagnosis of NPC, the DBS sample was used as a control for validation of b-Galactosidase by UPLC-MS/MS. During this analysis, it was accidentally discovered a very low activity, a result that may be suggestive of GM1. The analysis of the activity of b-Galactosidase by fluorimetry was also suggestive of GM1. Thus, molecular analysis of the *GLB1* gene was performed by Next Generation Sequencing, in the same DBS sample, using the Ion S5 System platform, using a customized panel. The molecular analysis revealed that the patient was a compound heterozygote for two pathogenic variants in the *GLB1* gene, p.Thr239Met/p.Asp441Asn. After all the analyses, it was possible to complete the patient's diagnosis, which departed from an accidental finding, highlighting the importance of using a broad panel of biomarkers when investigating cases with suspicion of LSDs that have overlapping clinical phenotypes.

P-087 - CLINICAL PRESENTATION OF METACHROMATIC LEUKODYSTROPHY ACCORDING TO CLINICAL PHENOTYPES: DESCRIPTIVE STUDY IN A SPECIALIZED CENTER.

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INTRODUCTION: Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by the deficiency of arylsulfatase A (ARSA) enzyme, which leads to sulfatide accumulation, resulting in progressive dysfunction of the central and peripheral nervous system. The three clinical phenotypes based on the age of onset are: late-infantile (LI), juvenile (J) and adult (A), being the late-infantile the most common form (40 - 50%). **OBJECTIVE:** Describe symptoms according to the different phenotypes of MLD and determine the time from clinical onset to disease diagnosis. **MATERIALS AND METHODS:** Retrospective and descriptive study. Medical records of patients with MLD, belonging to the Neurochemical Laboratory "Dr. N. A. Chamoles" Buenos Aires, Argentina, between 1978 and 2021, were analyzed. **RESULTS:** A total of 39 patients (54% male) from 36 unrelated families were included in the study. Sixty-nine percent corresponded to the LI phenotype. The first symptoms were loss of motor abilities (59%), gait disorder (22%) and squint (15%). The mean ages of symptom onset and

diagnosis were 16,7 months and 27,2 months respectively. Twenty-three percent of the patients belonged to the juvenile phenotype, corresponding 55% to early juvenile (EJ) and 45% to late juvenile (LJ). Most of the EJ patients experienced a loss of motor abilities and gait disorder. Fifty percent of the LJ patients showed behavior impairment and the other half, learning disorder. The mean age of symptom onset was 6.2 years and the mean age of diagnosis was 7.2 years. Only 3 patients corresponded to the adult phenotype, 2 of which started with psychiatric symptoms and 1 with cognitive impairment. The mean time to diagnosis was 4.6 years**. DISCUSSION:** In our study, symptom onset of the clinical phenotypes was consistent with the international literature. Regarding the time between symptom onset and diagnosis, LI phenotype was within the range of others studies. The mean time in J form was shorter and it was usually longer in the adult phenotype compared to the current bibliography. In conclusion, LDM is a rare illness that presents with a rapid motor decline, thus symptom awareness allows an early diagnosis, which can provide better therapeutic possibilities.

P-088 - LIMITATIONS IN THE DIAGNOSIS OF NIEMANN-PICK C: ANALYSIS OF A MEXICAN PATIENT

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Niemann-Pick type C (NPC) is an autosomal recessive lipid storage disease with a wide spectrum of clinical phenotypes. At the cellular level, the disorder is characterized by the accumulation of unesterified cholesterol and glycolipids in the lysosomal system resulting from mutations in either the *NPC1* or the *NPC2* gene. The classic clinical form begins in childhood with symptoms that appear between 2 and 4 years of age, but the diagnosis of NPC is often delayed due to the wide spectrum of clinical phenotypes. The most common neurological signs are vertical supranuclear gaze palsy, cerebellar ataxia, dysarthria, dysphagia, seizures and progressive dementia. A diagnosis of Niemann-Pick disease type C was made in a 3 years old boy. The institutional metabolic screening that was performed at born only covered five diseases. He was diagnosed with congenital rubella, BCGitis and hepatosplenomegaly at three months of age. At two and a half years old, on the grounds of progressive psychomotor retardation, hepatomegaly and refractive epilepsy gave suspicion towards NPC. Enzymatic detection of acid sphingomyelinase was a normal result (2.77 nmol/l; range 1.38 to 18.1 nmol/l). Exome sequencing was performed later, which reported a heterozygous state for the pathogenic variants c.530G>A (p.Cys177Tyr) and c.3104C>T (p.Ala1035Val) located in the *NPC1* gene. Including an expanded metabolic screening in public health institutions and knowledge of rare diseases by health, personnel are necessary for the timely diagnosis of patients with these diseases.

P-089 - FIVE CASES OF NIEMANN-PICK TYPE C DISEASE: CLINIC, DIAGNOSIS, TREATMENT AND FOLLOW-UP

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INTRODUCTION: Niemann Pick type C (NPC) disease is a progressive, irreversible, and debilitating neurovisceral lysosomal storage disorder. Biallelic pathogenic variants in one of the two genes cause NPC: *NPC1* in 95% of cases and *NPC2* in the remainder, confirm the diagnosis. The mutations lead an impaired intracellular lipid trafficking and subsequent accumulation of unesterified cholesterol, sphingosine and glycosphingolipids in the endolysosomal compartment. The estimated incidence is 1/100,000 births. There is a wide spectrum of clinical onset and progression of the disease. It occurs from the prenatal period to adulthood with visceral, neurological, and or psychiatric features. In the perinatal period and infancy, manifestations are predominantly visceral, from late infancy onward, neurologic and psychiatric. The progression is different in each patient. There is no curative therapy. Miglustat has been approved for the management of neurologic manifestations and it seems to be beneficial for survival. **OBJECTIVE:** To present our experience on clinic, diagnosis, treatment and follow-up of 5 NPC disease cases. **CASES REPORT:** From a biochemical point of view, two cases have elevated dried blood spots of chitotriosidase activity, four have elevated plasma oxysterols. All cases have molecular definitions (*NPC1*). Considering the age of onset, 3 patients belong to the early infantile (<2 years) and 2 to the juvenile (6 to <15 years) onset group. Sex: 2 males and 3 females. Isolated splenomegaly was the first clinical feature in two males and a female. All cases had splenomegaly at the

moment of the diagnosis. After the diagnosis was confirmed, all patients began scheduled clinical follow-up: thorough physical examinations and disability rating scales, every 6 months. The shortest follow-up time is 1 year and the longest 10 years. Three patients started treatment with Miglustat at different ages according to the moment of the onset of neurological signs or symptoms**. CONCLUSIONS:** Our series of cases of NPC disease represents a broad spectrum of the clinical onset and evolution of this progressive and damaging lysosomal genetic disorder. We highlight the importance of starting disease progression monitoring of each NPC patient as soon as the diagnosis is confirmed.

P-090 - NIEMANN PICK TYPE C: A CURIOUS CASE OF A PRESCHOOLER WITH REGRESSION SYNDROME AND VISCEROMEGALY

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INTRODUCTION: Niemann-Pick disease type C (NPC) is a neurovisceral atypical autosomal recessive disease of lipids storage with a wide clinical spectrum. Its clinical variability can include from the neonatal onset with fatal course to adult-onset forms with chronic progressive neurodegenerative involvement. Two genes are involved: *NPC 1* gene, which is responsible of 95% of cases, and *NPC 2* gene. **OBJECTIVE:** To report a case of Niemann Pick type C diagnosed in our country and to discuss its clinical and molecular findings. **METHODS:** retrospective medical record review of a patient diagnosed with NPC. **RESULTS:** We report a 3-years-old female patient with 9 months of the evolution of loss of skills with neurological impairment. She had neonatal jaundice associated with hepatomegaly and minor dysmorphic features that were studied as congenital cytomegalovirus that was ruled out. She has had several respiratory symptoms associated to deglutition disorder and multiple bronchoaspiration episodes which require gastrostomy for feeding and tracheostomy with ventilator support. She also has splenomegaly with portal hypertension. Comparative genomic hybridation (CGH) was performed and showed deletion of 1p36.22 and loss of heterozygosity in 8q23.1-q23.3 and 20q11.22.q-12. Using next genome sequencing (NGS) it's identified an *NPC 1* gene pathogenic variant in a homozygote state. LysoSM-509 biomarker concentration study was performed resulting positive**. DISCUSSION:** Niemann Pick type C is a rare lysosomal storage disease. It is caused by accumulation of unesterified cholesterol due to the impaired exit of the lysosomes. It can be present from the neonatal period to adulthood. There is a broad clinical spectrum that often includes neonatal transitory cholestasis associated to hepatomegaly or splenomegaly and later onset of neurological impairment. Our patient presented the same clinical course described. The diagnosis was made by finding a homozygote state *NPC 1* gene pathogenic variant and high concentrations of Lyso-SM-509. We think it's a very important case because the clinical variability and lack of clinical awareness of this disease result in underestimation of cases and late diagnosis.

P-091 - PREOPERATIVE THERAPY WITH DIHYDROTESTOSTERONE IN PATIENTS WITH DEFICIENCY OF 5 ALPHA-REDUCTASE IMPROVES SURGICAL RESULTS. PRESENTATION OF A CASE.

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INTRODUCTION: 5 Alpha reductase deficiency was reported for the first time in the Dominican Republic in Las Salinas, Barahona. It is the result of a mutation in the 5 alpha-reductase type 2 gene (*SRD5A2*) and is characterized by a female phenotype or incomplete virilization in an individual with a 46 XY karyotype, with male testes and internal genitalia. This pathology is a cause of anxiety and concern for both parents and health personnel since it is not always possible to make a timely diagnosis and, in turn, offer early therapy that allows the p atient to insert himself from the first years of life into the corresponding role. **CASE REPORT:** Preschool patient who attends the consultation for a review for the presence of masses in bilateral labia majora and slight growth of the clitoris since birth. There is a history of 2 maternal cousins with anomalies of genital development. Female-looking external genitalia, 2ml bilateral masses on the labia majora, 2cm clitoris with slight hypertrophy, and vaginal introitus. Laboratories: 46XY Karyotype Testosterone/Dihydrotestosterone ratio: 41.25. Genital ultrasound: 2 structures with characteristics of testicles of preserved dimensions and morphology. The epididymis without alteration, testicular measurements TD: 1.04 X 1.26 CMS, TI: 0.79 x 1.31 cms. Dihydrotestosterone gel therapy

was started at 0.2 mg/kg daily in the genital area for 4 months and subsequently, a masculinizing genitoplasty was performed. **RESULTS:** 5 alpha-reductase deficiency is diagnosed in most cases during physiological virilization that occurs at puberty, causing confusion and other psychological disorders that affect the patient's self-image, social and sexual performance. After 4 months of daily application of the preparation, longitudinal growth of the phallus was confirmed by 4.5 cm and a circumference of 4 cm, favoring reconstruction or genitoplasty at an early age with better results**. CONCLUSION:** Preoperative therapy with Dihydrotestosterone in the early years favors an elongation of the phallus resulting in a complete correction of the external genitalia and a genetic and gonadal sex-concordant appearance.

P-092 - ARE YOU ABLE TO RECOGNIZE THE ATTENUATED PHENOTYPE OF AADC DEFICIENCY?

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Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive neurometabolic disorder that leads to defective synthesis of the neurotransmitters dopamine and serotonin. Symptom onset typically occurs during the first months of life and is characterized by early-onset hypotonia, oculogyric crises, dystonia, impaired development and autonomic dysfunction. Only a few cases with a milder course have been reported. We describe 2 teenage brothers with AADC deficiency due to compound heterozygous *DDC* gene variants (c.201+5G>C and c.206C>T p). Both siblings presented with almost normal acquisition of early developmental milestones but with a mild course of neurodevelopmental features during childhood. The younger brother, the index case, age 13, has a behavioral phenotype consistent with hyperactive-impulsive type of ADHD. He also had abnormal dyskinetic movements, excessive hand sweating and sleep problems since toddler. He showed sporadic oculogyric crisis since age 2 y.o especially when tired. The older brother never presented oculogyric crisis, but he has always been observed due to motor clumsiness, tics and permanent drooling. Both attend normal school. AADC deficiency diagnosis was made by whole-exome sequencing and plasma enzymatic assay. Methylphenidate, dopamine agonists and melatonin treatment led to some clinical improvement. We believe that this form of presentation with nonspecific neurodevelopmental problems and mild dysautonomic symptoms should be underdiagnosed in the population of neuropediatric patients since the prevalence of AADC deficiency is still unknown.

P-093 - CIRRHOSIS BY CONGENITAL DEFICIENCY OF BILE ACID SYNTHESIS: RARE CLINICAL CASE IN COLOMBIA

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INTRODUCTION: inborn errors of bile acid metabolism (IEBAM) cause rare but treatable genetic disorders that can present as neonatal cholestasis that can lead to progressive cirrhosis or liver failure. Here we describe the clinical features, laboratory examinations and treatment responses of a child presenting with early cirrhosis. **CASE REPORT:** Male 3-year-old patient with a history of symptomatic focal epilepsy secondary to meningitis and hemorrhagic stroke at 6 months of life, consanguine parents (uncle and niece). He developed jaundice one month of evolution secondary to direct predominance hyperbilirubinemia with hepatosplenomegaly and abdominal CT scanning and Endoscopic retrograde cholangiography report of a single gallstone of 10 mm in diameter, and retroperitoneal mesenteric lymph disease, with suspected lymphoproliferative syndrome. Rheumatologist rules out autoimmunity disease. The laboratory showed level serum total bilirubin 13.2mg/dl, direct bilirubin 9.6mg/dl, ALT 116 U/l and AST 62 U/L, but normal GGT 46 U/l. The surgeon performs hepatic wedge by laparoscopy upper digestive tract endoscopy + ligature of esophageal varicose veins. Liver biopsy was conclusive of cirrhosis suggestive of metabolic disease. GC/MS: bile acid was analyzed at Saint Joseph Hospital in Paris. Primary bile acids: cholic acid 1.84 umol/l, chenodesoxycholic acid 0.37 umol/l. Secondary bile acids: deoxycholic acid 1.38 umol/l, lithocholic acid 0.00

umol/l. Finally: the chromatographic analysis with GC/MS shows: Presence of peak characteristics of 3b-hydroxy-C27-steroid oxidoreductase deficiency (3 β HSD deficiency). The chromatographic analysis with LC/MS shows: the presence of cholate 8.5%, presence of peak characteristic of 3 β HSD deficiency 91.5% (MIM # 607765). He has been receiving treatment with cholic acid for 9 months, and fat-soluble vitamins, which jaundice disappeared and hepatosplenomegaly, transaminases and bilirubin decreased. **CONCLUSION:** the association of cholestasis with normal gamma-glutamyl transferase guided the search for a deficit in bile acid synthesis. Early infant diagnostic is important because maybe successfully treated with a favorable response to oral bile acid therapy.

P-094 - CONGENITAL DEFECTS OF BILE ACID SYNTHESIS TREATED WITH PRIMARY BILE ACIDS: 10-YEAR FOLLOW-UP

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INTRODUCTION: Inborn errors of bile acid synthesis are very low-frequency defects. Deficiency of 3βhydroxy-Δ5-C27-steroid dehydrogenase (type 1) and Δ4-3-oxosteroid-5β-reductase (type 2), both autosomal recessive defects, present as progressive cholestatic liver disease and malabsorption of fatsoluble vitamins, secondary to failure to produce normal bile acids and accumulation of unusual bile acids. Oral administration of primary bile acid has been shown to be efficient in improving clinical manifestations, correcting the deficiency and inhibiting the synthesis of toxic bile acids. **OBJECTIVES:** To report the clinical follow-up of 6 cases treated with primary bile acid supplementation over a period of 10 years. **RESULTS:** Five patients with type 1 defect aged between 3 years and 13 years and one patient with type 2 defect aged 5 years. All patients except one with biochemical and molecular confirmation. In all cases cholestatic hepatitis and hepatomegaly were present during the first two years of life, in two cases decreased levels of fat-soluble vitamins were shown, one case debuted with clinical rickets due to vitamin D malabsorption, one case died at 12 months due to progressive hepatic disease/cirrhosis without treatment. One patient was treated with chenodeoxycholic acid (15-20 mg/k/day) and 4 patients treated with cholic acid (10-15 mg/k/day) normalized liver function in an average of 3 months and have remained asymptomatic in a follow-up period of 3 to 10 years and without the requirement of fat-soluble vitamins**.** **CONCLUSIONS:** Bile acid synthesis defects are treatable pathologies, so they should be included in the differential diagnosis of cholestatic liver disease and start primary bile acid supplementation early, preventing progression to liver cirrhosis/liver failure and death.

P-095 - ALPHA 1 ANTITRYPSIN DEFICIENCY IN COSTA RICA: ENZYMATIC LEVELS AND PHENOTYPES DETECTED IN SUSPECTED PATIENTS

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INTRODUCTION: The α1-Antitrypsin deficiency (A1ATD) is an inherited disorder caused by mutations in the *SERPINA1* gene, which encodes the protease inhibitor alpha-1 antitrypsin (A1AT). It is considered the most important genetic cause of liver disease in children and emphysema in adults. The standard diagnostic approach involves the assessment of serum A1AT levels, followed by phenotyping, genotyping, gene sequencing, or combinations of the previously mentioned. The normal allele is PiM, which is associated with normal serum A1AT concentration, but more than 90 variants have been identified. The most common deficiency variants are PiS and PiZ characterized by serum A1AT concentrations between 50%–60% and 10%–15% of the normal range, respectively. **OBJECTIVE:** To describe the enzymatic levels and phenotypes detected in 42 patients suspected of α1-Antitrypsin deficiency. **MATERIALS AND METHODS:** This study included 42 patients with clinical suspicion of A1ATD and low A1AT levels. Quantification of A1AT serum was made by turbidimetric test and identification of the different phenotypes was performed by isoelectrofocusing on agarose gel using the semi-automatic HYDRASYS system followed by immunofixation with anti-Alpha-1 antitrypsin Antiserum. **RESULTS:** The average serum levels according to the phenotypes found were: MM 65 mg/dl, MZ 69 mg/dl, ZZ 26 mg/dl, MS 5 mg/dl, SS 65 mg/dl, Null 0 undetectable, MNull 70 mg/dl and rare phenotype 65mg/dl. The phenotypes detected in the patients studied were: 40% MZ (17 patients), 26% ZZ (11), 12% MM (5), 12% MS (5), 2%SS (1), 2% NULL (1), 2% M/NULO (1). 2% (1) rare phenotypes could not be identified **CONCLUSIONS:** The most common phenotype detected was the MZ, followed by the ZZ phenotype. The average concentrations of serum A1AT for each phenotype are close to those previously reported in the

literature. It is recommended to use complementary techniques such as genotyping, to identify Alpha-1 antitrypsin phenotypes detected but not characterized with this technique, due to the resolution and sensitivity limits of zone electrophoresis, it is possible that some Alpha-1 antitrypsin isoforms may not be detected with this method and neither differentiates the rare variants that migrate close to the S, Z and especially M fractions.

P-096 - AICARDI-GOUTIERES SYNDROME: CLINICAL, NEUROIMAGING AND GENETIC FINDINGS.

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INTRODUCTION: Aicardi-Goutières Syndrome (AGS) is an early-onset progressive encephalopathy with basal ganglia and periventricular white matter calcifications, leukodystrophy, brain atrophy and/or cerebrovascular disease. Clinically, AGS is characterized by variable degrees of neurologic impairment, and systemic manifestations including skin inflammation with chilblain-like lesions, lupus-like disease or polyarthritis. Mutations in genes involved in the intracellular metabolism or sensing of nucleic acid (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, *IFIH1*, *LSM1*1 or *RNU7-1*) result in an abnormal overproduction of type 1 interferons alpha. **AIM:** To describe clinical, neuroimaging and genetic features of patients with a genetically confirmed diagnosis of AGS. **METHODS:** We reviewed the medical records, neuroimaging findings, and genetic mutations of patients with AGS from a National Reference Centre for Rare Diseases. **RESULTS:** We report on five patients from four families with a genetically-confirmed diagnosis of AGS, four of them with a subacute encephalopathy with onset after 1 year of age. In three patients, autosomal recessive variants were identified. A 3 years 7 months old male patient with global developmental delay and neurodevelopmental regression by 6 months of age, spasticdystonic quadriparesis, acquired microcephaly, brain atrophy, leukodystrophy and calcifications, with mutations in *RNASEH2B*. A 2 years 8 months old female patient with a subacute encephalopathy with onset at 12 months of age, basal ganglia calcifications and leukodystrophy, chilblain skin lesions on the fingers and toes, and mutations in *RNASEH2B*. A 9 years old male patient with *ADAR1* variants, with neurodevelopmental regression at 13 months of age, dystonic quadriparesis, bilateral striatal necrosis and calcifications. An increased expression of interferon-stimulated gene transcripts in peripheral blood was demonstrated. A 17 years old male and 7 years old female siblings had subacute onset with gait disturbances after 1 year of age and a static or slowly progressive combination of spasticity and dystonia with a pathogenic variant in the *IFIH1* gene, a known cause of an autosomal dominant form of AGS. The male sibling developed the lupus-like disease, an important clue that contributed to guiding the diagnosis**. DISCUSSION:** AGS is a rare disease. Recent reports suggesting encouraging results with new treatments underscores the importance of early diagnosis.

P-098 - URINARY ORGANIC ACID PROFILE BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY (GC/MS) AS A USEFUL TOOL FOR THE DIAGNOSIS OF PEARSON SYNDROME. A CASE REPORT.

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BACKGROUND: Pearson syndrome (PS) is an infancy/early childhood disorder, sporadic and very rare syndrome, usually caused by deletions or duplication of a part of the mitochondrial DNA. PS is a multisystemic disease characterized by refractory sideroblastic anemia, vacuolization of bone marrow precursors and exocrine pancreatic dysfunction. Clinical phenotype changes with age, thus several tests are needed to confirm the diagnosis such as bone marrow biopsy and urinary and molecular tests. Differential diagnosis includes other mitochondrial disorders and some organic acidurias. Urinary organic acids determination is not commonly used in these cases. The aim of this work is to show the usefulness of the semi-quantitative urinary organic acids analysis in the diagnosis of PS. **CASE REPORT:** 2-year-old male patient, presenting lactic acidosis, aplastic anemia, global developmental delay, failure to thrive, microcephaly, café-au-lait spots, and a family history of two previous abortions. Organic acids determined by mass gas chromatography showed a significant elevation of lactic, pyruvic, 3-hydroxybutyric, fumaric, malic and 2-ethyl-3-hydroxypropionic acids. Clinical data and urinary organic acids profile were suggestive of a mitochondrial disorder. A significant increase in lactic and pyruvic acids and ketone

bodies, as well as low levels of some amino acids (HPLC) were also found. The diagnosis was confirmed with a mitochondrial genome sequencing, which resulted in a heteroplasmic deletion of 3762 bp, comprising 8 genes consistent with the diagnosis of Pearson Syndrome and Kearn-Sayre Syndrome**. CONCLUSION:** The variable expressiveness of mitochondrial diseases complicates their diagnosis. The determination of urinary organic acids is very useful in the approach to these diseases, especially in cases like our patient, who did not show the characteristic sideroblastic anemia of PS.

P-099 - A NEW CASE OF SFXN4 (SIDEROFLEXIN-4): NOVEL MUTATION AND FURTHER EVIDENCE OF MITOCHONDRIAL DYSFUNCTION IN FIBROBLASTS

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BACKGROUND: *SFXN4* defects cause autosomal recessive combined OXPHOS deficiency-18. Only 3 patients have been reported with homogeneous clinical presentation, ultrastructural mitochondrial abnormalities, deficiencies in electron transport chain (ETC) activity and normal SFXN4 protein expression. *SFXN4* has a yet undefined but important role in Fe-S cluster biogenesis. **OBJECTIVES:** To report clinical, molecular characterization and functional studies in a 4th patient with*SFXN4* defect. **METHODS:** Fibroblast cultures were established from a skin biopsy. Western blots were performed for *SFXN4*, *NUPBL*, *FECH* and Complex I-V proteins and quantitative PCR for mtDNA copy number. Lactate was measured in cultured media. Mitochondrial ROS and iron levels were determined by flow cytometry, oxygen consumption rate (OCR) by Seahorse bioanalyzer and ETC activity by spectrophotometry. **RESULTS:** A male patient was born to consanguineous Pakistani parents after a pregnancy complicated by poor growth and oligohydramnios. Symmetric IUGR, dysmorphic features and a VSD were noted. At one year he was evaluated for FTT, lactic acidosis, elevated alanine and abnormal organic acids. WES revealed a novel homozygous mutation, c.649C>T (p.R217*), in *SFXN4*. The patient is currently 4.5 years, has mild delays and persistent lactate elevation. Consistent with a mitochondrial defect, Complex I protein expression and activity and OCR were low, while mtDNA copy number was high. Furthermore, lactate and ROS were increased. Expression of *SFXN4*, as well as the Fe-S cluster proteins FECH and NUBPL were decreased. However, mitochondrial iron levels were not increased in patient's fibroblasts at baseline or after treatment with iron**. CONCLUSION:** We report the 4th patient with an *SFXN4* defect due to a novel c.649C>T (p.R217*) mutation. Clinical presentation was similar to previously described. We demonstrate a clear mitochondrial defect in our patient's fibroblasts. In comparison with previous reports in knockout cell lines, we did not observe elevated mitochondrial iron in our patient, which may be due to a milder defect and/or compensation from other sideroflexin family members. Additionally, our results suggest that *SFXN4* may not be needed for ACO2 synthesis but appears to play an important role in the synthesis of *FECH* and *NUPBL*. Additional studies are underway to further elucidate these findings.

P-100 - A SEVERE CLINICAL CASE OF LEUKOENCEPHALOPATHY WITH THALAMUS AND BRAINSTEM INVOLVEMENT AND HIGH LACTATE (LTBL) DUE TO MUTATIONS IN THE *EARS2* GENE.

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INTRODUCTION: Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) is a rare mitochondrial hereditary disorder caused by biallelic variants in the nuclear *EARS2* gene which encodes mitochondrial glutamyl-tRNA synthetase (GluRS). LTBL has a broad clinical spectrum, ranging from neonatal-onset disease to relatively mild cases with neurological symptoms with spontaneous improvement. Brain Magnetic Resonance Imaging (MRI) distinctive pattern offers a reliable clue for diagnosis. **CASE REPORT:** A 2-year-old female infant, the first child of healthy nonconsanguineous parents, was born at 41 weeks of gestation after an uneventful pregnancy. Neurological regression began at 2 months of age with swallowing impairment, loss of eye contact, bubbling and social smile, with hypotonia and hyperreflexia, followed by lack of psychomotor development, persistent hypotonia, epileptic encephalopathy with treatment-refractory West syndrome, visual impairment, with subsequent stabilization but no clinical improvement. Brain MRI at 4 months of age

revealed extensive symmetrical T2-hyperintensities on the cerebral white matter, thalamus, basal ganglia, brainstem and cerebellum which restricted diffusion sequences. The periventricular rim was spared. The corpus callosum was abnormally thin. Magnetic resonance spectroscopy showed a lactate peak. Analysis revealed elevated levels of serum and cerebrospinal fluid lactate. Whole-exome sequencing identified compound heterozygous *EARS2* missense variants. An MRI at 10 months of age showed persistent lesions with progressive atrophy of the affected structures**. DISCUSSION:** LTBL is an extremely rare mitochondrial disease with leukodystrophy first described just 10 years ago and with very few reported clinical cases in the international scientific literature. LTBL has a broad clinical spectrum, ranging from infantile-onset disease (usually after six months of age) with relatively mild neurological symptoms, followed by spontaneous clinical, biochemical, and radiological improvement, to more severe phenotypes with neonatal/early-infantile onset and rapidly progressive CNS disease that stabilizes but does not improve, with seizures, hypotonia, spastic tetraparesis or dystonia, persistent lactate elevation. The clinical picture correlates well with the severity of neuroimaging. Phenotypes of intermediate severity between the two aforementioned forms have been described. Our report contributes to outlining the clinical, biochemical and neuroimagenological features in a severe clinical case of this extremely rare mitochondrial disease.

P-101 - LEUKOENCEPHALOPATHY WITH BRAIN STEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION (LBSL): NOVEL DARS2 MUTATION AND MITOCHONDRIAL DYSFUNCTION

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BACKGROUND: LBSL is a mitochondrial disorder caused by mutations in the mitochondrial aspartyltRNA synthetase gene *DARS2*. Clinical presentation varies from severe infantile to chronic, slowly progressive neuronal deterioration in adolescents or adults. A distinctive brain MRI shows hyperintensities in periventricular cerebral white matter, brainstem, and spinal cord, and MRS demonstrates increased brain lactate. Most patients are heterozygous, harboring one splice defect in a hotspot in intron-2, resulting in partial expression of the full-length protein. **OBJECTIVES:** We present the clinical and molecular characterization of two patients with a novel *DARS2* mutation and functional studies on patients' fibroblasts. **METHODS:** A skin biopsy was used to establish fibroblast culture. Western blot was performed for *DARS2* protein levels and RT-PCR for mRNA. Lactate was measured in culture media. Mitochondrial ROS was determined by flow cytometry, oxygen consumption rate (OCR) by Seahorse bioanalyzer and mitochondrial morphology by fluorescence microscopy. **RESULTS:** An 8-yearold boy was referred due to headaches and abnormal MRI, suggestive of LBSL. Genetic testing revealed a previously reported c.492+2T>C mutation and a novel c.228-17C>G in the intron-2 hotspot in the proband and well as in his asymptomatic 4-year-old sibling, who was found on a follow-up to have abnormal MRI. Fibroblasts from both patients showed decreased expressions of DARS2 mRNA and protein. RT-PCR results suggested skipping of exon 3 in the father and the two patients. Mitochondrial dysfunction was demonstrated by significantly decreased spare respiratory capacity, as well as elevated lactate and mitochondrial ROS. Fluorescence microscopy demonstrated significantly lower mitochondrial intensity, shorter mitochondrial length and smaller size of mitochondrial network in both patients, indicating fragmented mitochondria**. CONCLUSIONS:** We present a new family affected with LBSL and describe a novel mutation in the *DARS2* intron-2 hotspot. The proband in this family presented only with headaches, despite findings of extensive white matter disease in the brain and spine. Moreover, a younger asymptomatic sibling was ascertained only due to molecular testing, while he also had extensive white matter lesions. Our in-vitro results confirm the expression of the disease in fibroblasts and expand on the nature of mitochondrial dysfunction in LBSL, providing additional metrics for future therapeutic interventions.

P-102 - RECURRENT HYPERAMMONEMIA SECONDARY TO ATP-SYNTHASE (MITOCHONDRIAL COMPLEX V) DEFECT: REPORT OF A CASE

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INTRODUCTION: Hyperammonemias occur due to hepatic disease or due to inherited metabolic diseases, such as urea cycle defects, organic aciduria, fatty acid oxidation defects,

and mitochondrial disease. We present the case of a preschool child with recurrent hyperammonemia due to a defect in the V respiratory chain complex (VRCCD), a very rare cause of hyperammonemia, associated with developmental disorders and dysmorphisms, inherited as an autosomal recessive trait. **CASE REPORT:** Male, 5 years old, non-consanguineous parents. Neonatal period: 36 weeks, low weight (1875 g), facial dysmorphia, low set ears, hypospadias. Evolution with poor weight gain, mild hypotonia and moderate psychomotor development delay (PMDD). First metabolic crisis at 29 months, unidentified cause (infection was ruled out). Ammonium 385 ug/dl (normal ≤ 80), metabolic acidosis (pH 7.2), hyperlactacidemia (77 mg/dl; normal ≤ 22), hyperketosis. Second crisis at 39 months, associated with a respiratory infection. Ammonium 513 ug/dl, mild metabolic acidosis, hyperlactacidemia (44 mg/dl), hyperketosis. In critical samples, the acylcarnitine/amino acid profile in blood and organic acids and orotic acid in urine were normal. Molecular study for inherited hyperammonemias demonstrates mutations in both alleles of the *TMEM70* gene (8q21.11). Nutritional treatment, L-Carnitine and CoenzymeQ10 were indicated. The patient has remained without a metabolic crisis. He presents moderate cognitive delay. **DISCUSSION:** Our case coincides with others reported in the literature in the presence of facial dysmorphia, low set ears, hypospadia, PMDD, and hyperammonemia and hyperlactacidemia crisis. To our knowledge, this is the first case of VRCCD due to *TMEM70 mutation reported in Chile.*

P-103 - GENOMIC FACTORS INVOLVED IN NEURODEVELOPMENT DISORDERS. CASE REPORT.

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INTRODUCTION: Intellectual disability is part of neurodevelopmental disorders, affecting the population between 1 to 3%. The etiology is multifactorial, being genetic factors an important aspect in the alterations of adaptive and intellectual abilities, its heterogeneous presentation makes clinical and genetic diagnosis more difficult, the importance of the study of bioinformatics, a discipline that is part of biology in which technological tools are used that allow us to organize, analyze and distribute biological data, using DNA, RNA, amino acid sequences, proteins, molecular structures, gene interactions and metabolic pathways. ***OBJECTIVES:*** Describe phenotypically and genotypically a patient with a neurodevelopmental disorder. ***MATERIALS AND METHODS:*** 12-year-old male, with neurodevelopmental delay identified since four months, cognitive disability associated with dysmorphic features, L5 spinal dysraphism, dolichocephaly and short stature, with normal metabolic and molecular chromosomal studies. A bioinformatic study was requested to reclassify the significance of gene variants found in clinical exome sequencing. ***RESULTS:*** The clinical exome sequencing NGS methodology reported three variants in the genes, GEN *BCL1B* (heterozygous), GEN *FANCI* (heterozygous), GEN *GHR* EX3 De (homozygous), with a report of uncertain initial clinical significance, with subsequent confirmation of pathogenic variants through bioinformatics study**.** ***DISCUSSION:*** The pathogenic variant in *BCL11B* has been associated with intellectual development disorder, speech delay, dysmorphic facies and abnormalities of T cells (IDDSFTA), the variant in the *FANC1* gene, with pathogenic mutations that cause Fanconi anemia, a disorder characterized by decreased bone marrow function, increased risk of cancer and congenital abnormalities and the variant in the *GHR* gene, associated with Laron syndrome, clinical picture with short stature, obesity, dysmorphic features, despite producing growth hormone, the receptors are defective and prevent cells from responding to the hormone. The pathogenic reclassification of gene variants and the interaction networks between them allows us to establish the phenotype/genotype of the patients, in order to obtain a timely diagnosis, specific and targeted treatment, adequate follow-up, prognosis and genetic counseling.

P-104 - MOLECULAR CHARACTERIZATION OF INBORN ERRORS OF METABOLISM THROUGH TARGETED NGS IN ARGENTINEAN PATIENTS: HIGH DIAGNOSTIC YIELD AND LOCAL VARIANTS RATE.

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INTRODUCTION: Inborn errors of metabolism (IEMs) comprise heterogeneous and rare monogenic disorders with a variety of overlapping or unspecific clinical phenotypes. IEMs are individually rare but collectively common and are significant causes of morbidity and mortality in children. Diagnosis of an IEM is supported by clinical suspicion and biochemical studies and is confirmed by molecular analysis and/or enzymatic analysis. Next-generation sequencing (NGS) is a valuable tool, allowing the analysis of various genes

simultaneously. This minimizes the turnaround time, which is crucial for some IEMs. **OBJECTIVE:** The aim of the study was to evaluate the performance of targeted NGS in confirming the diagnosis of IEMs in a clinical setting. **MATERIALS AND METHODS:** 135 patients with clinical and biochemical suspicion of IEM were analyzed between July 2019 and December 2021 with a custom NGS panel of 87 genes. Bioinformatics tools were applied to detect and prioritize small variants, and to predict copy number variations. **RESULTS:** Global diagnosis rate was 75%, but when dividing patients according to their previous studies, in those with a defined biochemical and clinical suspicion the diagnostic yield was 85%, meanwhile when previous findings were not conclusive, it was 12% ($p < 0.0001$). Diagnostic rates also showed differences related to the nosological group: The best yield was achieved in those patients with Aminoacidopathies (100%) and Organic Acidemias (95%). A total of 122 variants related to the clinical suspicion of the patients in 32 genes were identified: 37% were absent from population and disease-based databases; nevertheless, 78% of them could be classified as pathogenic or probably pathogenic, according to the ACMG consensus criteria. Only 18 variants were identified in more than one patient**. CONCLUSIONS:** This is the first attempt towards a better knowledge of the molecular basis of more than 40 IEMs in our population. NGS technology applied to this cohort of patients evidenced the high allelic heterogeneity and the low representation of local variants in genetic databases. The highest diagnostic yield is achieved when clinical and biochemical characterization allows candidate genes identification. Genetic diagnosis, especially when performed rapidly, can be determinant for the management of IEM patients.

P-105 - NEW PATHOGENIC SYNONYMOUS VARIANT OF THE *PLCG2* GENE RELATED WITH AUTOINFLAMMATION AND *PLCG2*-ASSOCIATED ANTIBODY DEFICIENCY AND IMMUNE DYSREGULATION (APLAID): CASE REPORT

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INTRODUCTION: The growing evidence that part of the synonymous variants has important functional roles in the proteins allows us to conclude that these variants could be directly related to human diseases. Research papers demonstrate that there are more than 400 human diseases associated with synonymous mutations. Pathogenic variants of *PLCG2*, the gene that encodes phospholipase C gamma 2 enzyme, was first reported in 2012. Autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation syndrome (APLAID) is one representative example of *PLCG2* pathogenic variants. APLAID is an autosomal dominant autoinflammatory rare disease characterized by skin, musculoskeletal, ophthalmic and gastrointestinal symptoms. Its diagnosis relies on advanced techniques are required to diagnose them precisely. **OBJECTIVE:** Correlating the clinical phenotype of APLAID with a new synonymous variant with pathogenic significance in the *PLCG2* gene. **METHODS:** Female 42 years old patient with a clinical history of hypersensitivity reactions during childhood, hidradenitis suppurative and asthma. Her only relevant medical family history was her son with osteopetrosis; she had no relatives with immune disorders. As the tests showed no conclusive results, a Massively Parallel Sequencing of the Multigene Immunodeficiency Panel (MPSMIP) was conducted. **RESULTS:** The conducted MPSMIP detected a variant in the *PLCG2* gene, one deoxyribonucleic acid change (c.1854C>G, protein p.Arg618=), with heterozygotic state, followed up by bioinformatics study using diverse prediction software for variants (SIFT, DbDSM, SilVa, Human Splicing Finder and UMD Predictor), obtaining pathogenic clinical significance according to the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. This variant has not been previously reported in databases such as Exac, Clinvar or 1000 genomes, associated with affected patients**. CONCLUSION:** APLAID occurred in the context of the synonymous variant of the *PLCG2* gene, showcasing multiple episodes of immune disorder, hypersensitivity reactions, hidradenitis suppurative and asthma, which coincide with the clinical phenotype of patients with mutations in this gene. Diagnosing this kind of disease by the clinic and basic laboratory is a hard task; hence the importance of omic sciences in searching for pathogenic synonymous variants to make opportune diagnosis approaching patients through precision medicine and genetic counseling.

P-106 - GLUTARIC ACIDURIA TYPE 1 (GA1): CLINICAL HIGHLIGHTS FROM A CASE SERIES

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INTRODUCTION: GA1 is an autosomal recessive aminoacidopathy due to deficiency of the enzyme glutaryl-CoA-dehydrogenase. It presents as acute encephalopathy with severe dystonia and/or seizures or as chronic encephalopathy with psychomotor development delay (PMDD) and hypotonia. It may be preceded by macrocephaly and atrophy of the Sylvian valleys in neuroimaging. **OBJECTIVES:** To report a series of cases highlighting the clinical variability of GA1. **MATERIALS AND METHODS:** A retrospective descriptive study, by reviewing the clinical records of 7 patients. **RESULTS:** Average age of presentation 5.5 months (4-8 months). Clinical presentation: Chronic encephalopathy in 2/7 patients. Acute encephalopathy in 5/7, associated with acute febrile respiratory or digestive infection. 2/5 with focal epileptic seizures. Viral encephalitis was suggested, finally ruled out. 2/5 with mild hyperlactacidemia and mild metabolic acidosis. Brain computed tomography and/or brain magnetic resonance imaging (MRI): 7/7 presented characteristic Sylvian valley atrophy. 4/7 MRI: 4/4 with basal ganglia involvement, 2/4 with white matter involvement. Previous symptoms: 7/7 with mild to moderate PMDD, 6/7 with macrocephaly and hypotonia. Treatment: 5/7 patients had access to an adequate diet with a special formula (without lysine or tryptophan). 7/7 received l-carnitine and riboflavin. 5/7 needed 2 or more drugs for management of dystonia. **EVOLUTION:** follow-up for 16 months to 13 years. 7/7 presented mild to severe tetraparesis and dystonia and/or dyskinesia. 5/7 presented mild to the moderate cognitive deficit. 1/7 presented a drug responder epilepsy. The 2 patients without access to special formula died at 9 and 12 years of age due to repeated metabolic decompensations. Genetic study 4/7 patients; 4/8 alleles with c.337T> C mutation**. CONCLUSIONS:** As previously described, our series shows that AG1 presents as a chronic or acute encephalopathy. This latter is preceded by symptoms that allow an earlier diagnosis (macrocephaly, hypotonia, PMDD). The key diagnosis in our patients was the neuroimaging finding of the characteristic Sylvian valley atrophy (7/7 patients). Access to the correct treatment improves the neurological and vital prognosis of patients. In our series, a common mutation in 4/8 alleles was described. This mutation (c.337T> C) has been previously described in the literature in 3 Chilean patients.

P-107 - CLINICAL, BIOCHEMICAL, MRI AND MOLECULAR FINDINGS OF 8 URUGUAYAN PATIENTS WITH GLUTARIC ACIDURIA TYPE I

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INTRODUCTION: Glutaric aciduria type I (GAI) is caused by an autosomal recessively inherited deficiency of glutaryl-CoA dehydrogenase. Clinically, patients develop a complex movement disorder described as dystonic movement disorder (DMD) often between 3-36 months. Putatively neurotoxic compounds, glutarate and 3-hydroxyglutarate, are increased in urine but in patients with a low-excreter phenotype may be intermittently normal. There are characteristics of MRI changes. Diagnosis is confirmed by the identification of disease-causing mutations. Newborn screening (NBS) using glutarylcarnitine might identify patients, although a low-excreter can show the normal result. Early diagnosis by NBS in combination with metabolic treatment has significantly improved the clinical outcome for asymptomatic newborns. **OBJECTIVE:** To present clinical, biochemical, MRI and molecular findings of our 8 cases with GAI. **CASES REPORT:** Of the total of 8 cases one was diagnosed at 4 years of age because of hypotonia and macrocephaly, one because of encephalopathic crises at age one year; one other because insidiously DMD identified at age 13 years; one showed significant hypotonia and macrocephaly from birth; one has normal psychomotor development up to the present time with one year and eight months and one has no adherence to metabolic treatment and is affected by DMD that appeared insidiously. The latter three patients were diagnosed by NBS. Two cases were not identified by NBS (false negative): one was diagnosed because of encephalopathic crises during febrile illness at 21 months of age (NBS result: C5DC: 0.41 µmol/l, cutoff: 0.46); one patient, started DMD insidiously at age 12 and diagnosis was confirmed at age 14 months, NBS showed slight elevation C5DC (0.38 µmol/L. Cutoff: 0.36) that was normal on repeat. The procedure was changed: an initial elevated C5DC was an immediate referral for confirmatory testing. All 8 cases showed 3-hydroxiglutarate in urine (qualitative organic acids) and molecular assay identified pathogenic variants. **CONCLUSION:** We present clinical, biochemical, MRI findings and genetic mutations of our 8 cases of GAI. Among them, there is a spectrum of clinical presentation, MRI findings, molecular mutations and amount of urinary 3-hydroxiglutarate acid.

P-108 - DESCRIPTION OF THE IMMUNOPHENOTYPE OF PEDIATRIC

PATIENTS WITH PROPIONATE DEFECTS WITH AND WITHOUT METABOLIC DECOMPENSATION

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INTRODUCTION: Repeated infections in propionate defects are common and result in severe metabolic decompensations that increase the risk of mortality. There is limited evidence about the pathophysiology of recurrent infections, and few studies have described the immune system of patients with these pathologies. **OBJECTIVE:** This study aims to describe the immunophenotype of patients with propionate defects, metabolically stable and in metabolic decompensation. Methods and materials: An observational, descriptive, and transversal study was conducted. A 5 ml blood sample and dried blood spots were taken. Absolute count of lymphocytes, immunoglobulins levels, amino acids, acylcarnitines, ammonium, blood gases and nutritional status markers were determined. An anthropometric evaluation was carried out since the nutritional status affects the immune system. Descriptive statistics were used. **RESULTS:** Five patients were included in the study; two with methylmalonic acidemia and three with propionic acidemia. The average age was 43.6 months (3-132 months). 2/5 were metabolic decompensated, evidenced by high ammonium levels and metabolic acidosis. Elevation of propionylcarnitine (C3) was found in 4/5 patients, the highest level was presented by a decompensated patient. The amino acid profile showed that 2/5 had elevated glycine despite being stables; low valine levels were observed in the same two patients and one of them also presented a deficiency of isoleucine and leucine. Deficiency of IgG was found in 3/5 patients, two metabolically stable and one decompensated who also presented low levels of IgA. The absolute counts of CD4 + and CD3 + were low in 2/5 patients, 3/5 had absolute low levels of CD19, and 1/5 had low levels of CD8+, all these patients were metabolically stable. 4/5 patients had a normal BMI Z-score, 1/4 was underweight (BMI Z-score -1.17). All subjects had normal levels of prealbumin, transferrin and folates; vitamin D insufficiency was observed in 3/5 patients, and 1/5 had anemia. **CONCLUSIONS:** Immunodeficiency is frequent in patients with propionate defects regardless of their metabolic and clinical status. Thus, immunophenotype determination is recommended in this population. Further studies are required.

P-109 - PROPIONIC ACIDEMIA. THE EXPERIENCE OF THE MEDICAL PRACTICE IN ONE PATIENT IN MEXICO

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INTRODUCTION: Propionic acidemia is caused by the deficiency of propionyl-CoA carboxylase, producing an alteration in the catabolism of amino acids; the common symptoms are: neurological, liver, and metabolic diseases with fatal outcomes. Biochemical alterations include metabolic acidosis with ketosis, hyperammonemia, and hypoglycemia. **OBJECTIVE:** Describes the management of this patient in our institution. **MATERIAL AND METHODS:** A case report results, Female 14 years old, the patient had a normal delivery, at 11 days old, she was admitted to NICU with a diagnosis of sepsis, the diagnosis confirmed at 3 months old. She had mental retardation and multiple periods of respiratory infections that caused metabolic acidosis with hyperammonemia encephalopathy, she has maintained a basic treatment with levocarnitine, sodium benzoate, and biotin, however, since January 2019, the persistence of accumulations of free radicals, caused greater damage at the neurologic level, with progressive encephalopathy, enzyme Q10 was indicated as a detoxifier of oxidative cellular metabolism, and the sodium benzoate prescription was withdrawn, management begins with carglumic acid at 50mg/kg/day with good evolution and the encephalopathy has decreased. During the medical follow-up, the patient acquired a viral upper respiratory infection with mental alteration, refractory lactic acidosis (20 mmol/L), she did not respond to slow continuous renal replacement therapy and died on January 26th, 2020**.** **DISCUSSION:** Propionic acidemia, although rare, is one of the most frequent metabolic errors, 1/100,000 live births. The pathophysiological mechanism of the acute metabolic crisis leads to hyperammonemia, like our patient. The most frequent early neonatal form begins with vomiting, hepatomegaly, thrombocytopenia, and lethargy, in the case of our patient, she had a diagnosis of sepsis, and maybe she could have been in this form. The treatment consists adequate supply of calories to avoid catabolism and protein restriction, and a supplement of carnitine and biotin, we had to administer a new drug for the treatment of hyperammonemia, carglumic acid in addition to

the enzyme Q10 for the accumulation of free radicals, with good evolution for a couple of months, but the chronic accumulation of toxic metabolites, developed a refractory lactic acidosis with fatal consequences.

P-110 - COMBINED METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA IN ARGENTINEAN PATIENTS. FROM ACQUIRED DEFICIENCIES TO INBORN ERRORS OF METABOLISM: CLINICAL PRESENTATION, BIOCHEMICAL DIAGNOSIS AND MANAGEMENT.

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INTRODUCTION: Combined methylmalonic aciduria and homocystinuria (MMA/HCY) is an inborn error of metabolism of cobalamin that is characterized by variable phenotypes including intellectual disability, hematologic, neurologic, metabolic, ophthalmologic, and dermatologic clinical findings may also occur. Although considered a disease of infancy or childhood, some individuals develop symptoms in adulthood. It's a rare autosomal recessive disease in which there are several variants depending on the pathogenesis of the metabolic disorder (cblC, cblD, cblF and cblJ). The more frequent and severe is the cblC variant, caused by mutations in the *MMACHC* gene. In addition to the primary forms, there are acquired forms due to nutritional deficiencies. Infants from mothers with severe cobalamin deficiency during pregnancy and breastfeeding are at high risk of cobalamin deficiency. Early diagnosis and treatment can alter the course and outcome. **OBJECTIVE:** To describe clinically, biochemically and molecularly, patients with MMA/HCY, either of the acquired origin or due to an inborn error of cobalamin metabolism. **MATERIAL/METHODS:** Twenty-six patients with MMA/HCY were compared according to disease onset, age at diagnosis, main/initial clinical manifestations, biochemical and molecular findings, treatment, and outcome. For this retrospective study, we collected data from the medical records of the patients studied in our Center between the years 2005-2021. Urinary organic acids were determined by GC and total plasma homocysteine levels by HPLC in all patients. In most cases, plasma amino acids, serum levels of vitamin B12 and acylcarnitines in DBS were also determined. Molecular studies were performed on the *MMACHC* gene in five patients. **RESULTS:** The mean age of onset of symptoms was 1.23 years (range 0.01-16). Neurological manifestations predominated as presenting symptoms in 61% (16/26) of the subjects, followed by hematological symptoms 54% (14/26) and feeding difficulties 46% (12/26). Regarding clinical outcomes, 88% (23/26) of the patients reverted the symptoms with the specific therapy. The molecular study of the *MMACHC* gene allowed to identify 4 unrelated patients with the c.271dupA variant (3 with hypotonia and difficulty feeding, 2 with neurological and hematological manifestations). **CONCLUSION:** Early diagnosis and treatment in patients with MMA/HCY, even when caused by cofactor deficiency, can favor the neurological and functional prognosis.

P-111 - METHYLMALONIC ACIDEMIA AND HOMOCYSTINURIA CBLC TYPE: FIRST CASE OF EPICBLC IN LATIN AMERICA?

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INTRODUCTION: Methylmalonic acidemia and homocystinuria cobalamin C type (CblC disease) is the most common inborn error of cobalamin metabolism, is characterized by elevated methylmalonic acid and homocysteine and is associated with high mortality rates and multisystem involvement, especially in the early-onset form. The clinical course and response to treatment are variable, leaving sequelae, especially in those who receive late or inadequate treatment. CblC is generally caused by bi-allelic *MMACHC* genetics variants. Recently, compound heterozygous patients with a pathogenic variant in *MMACHC* and another in the *PRDX1* have been reported, which is considered an epimutation, since it leads to a hypermethylated sequence that encompasses the promoter and first exon of the *MMACHC*. This disorder has been named epi-CblC. **OBJECTIVE:** The aim is to report *PRDX1*: c.*2C>T variant as a probable cause of epi-CblC. **METHOD:** A clinical and biochemical diagnosis of cblC disease was made and the molecular diagnosis was by whole-exome sequencing (WES). **CASE REPORT:** We report a male patient, born to non-consanguineous parents, normal second pregnancy with adequate weight and height, presented with jaundice during the

first month of life, his development was normal until 3.5 months and then regressed. He was referred for evaluation at 5 months of age, on examination, he was lethargic, with microcephaly, was hospitalized, had persistent metabolic acidosis, and was treated for sepsis. He remained hospitalized for 5 months, had hospital-acquired pneumonia, COVID, required mechanical ventilation, tracheostomy, optic nerve compromise, and multiple thrombotic events that deteriorate him. Increased methylmalonic acid in urine and homocysteine in blood were detected. Currently, receives vitamin B12, Betaine anhydrous, L-carnitine, pyridoxine, enoxaparin, multivitamins and a diet with 1gm/kg of protein. Methylmalonic acid and homocysteine have decreased markedly. The patient has sequelae but has improved significantly, establishes contact with his environment and makes sounds and swallows food. **RESULTS:** WES identified a heterozygous pathogenic variant in the *MMACHC*: c.394C>T and a heterozygous variant of uncertain significance in the *PRDX1*: c.*2C>T gene**. CONCLUSIONS:** cblC is a serious condition, its timely diagnosis and treatment seem encouraging for these patients. Probably, several *PRDX1* mutations cause epimutations in *MMACHC*. Diagnostic molecular panels for this condition should include the *PRDX1*.

P-112 - COMBINED METHYLMALONIC ACIDEMIA AND HOMOCYSTINURIA CBLC TYPE: A PERUVIAN SERIE

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INTRODUCTION: Methylmalonic acidemia (MMA) and homocystinuria cobalamin C type(cblC) is the most frequent inborn error of intracellular cobalamin metabolism, is characterized by elevated methylmalonic acid and homocysteine and multisystem involvement with high mortality rates. **OBJECTIVE:** To present the genotypes and phenotypes found in our patients with cblC. **METHOD:** We review the medical records, clinical/biochemical characteristics and results of molecular tests. **RESULTS:** All patients are male and all have different genotypes. Case 1: Male patient, third pregnancy, non-consanguineous parents; suitable height and weight. Two sisters died at 3 and 20 months; one with pancytopenia and sepsis and the other with an unknown rare disease? He has a developmental delay, he was prostrate, hypotonic, weak, and lethargic. He came with a clinical diagnosis of MMA with homocystinuria, he was admitted with homocysteine> 150mcmol/L; thrombosis in the lower left limb was found and cerebral and cerebellar atrophy in MRI was also found. Enoxaparin and betaine were added to the treatment. He has not been hospitalized again. Two pathogenic variants were found in *MMACHC*: c.658_660delAAG(p.Lys220del) and c.394C>T(p.Arg132Ter). Case 2: A 7.5-year-old male who was hospitalized, has abdominal pain, vomiting followed by extreme tiredness and severe drowsiness. From 1 year of age, he had developmental delay and later regression, involuntary movements, megaloblastic anemia, neutropenia and significant eosinophilia (up to 48%). He had two episodes of metabolic decompensation and encephalopathy. He currently receives Betaine, injectable hydroxocobalamin, Lcarnitine, anticonvulsants, etc. Two pathogenic variants, c.271dup(p.Arg91Lysfs*14) and c.394C>T(p.Arg132*), were identified in *MMACHC*. Case 3: Male patient, born of a second pregnancy, nonconsanguineous parents, normal weight and height. His development was normal until 3.5 months and then regressed. He was hospitalized at 5 months of age, lethargic, with microcephaly, had persistent metabolic acidosis and was treated for sepsis, presented hospital-acquired pneumonia, COVID, and multiple thrombotic events, required mechanical ventilation and tracheostomy, currently with optic nerve compromise. Increased urine methylmalonic acid and blood homocysteine were detected. He receives Hydroxocobalamin, Betaine anhydrous, L-carnitine, pyridoxine, enoxaparin, multivitamins. The patient has sequelae but has improved significantly. Pathogenic variant and epimutation identified in *MMACHC: MMACH*: c.394C>T(p.Arg132*) and *PRDX1*: c.*2C>T(p.?). **CONCLUSIONS:** All patients have the variant *MMACHC*: c.394C>T(p.Arg132*). They have a similar clinical presentation

P-113 - TWO CASES OF COBALAMIN C DEFICIENCY WERE DETECTED BY NEWBORN SCREENING IN URUGUAY.

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INTRODUCTION: Newborn screening (NBS) for the cobalamin C (CblC) defect should be considered since survival and prevention of severe complications such as hemolytic uraemic syndrome, hydrocephalus and hematological

abnormalities in early-onset patients can be prevented by early treatment. The impact of early treatment on neurocognitive development is unclear and has little influence on eye disease. The cblC defect is screened by measuring propionylcarnitine (C3), and ratio with acetylcarnitine (C3/C2), combined with the second tier markers: methylmalonic acid (MMA) and homocysteinemia (Hct). The cblC defect is caused by mutations in the *MMACHC* gene. In Uruguay NBS for CblC defect is part of a pilot program. **OBJECTIVE:** To present two cases of Cbl C deficiency detected by NBS in Uruguay. **CASES REPORT:** Case 1: 9 years of age male, a product of G3P3 of a nonconsanguineous healthy couple. Normal pregnancy and delivery. NBS sample collected at 40 hours of life, demonstrated: C3: 13 umol/L (N <5,7), C3/C2: 0,42 (N <0.26). Urine MMA result: 591 umol/mmol of creatinine (N <6) Hct: 89 umol/L (N 3,3-8,3) Normal plasma B12 vitamin and folic acid. Sequencing of *MMACHC*, evidenced two pathogenic variants: c.271dupA/c.565C>A. Therapy was initiated with parenteral hydroxycobalamin (1 mg IM a week) and biochemical parameters improved. He developed hypotonia and global developmental delay with greater impairment in language skills. Case 2: 6 months of age female patient product of G2P2. Pregnancy is complicated with gestational diabetes. Normal delivery at term. Excessive sleepiness, lethargy, hypotonia and feeding difficulties were noticed from birth. NBS sample collected at 40 hours of life, demonstrated: C3: 9,1 umol/l (N <5,7), C3/C2: 0,42 (N <0.26). Urine MMA: 1987 umol/mmol (N <6). Hct: 110 umol/L (N<11). Normal plasma B12 vitamin and folic acid. Therapy was started with parenteral hydroxycobalamin (1 mg IM a week) and there was clinical improvement as well as the biochemical parameters. Sequencing of *MMACHC* demonstrated: c.271dupA/c.271dupA. Visual impairment was observed. **CONCLUSION:** NBS for the CblC defect should be considered since by early treatment survival improve and severe complications can be prevented. The impact of early therapy on neurocognitive development and on eye disease is unclear yet.

P-114 - MOLECULAR AND BIOCHEMICAL CHARACTERISTICS IN MEXICAN PATIENTS WITH INHERITED COBALAMIN C DISORDER

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INTRODUCTION: Cobalamin (cbl) is an essential molecule for human metabolism since it is a cofactor of methylmalonyl-CoA mutase and methionine synthase enzymes. Of the nine genetic disorders of cobalamin described to date, cobalamin C disorder (Cbl C) is the most common. A biochemical profile with the elevation of propionylcarnitine (C3) and methylmalonic aciduria combined with homocystinuria is characteristic of cblC. Pathogenic variants in *MMACHC* gene are causative of cbl C deficiency. Genotypification allows adequate and specific therapy. In Mexico, the pathogenic variants of cblC patients are poorly studied. **OBJECTIVE:** To describe the molecular spectrum of patients with cbl C disorder and their biochemical characteristics. **MATERIALS AND METHODS:** Retrospective study of cblC patients. The genotype and biochemical characteristics at the time of diagnosis were analyzed. A multivariate analysis of metabolic profiles of cbl C patients was performed. RESULTS. Five cblC patients were included in the study. The mutational spectrum showed four different variants, three missense and one frameshift duplication. The most frequent variant was c.(271DupA) or p.(Arg91KfsX14), identified in 5/10 alleles, followed by c.(482G>A) or p.(Arg161Gln) and c.(578T>C) or p.(Leu193Pro) both found in 2/10 alleles. Five different genotypes were found. The mean diagnostic values of characteristic biomarkers were 10.3 μM for C3, 1.1 for C3/C2 ratio, 6.02 for C3/C16 ratio and 61.7 μM for homocysteine. Multivariate analysis of subsequent follow-up metabolic profiles showed a marked elevation of long-chain acylcarnitines in patients compared with controls, despite the patients were under adequate metabolic control, eutrophic, and with no dietary protein restriction. **CONCLUSIONS:** The molecular spectrum of Mexican cblC patients is heterogeneous, with a predominance of c.(271DupA) or p.(Arg91KfsX14) variant. The elevation of long-chain acylcarnitines in these patients could be due to a preference for fatty acid utilization as an energy source, further studies are required to elucidate this hypothesis.

P-115 - DIFFICULT DIAGNOSTIC METABOLIC ACIDURIA: CASE OF NOVEL MUTATION IDENTIFIED IN 3-METHYLGLUTACONIC ACIDURIA TYPE VII

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INTRODUCTION: 3-methylglutaconic aciduria type 7 or CLPB deficiency (MGA7), this rare autosomal recessive disease is caused by mutations in the *CLPB* gene and is characterized by increased urinary excretion of 3-methylglutaconic acid, variably associated with neutropenia (sometimes causing recurrent severe infections and potentially resulting in leukemia) and progressive neurologic manifestations, such as global developmental delay, intellectual disability, hypotonia, movement disorder, and seizures. **OBJECTIVE:** Report a new variant related to the disease. **METHODS:** The patient was evaluated for the global developmental delay associated with immunodeficiency and microcephaly at a pediatric hospital in Lima, Peru. Molecular diagnosis was made by clinical sequencing of the immunodeficiency panel through an international program to assist in the genetic diagnosis of primary immunodeficiencies. **RESULTS:** A 2-year-old girl, a product of the first pregnancy without complications, at term, but small for gestational age. Non-consanguineous parents. Weak suction from birth, being hospitalized at 20 days due to dehydration and jaundice with a diagnosis of hypotonia. She was referred to our hospital for congenital cataracts in addition to developmental delay at 4 months. Evaluations found microcephaly, hypotonia with severe developmental delay, as well as growth retardation with short stature, cortical cataract, cystic dysplasia of the right kidney, congenital neutropenia, and hypoplasia of the cerebellar vermis by brain MRI. Progressively, it presents specific disorders that affect the mechanism of immunity, not classified, which is why it enters the International program to help diagnose primary immunodeficiencies. The primary immunodeficiency panel reveals a probable pathogenic *CLPB* c.803C>T(p.Thr268Met) and c.1700A>C(p.Tyr567Ser) compound heterozygous variant of uncertain significance. In the case of MGA7, no dietary treatment or other specific metabolic treatment is available, but carnitine is being administered, which is an indication for other types of methylglutaconic aciduria, with erratic results and no clinical improvement. **CONCLUSIONS:** In all patients with developmental compromise and even more so if they come with additional systemic compromise, inborn errors of metabolism (IEM) should be evaluated.

P-116 - 2-METHYL-3-HYDROXYBUTYRYL-COA DEHYDROGENASE (MHBD) DEFICIENCY: TWO NEW CASES

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INTRODUCTION: MHBD deficiency is a recently described X-linked recessive defect of the isoleucine pathway. This enzyme catalyzes the conversion of 2-methyl-3-hydroxybutyryl-CoA to 2-methylacetoacetyl-CoA. It is characterized by an early-onset neurodegenerative course. **OBJECTIVES:** Only a few cases have been reported, we now present two new cases, one of them without neurodegenerative involvement. **MATERIALS AND METHODS:** Information was obtained from the clinical follow-up registry. **RESULTS:** We report two Chilean patients with different phenotypes. Both children of non-consanguineous parents, born at the term of normal pregnancies and without perinatal pathology. The first patient was previously healthy, at 7 months of age and after 8 days of mild respiratory infection associated with poor feeding, presented encephalopathy, severe metabolic acidosis with a high anion gap, normal ammonia and mild hyperlactacidemia. The second patient had a developmental delay from the first month of life, at 9 months he started West syndrome and neurological regression. Both have plasma tiglylcarnitine elevated and low free carnitine. Urine organic acid showed markedly elevated excretion of 2-methyl-3-hydroxybutyric acid and tiglylglycine, 2-Methyl acetoacetate was not detected. This profile was consistent with MHBD, which was confirmed by enzymatic activity in fibroblasts and molecular study. The first patient is currently 7 years old, without new serious episodes, without neurological compromise. On the other hand, the second patient has evolved with a severe neurodegenerative phenotype**. CONCLUSION:** MHBD deficiency is a recently described defect with few known cases. These two new patients contribute to the knowledge of the natural history of the disease.

P-117 - DETECTION OF ORGANIC ACIDURIAS AND OTHER HEREDITARY METABOLIC DISEASES BY URINARY ORGANIC ACID ANALYSIS IN A 13-YEAR PERIOD IN BRAZIL

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INTRODUCTION: Gas chromatography/ mass spectrometry (GC/MS) of urine samples is the method of choice in the diagnosis and follow-up of Organic acidurias/ acidemias (OA) that form a heterogeneous group of hereditary metabolic diseases (HMD) that involve metabolic pathways related to the degradation of amino acids, carbohydrates and fatty acids.

OBJECTIVE: To describe the OA, aminoacidopathies (AA), urea cycle disorders (UCD), and fatty acid beta-oxidation defects detected by the analysis of urinary organic acids in a Brazilian private reference laboratory for HMD. **MATERIAL AND METHODS:** A cross-sectional study was performed. Urine samples were obtained over a thirteen-year period from patients with a clinical suspicion of HMD. The results of the exams were classified as "profiles of HMD", "undetermined results", "nonspecific profiles" and "negative results". Among the profiles of HMD, the OA, AA, UCD, and fatty acid beta-oxidation defects were described. The analysis consisted of frequency distribution. **RESULTS:** Of the 14,652 urine specimens analyzed, 21.3% presented profiles of HMD and 5.8% were classified as OA, AA, UCD and fatty acid beta-oxidation defects which corresponded to 374 patients. Undetermined results that would have to be characterized by other methodologies were 5.8% of the sample and 9.6% presented nonspecific profiles. Characteristic profiles of 36 different HMD were revealed from 374 patients. OA, AA and fatty acid beta-oxidation disorders were predominant. Methylmalonic aciduria (56/374; 14.97%), glutaric aciduria type 1 (50/374; 13.36%), maple syrup urine disease (39/374; 10.42%), undefined urea cycle disorders (37/374; 9.89%) and propionic acidemia (23/374; 6.14%) were the most frequent**. CONCLUSIONS:** The high prevalence of methylmalonic acidemia is in agreement with other studies. Also, In Brazil, glutaric aciduria type 1 seems to have a high prevalence, according to other Brazilian studies, excluding lactic academia that was not considered in the present study as a specific HMD profile; lactic aciduria may be due to secondary causes. The analysis of urinary organic acids, especially when combined with the analysis of acylcarnitines is very useful in the diagnostic evaluation of patients with a clinical suspicion of an HMD and the interaction between the clinician and the laboratory is fundamental.

P-118 - DIFFERENCES BETWEEN URINARY ORGANIC ACIDS OF PATIENTS TREATED WITH LDOPA VERSUS PATIENTS WITH AROMATIC AMINO ACID DECARBOXYLASE DEFICIENCY.

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INTRODUCTION: Aromatic L-aminoacid decarboxylase (AADC) deficiency is a primary neurotransmitter defect of the biosynthesis of catecholamines and serotonin which leads to some key clinical symptoms: hypotonia, movement disorders and autonomic symptoms. Onset typically occurs after birth, but milder presentations have been described. **AIM:** Analyze the differences between the organic acid profile of patients confirmed with AADC deficiency and patients in treatment with L-dopa. **MATERIALS AND METHODS:** Retrospective medical records of two patients with AADC deficiency and two patients treated with L-dopa in whom AADC deficiency was ruled out were analyzed. Urine organic acids (UOA) were measured by GC-MS and vanillactic / vanilmandelic (VLA/VMA) acids ratio was calculated. AADC activity was measured in plasma by HPLC- Electrochemistry and 3-OMD by tandem mass spectrometry. Molecular tests were performed by NGS-Ilumnin and qPCR. **RESULTS:** Patients(n=2) with pathogenic variants in the *DDC* gene presented the characteristic biochemical profile of AADC deficiency: high VLA and vainilpiruvic acids in UOA with elevated VLA/VMA ratio, elevated 3-OMD and decreased enzyme activity. Patients (n=2) treated with L-Dopa presented elevated excretion of VLA, vainilpiruvic, homovainillic (HVA) and 3-4-di-hydroxy-phenylacetic acids in UOA with elevated VLA/VMA ratio and elevated 3-OMD. No pathogenic variants were found in molecular tests. **DISCUSSION AND CONCLUSIONS:** The international guidelines consider the quantification of 3-OMD and UOA analysis as complementary studies in the diagnosis of AADC deficiency. Since AADC deficiency presents with movement disorders, some patients suspected of this disorder, have L-dopa as treatment. In these cases, UOA analyses and 3-OMD can suggest an AADC deficiency. At present, the only way to differentiate this situation will be with molecular studies. UOA could help differentiate patients treated with L-dopa and patients with AADC deficiency. Patients treated with L-dopa, unlike patients with AADC deficiency, excrete a large amount of HVA and 3-4-di-hydroxy-phenylacetic acids in UOA.

P-119 - PREVALENCE ESTIMATION OF PRIMARY CONGENITAL HYPOTHYROIDISM OF A NEWBORN SCREENING PROGRAM IMPLEMENTED IN MEXICO, DATA FROM 2005-2020

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INTRODUCTION: Congenital hypothyroidism (CH) is a condition that involves low thyroid hormone production. Patients are usually asymptomatic at birth; however, they may present altered physical and mental development if not properly treated. Despite its high reported frequency in Mexico (2.50 – 3.33 per 10,000 newborns), the fragmented healthcare system and its inefficient operational practice challenge data reliability. **OBJECTIVE:** To estimate the prevalence of primary CH of a Newborn Screening (NBS) program with a non-probabilistic sample from a population across Mexico for the past 16 years. **MATERIALS AND METHODS:** From January 2005 to December 2020, we analyzed 268,950 NBS reports. The DBS were processed at PerkinElmer Genomics to detect primary CH through TSH levels in blood. The laboratory cutoff values for screening were < 28.5mU/ml and < 15.0mU/ml for newborns with ages less and older than 7 days, respectively. For those presumptive positive cases, thyroid function test was performed. We assessed the prevalence of primary CH in this program regionally and nationwide. Furthermore, the TSH cutoffs were evaluated through a ROC curve analysis. **RESULTS:** The study showed an overall primary CH prevalence of 5.32 per 10,000 newborns (143 confirmed cases) for the program performed throughout the country; presenting the southeast region (9.54) with the highest prevalence and the west with the lowest (3.71). The prevalence in males and females was 3.86 and 7.28 (ratio of 1: 1.88). Finally, the ROC curve indicated that this protocol had 100% of sensitivity and a specificity-associated of 98.23%. The area under the curve (AUC) was 0.9995 (P-value=7.67e-08)**. CONCLUSION:** This study indicates that the overall prevalence is almost two times higher in relation to worldwide reports; however, the prevalence in some regions was found to be similar to those reported in the literature. To the authors' knowledge, there were no false negatives for primary CH in this program during this period. The difference of prevalence that most NBS programs presents in different countries might be due to ethnicity, sex, number of patients, and birth outcomes.

P-120 - PREVALENCE OF CONGENITAL HYPOTHYROIDISM IN NEWBORNS IN THE STATE OF YUCATÁN, MÉXICO.

Sauri-Vivas M [1], Hernández-Fuentes CI [2], Ademar-Zaldívar J [3], Centeno-Navarrete YA [4], Maldonado-Solís FA [5], Moreno-Graciano CM [5], Herrera-Pérez LA [5], Quintero-Rodríguez GI [5], Canche-Bacab LF [5], Burgos-Lizama JY [5]

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INTRODUCTION: Congenital hypothyroidism (CH) is a condition resulting from an absent or underdeveloped thyroid gland, or a disfunction in the thyroid hormones. No evident signs or symptoms are present at birth. The neurological prognosis depends on timely initiation of appropriate treatment. Therein lies the importance of early detection of CH through neonatal screening. CH prevalence in Mexico has been estimated in 7.3 per 10,000 newborns (NBs) (1: 1,373). **OBJECTIVE:** To determine the CH birth prevalence in the state of Yucatan, Mexico through a comprehensive neonatal screening program. **MATERIALS AND METHODS:** Between December 2008 to October 2021, 211,683 NBs were screened in the medical units belonging to the Ministry of Health of the State of Yucatan, Mexico. Five drops of blood were collected on Guthrie cards. Thyroid stimulating hormone (TSH) was quantified by time-resolved fluoroimmunoassay. All samples with TSH above 10 µIU/L were considered suspicious, which required immediate localization of the newborn and confirmatory tests; the final diagnosis was made by pediatric endocrinologists from the public hospital. CH birth prevalence was calculated as the number of confirmed cases per 10,000 screened newborns, in that period. **RESULTS:** 412 suspicious cases were detected, 218 were false positives and 194 were confirmed cases, of which there were a predominance of women (123 female/71 male). The prevalence rate found was 9.16 per 10,000 NBs (1: 1,091) with 96 % coverage. The mean age of initiation of treatment was 20.2 days**. CONCLUSIONS:** The prevalence of CH in Yucatan, Mexico is higher than that previously reported at the national level. The high prevalence found may be due to the fact that the neonatal screening strategy has substantially improved for the detection of the disease, as well as due to genetic, immunological and environmental factors. This study does not exclude transient CH cases, something that undoubtedly positively influences the high prevalence observed.

P-121 - PREVALENCE OF HYPERTHYROTROPINEMIA IN NEWBORNS IN THE STATE OF YUCATAN, MEXICO.

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INTRODUCTION: Hyperthyrotropinemia (HTT) is usually defined as an abnormal elevation of the thyroid stimulating hormone (TSH) with normal thyroxine (T4) and triiodothyronine (T3) levels. Early diagnosis and follow-up is necessary to prevent possible complications. Before newborn screening era, most HTT cases remained unidentified due to inapparent clinical course. **OBJECTIVE:** To report HTT prevalence in screened newborns (NBs) of the comprehensive expanded neonatal screening program (PITNA) in Yucatan, Mexico. **METHODS:** 211,683 NBs samples obtained by heel prick between December 2008 and October 2021 in PITNA were studied. NBS TSH was measured by time-resolved fluoroimmunoassay and serum TSH by electrochemiluminescence immunoassay (ECLIA) method. All TSH >10.0 uU/ml were considered suspicious for congenital hypothyroidism (CH) and required immediate localization for serum TSH, FT4, and FT3 determination. HTT diagnosis was established if serum TSH was between 5.0-10.0 uUI/ml with normal FT4 (cutoff: 0.8-2.2 ng/dl) and FT3 (cutoff: 1.9-6.0 pg/ml). Prevalence is indicated per 10,000 NB. All confirmed cases were evaluated by pediatric endocrinology in order to determine treatment and follow-up. **RESULTS:** 194 CH suspicious cases were detected, and 37 of them were classified as HTT, with female predominance (22 female/15 male). The HTT prevalence was 1.75 per 10,000 NBs. Mean age for HTT diagnosis was 19 days. Mean serum TSH in HTT was 7.5 uUI/ml, FT4 1.51 ng/dl, and FT3 3.68 ng/dl**. DISCUSSION:** The prevalence of HTT in Yucatan is higher than the reported for other states in Mexico. An adequate diagnosis strategy must be applied in order to get an early HTT diagnosis. Further studies must be performed to determine the main factors associated with HTT in Yucatan, Mexico. Levothyroxine treatment must be considered in cases with persistent high TSH levels, always assessed by pediatric endocrinologist.

P-122 - CENTRALIZED NEONATAL SCREENING PROGRAM FOR CONGENITAL HYPOTHYROIDISM OF THE BOGOTÁ DEPARTMENT OF HEALTH: PERFORMANCE AND CASES CHARACTERIZATION

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INTRODUCTION: Congenital hypothyroidism (CH) is considered a form of preventable and treatable cognitive disability, for which early diagnosis and treatment are considered a medical emergency. CH neonatal screening program was established in Colombia since 2000. **OBJECTIVE:** Evaluate the performance of the centralized neonatal screening program for CH of the Bogotá Department of Health and characterize the presumptive and confirmed cases of CH. **MATERIALS AND METHODS:** A retrospective descriptive observational study was designed. Newborns from 32 health centers from June 2005 to May 2021 were included. Compliance with health indicators in accordance with the Colombian neonatal screening program guidelines was determined. The prevalence of CH in the population was calculated. In addition, the presumptive and confirmed cases of CH were characterized. **RESULTS:** 406,053 newborns were included into the program. Sample collection was made from umbilical cord immediately after the delivery and by heel puncture between 48-72 hours in 98% of newborns. In 92% or more newborns, the results were available in the first week of life. However, the diagnostic confirmation was performed to 63% of newborn in the next week after the screening results were available, and the treatment was initiated in the first month of life in 59% of the 66 newborns with information regarding treatment. More than 98% of samples met the quality conditions. 638 presumptive cases (0.16%) and 83 confirmed cases (prevalence 1: 4892) were identified. 94% of presumptive and 99% of confirmed cases were term newborns and they had an adequate birth weight in 75% and 82% for each group, respectively ($p<0.005$). CH was confirmed in 1.7 girls per 1 boy. 75% of children with confirmed CH had serum TSH levels between 97.8 - 422.5 mIU/L, with normal or low FT4 levels (between 0.33 - 1.03 ng/dl)**. CONCLUSIONS:** The screening program has a good performance and complies with the sample collection and screening results indicators. The delay in CH confirmation was related to difficulties in recalling positive patients and to the lack of assistance to the confirmation sample collection. There are failures in the follow up and in treatment registration of the confirmed cases which explain the low indicator obtained.

P-124 - EVALUATION OF IODINE NUTRITIONAL STATUS IN PREGNANT WOMEN AND THEIR NEWBORNS WITHIN NEONATAL SCREENING PROGRAM FOR CONGENITAL HYPOTHYROIDISM IN NICARAGUA

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INTRODUCTION: The importance of iodine nutritional deficiency lies in the fact that this halogen participates in the structure of thyroid hormones. Iodine deficiency (ID) is important during pregnancy, where the foetus can suffer irreversible changes due to both, low supply of iodine and thyroid hormone (thyroxine) from the mother has been targeted as a major cause of intellectual impairment. **OBJECTIVE:** Assess the nutritional status of iodine in a selected population of Nicaragua: pregnant women and their newborns, by means of different biochemical techniques: measurement of urinary iodine excretion (UIE) as well thyrotropin (TSH) and thyroglobulin (Tg) in serum from cord blood (CB), and the iodine content of commercial salt. **MATERIAL AND METHODS:** Pregnant women and their newborns were recruited in a public hospital. Newborns´ CB data belong to the population screened for congenital hypothyroidism (CH) in ten departments of Nicaragua. The iodine concentration was measured in urine samples of 419 pregnant women, 201 newborns were studied for serum of CB TSH and Tg concentrations in 2015. TSH in CB collected on filter paper was evaluated in 272,338 newborns in 2005-2015, using a cutoff level of 20 mUI/L. Iodine content was measured in 11 samples of salts. **RESULTS:** The median (interquartile range) UIE in pregnant women was 60 µg/l (116.5), iodine levels were < 150 µg/l, defined as insufficient according to the WHO criteria. 16% of newborns had increased TSH values (Reference values (RV) < 10 mUI/L), while Tg (RV< 54 ng/ml) was increased in 71 %. A statistically significant correlation was found between the UIE of the mothers and the TSH of the neonates ($p< 0.05$). 80 neonates were identified with CH, with a prevalence of 1: 3400 and17% of false positives. 45% of salt samples had iodine content below the recommended by WHO (20-40 mg/Kg)**. CONCLUSIONS:** Both the low UIE in pregnant women and the number of newborns with elevated levels of TSH and Tg are indicative of the existence of iodine nutritional deficiency. An association was verified between iodine deficiency in pregnant women and the thyroid function of their newborns that may be influencing the phenotype of Nicaraguan children with CH.

P-125 - EPIDEMIOLOGICAL PROFILE, CLINICAL AND BIOCHEMICAL ASPECTS IN PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA AT THE DR. AGUSTÍN O´HORÁN GENERAL HOSPITAL

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CONTEXT: Congenital adrenal hyperplasia (CAH) is a rare genetic disease with autosomal recessive inheritance. It has a worldwide prevalence of 1 in 10,000 and 1 in 4,543 live births in Yucatán, México. CAH occurs due to accumulation of 17-hydroxyprogesterone (17-OHP) caused by 21-hydroxylase deficiency in most of cases. **OBJECTIVE:** This work aimed to determine the epidemiology, clinical and biochemical aspects of patients with CAH treated at the Dr. Agustín O'Horán General Hospital. **METHODS:** An epidemiological, descriptive and retrospective study was conducted, comprising CAH patients diagnosed between 2008 and 2018. **RESULTS:** 21 patients were evaluated, 16 (76.2%) were mayan. All 21 patients detected underwent metabolic screening, 17 showed elevate 17-OHP and 4 normal levels, which were recognized at 6 months, 7, 8 and 13 years of age. 3 of them had non-classical 21-hydroxylase deficiency and in the remaining one an elevation of 11-deoxycortisol was detected (>10,000 ng/dl, therefore 11β-hydroxylase deficiency was suspected). Out of 21 patients, 9 (43%) were born with ambiguous genitalia (karyotype 46, XX) and Prader scale II to V (5 patients with Prader scale IV). 12 (57%) patients were born with well-differentiated genitalia (6 female and 6 male). Only 9 (43%) patients had an adrenal crisis, of which 7 had differentiated genitalia and 2 undifferentiated. Of all the patients with 21-hydroxylase deficiency, 16 (76.2%) had classic CAH: 15 with the salt-wasting variant and 1 with the virilizing variant, and 5 (23.8%) with the non-classic form. **DISCUSSION AND CONCLUSION:** In Yucatán, southern México, the prevalence of CAH is above the world average, with classic CAH, losing salt, due to 21-hydroxylase deficiency the most frequently reported. The neonatal metabolic screening in the Health Services of Yucatán covers 95% of the population it assists. This has allowed the timely detection of patients with

CAH, both in patients with ambiguous genitalia and in patients with differentiated genitalia.

P-126 - CONGENITAL ADRENAL HYPERPLASIA, BEFORE AND AFTER NEONATAL SCREENING. 13 YEARS OF EXPERIENCE IN SANTA CRUZ - BOLIVIA

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INTRODUCTION: Congenital Adrenal Hyperplasia (CAH) is due to the 21-hydroxylase deficiency and is the cause of more than 90% of cases of the various forms of CAH. Its deficiency produces the deterioration of the synthesis of cortisol and aldosterone, increases the adrenal androgens and causes virilization of the female fetus, in males it can go unnoticed. Newborn screening (NBS) has been carried out in Santa Cruz - Bolivia since 2013 and for various reasons, it was temporarily interrupted or was not performed on all newborns throughout the study period. **OBJECTIVE:** Analyze the status of CAH diagnosis before and after NBS implementation, demonstrate its importance regarding diagnosed cases that were not screened, and promote NBS implementation throughout the country.**MATERIALS AND METHODS:** Clinical histories of patients diagnosed with CAH in the Endocrinology Service of the Dr. Mario Ortiz Suarez Children´s Hospital from 2008-2021, before and after of NBS implementation, were evaluated. Variables analyzed were: gender, clinical manifestations, plasma level of 17 Hydroxyprogesterone, Androstenedione, Na^+ and K^+, pelvic ultrasound and treatment. NBS was performed in blood samples obtained by heel puncture using the DELFIA method, being considered abnormal values of 17 Hydroxyprogesterone those >30 nmol/L for all newborns regardless of gestational age or birth weight. **RESULTS:** 33 patients were diagnosed with CAH, 21 female and 12 male. Before NBS, CAH was confirmed in 5 female patients, being the clitoral hypertrophy the more relevant clinical data. The median age at diagnosis was 30 days. Mean plasma concentrations of Na^+ = 123mEq/L, K^+ = 6mEq/L, 17 Hydroxyprogesterone: > 50 ng/dl, and Androstenedione = 6 ng/dl. Pelvic ultrasound revealed the presence of the uterus and ovaries in girls. The treatment was done with Hydrocortisone 10-15 mg/m^2/day, Fludrocortisone 0.1 mg/ day and NaCl 1 gr. After NBS implementation, CAH was diagnosed in 28 patients, 16 female and 12 male, however only 8 of them (28.6%) were diagnosed by NBS and 6 were male. Three girls were assigned as male. Laboratory markers and age at diagnosis were similar to those corresponding to the previous period**. CONCLUSIONS:** There were no changes at the age of diagnosis in CAH after NBS implementation, the laboratory parameters were similar in both groups, and the percentage of newborn detected through NBS was only 28.6 % of the total diagnosed. It is important to note that 75% of the total screened patient corresponded to the male sex. It is necessary to improve NBS coverage in our city.

P-127 - NEWBORN SCREENING PROGRAM FOR CYSTIC FIBROSIS IN CUBA USING THE ULTRAMICROANALYTICAL SYSTEM: TWO YEAR´S EXPERIENCE

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INTRODUCTION: In Cuba, newborn screening (NBS) for cystic fibrosis (CF) was introduced on January 2019, using the ultramicroanalytical system. **OBJECTIVE:** To show the main results obtained during the first two years of Cuban CF NBS program. **METHODS:** The studied group included all neonates born between January 2019 and December 2020. Samples were collected between the 5th and 7th days of life. An IRT1/IRT2/DNA protocol was followed using a cut-off value of 50 ng/mL. **RESULTS:** A total of 184594 samples were studied. Among neonates screened, 1445 samples had values ≥ 50 ng/ml and IRT was measured again by a second heel prick (recall rate=0.78%). In 485 (0.26%) of these children, IRT was still elevated and they were referred to specialist CF centres for clinical evaluation. Fourteen children were confirmed (incidence 1: 13185) by sweat test and when evaluated by molecular biology technique (eight mutations panel), CF mutations were detected. Eleven newborns presented mutation F508del, either in a homozygous or heterozygous state. A false negative case with IRT2 ≤ 50 ng/ml was reported during NBS which was referred to a genetics consultation for presenting symptoms consistent with the disease and history of CF in his family. Complete demographic data of the first 32764 samples were collected to compare some NBS quality indicators with those obtained in the pilot study. The average age of sampling was six days with results available at 11 days of life. 1.7% of the samples were collected 20 days after the child was born and 0.84% of them corresponded to samples taken after 30 days. The mean IRT1 value was 12.7±11.7 ng/mL (ranging between 0–283 ng/mL) and the median was 9.8 (IQR 5.9–16.4) ng/mL. The 97.5, 98.5, and 99.5 percentile values were 38.4, 42.4, and 59.7 ng/mL,

respectively. On average, samples were processed five days after collection and two days after they were received at the laboratory**. CONCLUSIONS:** Although CF NBS program in Cuba is just beginning and more newborns should be studied to define the real incidence of this disease, it can be predicted that CF will be one of the most frequent inherited-metabolic diseases in the Cuban population.

P-128 - 10 YEARS OF NEWBORN SCREENING FOR CYSTIC FIBROSIS IN URUGUAY

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INTRODUCTION: Newborn screening (NBS) for Cystic Fibrosis (CF) in Uruguay has been mandatory since June 2010. Throughout these years we have used several commercial IRT kits. Pancreatitis-associated protein (PAP) analysis was incorporated as a second marker. However, two screening strategies have been maintained simultaneously: IRT/IRT and IRT/PAP. Our laboratory also performs confirmatory tests. **OBJECTIVE:** To show the results obtained over these 10 years of CF NBS in Uruguay. **MATERIALS AND METHODS:** Samples used were dried blood spots obtained at 40 hours of life from june 2010 to june 2020. IRT is currently performed with a Perkin Elmer AutoDelfia kit, establishing a calculated cut-off point of 59 ng/ml. MucoPAP Reagent Kit (Dynabio) is used to assay PAP, with a cut-off point of 1.6 ng/ml, recommended by the manufacturer. For diagnosis we used sweat test (Gibson and Cook and for patients that do not sweat we use Macroduct) and CF-EU2v1 commercial kit of 50 mutations. **RESULTS:** In these 10 years, 471496 NBS samples have been processed, 56 were true positive for the diagnosis of CF, 12 (20%) of them had meconium ileus, and 3 were false negative of the screening. Global incidence was 1/8420. Comparing the IRT/IRT and IRT/PAP screening strategies, a significant decrease in the recitation rate of patients was found, from 0.7% to 0.1%. After calculating positive predictive values (PPV) and negative predictive values (PPN) for both screening strategies, it was found that for IRT/IRT the PPV was 2.5% and the PPN 99.9%, while for IRT/PAP the PPV was 12% and the PPN 99.9%. As it was expected, the most frequent mutation identified was Delta F508 in homozygosis (27%) or heterozygosis (37%)**. CONCLUSIONS:** Reviewing both strategies, we can conclude that IRT/PAP have a higher PPV and reduce the number of recitations, impacting in daily laboratory operations and family distress caused by false positives. To improve performance it is necessary to calculate the population cut-off point for PAP.

P-129 - EXPERIENCE OF A MULTIDISCIPLINARY MANAGEMENT UNIT IN PATIENTS WITH CYSTIC FIBROSIS IN THE DOMINICAN REPUBLIC.

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INTRODUCTION: Cystic Fibrosis (CF) is a congenital disease with the highest mortality rate in the Caucasian population. An estimated 1 in 2,500 people is a carrier of the cystic fibrosis gene. In the Dominican Republic, this disease has not been properly studied, the access to neonatal screening is partial, only a part of the Population can perform it, our country doesn't have in operation a national screening program that limits the timely diagnosis of rare diseases like Cystic Fibrosis and ciliopathies. Being a health condition, poorly investigated, known, and researched in our country. **OBJECTIVE:** to know the experience of a multidisciplinary management unit in patients with Cystic Fibrosis and Ciliopathies in the Dominican Republic. **MATERIALS AND METHODS:** we share our experience of a developing country with multiple limitations not only economic, knowledge, research of rare diseases, and without a national neonatal program in operation. **RESULTS:** After almost 10 years, we install a multidiscipline management unit in the Robert Reid Cabral Children's Hospital, for the integral management of patients with Cystic Fibrosis, a multidisciplinary team of health professionals offer their service to Cystic Fibrosis and Ciliopathies patient. In our unit in the last 6 months, 298 patients have been evaluated, 699 specialized consultations, 1,118 procedures, 1,054 follow-up procedures, 253 lung function tests, 64 diagnostic tests, 7 new patients with Cystic Fibrosis and Primary Ciliary Dyskinesia have been identified**. CONCLUSION:** The implementation of specialized management units has an important impact on the education, diagnosis, and management of rare diseases, wich is an important health problem for the attending physician, the patient, and their families.

P-130 - PARENTAL NEEDS FOR LEARNING ABOUT THE MANAGEMENT OF CYSTIC

FIBROSIS. BASELINE FOR THE DEVELOPMENT OF A SUPPORT PROGRAM.

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INTRODUCTION: Cystic Fibrosis (CF) is the congenital disease with the highest mortality rate in the Caucasian population. It is estimated that 1 in 2,500 people carry the cystic fibrosis gene. In the Dominican Republic, this disease has not been studied properly, which means that parents do not have sufficient educational tools to help them mitigate complications and thus be able to reduce the mortality of children who suffer from it. In a previously conducted study, parents of patients with cystic fibrosis presented a fair level of knowledge, which was caused by a misunderstanding of medical terminology. According to most of them, their knowledge could be improved through the implementation of educational talks by medical staff. **OBJECTIVE:** To assess the learning needs of parents about the management of cystic fibrosis. **MATERIALS AND METHODS:** An observational, descriptive and crosssectional study was carried out with a prospective collection of data offered by the parents of patients diagnosed with CF through an online data collection instrument. The data of all the patients attending the cystic fibrosis unit of the Robert Reid Cabral Hospital during the period august November 2021. The questionnaire was sent through the established contacts, and they were analyzed descriptively. **RESULTS:** The results were distributed in two categories, the needs corresponding to the daily management of the condition and the psychological or behavioral management of the child or adolescent. A total of 32 parents answered the form corresponding to 75% of the total number of patients enrolled in the program and that the form was sent to them. The most frequently expressed need by parents was related to feeding management with 97%, followed by cross-infection with 87%, the importance of hydration with 76%, lung care with 71%, nebulization practices in 68%, 50% would like to learn about respiratory therapy, and 28% showed interest in the behavioral management of these patients**.** **CONCLUSION:** The learning needs of parents for the management of their children were concentrated in the daily management of the problem, focusing on the feeding of patients with cystic fibrosis.

P-131 - A CYSTIC FIBROSIS CASE WITH 3 NON-CLASSIC MUTATIONS AND PSEUDO BARTTER SYNDROME: IMPORTANCE OF AN ADEQUATE DIAGNOSIS STRATEGY

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INTRODUCTION: Cystic Fibrosis (CF) is an autosomal recessive disease caused by the pathogenic variants in the Cystic Fibrosis Transmembrane Regulator gene (*CFTR*). Pseudo-Bartter syndrome (PBS) is characterized by episodes of dehydration, electrolyte imbalance, and acid base disorders in absence of tubular disease. Incidence of PBS in CF is estimated 12.0-16.8% live births, commonly associated with F508del *CFTR mutation*. Newborn screening (NBS) is available for CF early detection. **OBJECTIVE:** Report the importance of an adequate follow-up of the CF diagnosis pathway to avoid diagnostic delay. **CASE REPORT:** 8-month-old female, product of the second pregnancy of a non-blood relative couple. First product passed away at 8 months-old due to respiratory infection, without further explanation. Regular prenatal care, vaginal delivery with 3500 gr, and 53 cm at birth and 40 weeks. Screened at 10 days in another health care institution with first IRT blood concentration of 72.1 ng/ml (cutoff <60.0 ng/ml). A second IRT measurement at 4 months reported 23.3 ng/ml, no further studies performed. Two hospital admissions due to fever, dehydration, electrolyte imbalance, and pneumonia at 3 and 4 months. At 6 months was admitted due to severe dehydration, cyanosis, cough, fever, respiratory distress, hyponatremia (Na^+: 122.6 mEq/L), hypokalemia (K^+: 2.2 mEq/L), hypochloremia (Cl^-: 72.4 mEq/L), and metabolic alkalosis (pH: 7.53, pCO2: 29.0 mmHg, $HCO3^-$: 25.0 mEq/L). Bartter´s Syndrome (BS) was considered as the main diagnosis but discarded due to absence of tubular disease. Based on clinical records, chloride sweat test (CST) was requested and reported 98.0 mmol/L Cl^- (Cutoff values: Unlikely: < 30.0 mmol/L Cl^-, Borderline: 30.0-59.0 mmol/L Cl^-, Abnormal: ≥ 60.0 mmol/L Cl^-). Molecular analysis identified 3 *CFTR* mutations (p.Gly1047Ser; p.Arg347Cys; p.Trp356_Val358delinsIle) confirming CF and PBS as part of the clinical presentation. **DISCUSSION:** It is widely known that IRT blood concentration values are age-

dependent and inadequate interpretation of the results delays CF diagnosis, such as the reported case. CST and CFTR molecular analysis are available confirmatory tests that must be requested in highly-suspicious cases. CF and PBS must be considered in differential diagnosis in cases of metabolic alkalosis and electrolyte imbalance in which common causes are ruled out.

P-132 - CYSTIC FIBROSIS MOLECULAR DIAGNOSIS IN CUBA: 30 YEARS OF EXPERIENCE

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INTRODUCTION: Cystic Fibrosis (CF) is a recessive autosomal hereditary disease, and its frequency in Cuba, according to CF Cuban National Commission, is 1 in every 9862 live newborns. More than two thousand mutations have been found worldwide in the responsible gene (CF transmembrane regulator). However, only eight of those are looked for in Cuba, since they are those more commonly found in Spain and Sub-Saharan Africa, the two geographical regions that represent the main source of our genetically mixed population. **OBJECTIVE:** molecular characterization of patients with CF clinical symptoms, or those children positive to CF neonatal screening, in order to improve their clinical management of them and genetic counseling to their families. **MATERIALS AND METHODS:** descriptive research was done searching for eight mutations (F508del, G542X, R1162X, R334W, R553X, 3120+1G>A, I507del and G85E) in 850 CF clinical patients and 168 CF positive newborns, in all cases with official informative consent. Mutations were searched by PCR-ARMS (Amplification Refractory Mutation System), or PCR-RFLP (Restriction Fragment Length Polymorphism) methods. **RESULTS:** all searched mutations were present in the Cuban population, with frequencies higher than 1%, being F508del the most frequent (37%) as expected; 817 chromosomes carrying one of the searched mutations were found, and 239 prenatal diagnoses were done, allowing characterization of CF status of fetus at risk and confirming CF status of the patients. **CONCLUSION/DISCUSSION:** The results confirm a high molecular heterogeneity of CF in Cuba, as well as in other Latin-American countries, and the efficiency of the mutations panel. However, the introduction of other more powerful diagnosis methods (like High-Resolution Melting Curve, DNA Sequencing, and Multiplex Ligation-dependent Probe Amplification) is recommended in order to increase the number of mutations searched in the Cuban population.

P-133 - MOLECULAR AND BIOINFORMATIC CHARACTERIZATION OF GENOMIC VARIANTS OF THE GALT GENE IN PATIENTS IN SOUTHWESTERN COLOMBIA

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Classical galactosemia (GC) (ORPHA: 79239) belongs to a rare set of inherited disorders of galactose metabolism, caused by defects in the *GALT* gene. Patients have a wide spectrum of physical and cognitive disabilities becoming life-threatening. In order to identify and characterize the *GALT* gene variants in patients in the Colombian south-west, a cross-sectional, descriptive, non-experimental study was carried out, with the results obtained from the complete exome sequencing of 320 patients with different pathologies, without clinical suspicion of GC, They belong to the database of the Institute of Medical Genetics–GENOMICS (Cali-Colombia). The variants found were classified according to the standards and guidelines for the interpretation of the American College of Medical Genetics and Genomics and the Molecular Pathology Association using population databases such as ClinVar, Varsome and prediction software such as Sorting Intolerance From Tolerance, Mutation Taster, UMD-Predictor, Functional Analysis through Hidden Markov Models, Polymorphism Phenotyping v2, Mutation Taster and Protein Variation Effect Analyzer. As a result, 12 variants of the *GALT* gene was identified, of which 5 had benign clinical significance, 2 pathogenic, 3 of uncertain significance (VUS), and 2 reported no change in nucleotides and amino acids previously described in the literature. The pathogenic variants c.404C>T and c.652C>T were found to have a low allelic frequency (0.00625). Garcia DF, et al., in 2016 reported the variant c.404C>T (p.Ser135Leu) in a cohort of 19 Brazilian patients with type I and II galactosemia, with this being the most prevalent. A VUS variant (p.Asn314Asp) associated with Duarte alleles was identified in which *GALT* activity is lower than in other GC alleles, often approximately 8-11% in the general European population. In Colombia, type I

galactosemia is part of the proposal for the implementation of compulsory screening tests throughout the national territory, however, the neonatal screening program is slowly advancing, which represents a latent health problem throughout the country. The identification of pathogenic variants of the *GALT* gene in this paper supports the importance of early identification of possible patients in order to establish targeted treatments that lessen the morbimortality of this pathology by approaching precision medicine.

P-134 - IMPORTANCE OF EARLY IDENTIFICATION OF CLASSICAL GALACTOSEMIA: REPORT OF THE FIRST CASE BY CLINICAL WHOLE GENOME SEQUENCING IN PERU

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BACKGROUND: Classical galactosemia (CG), deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT), is a rare autosomal recessive disorder of galactose metabolism. This disorder is caused by mutations in the *GALT* gene. If untreated, it can lead to growth retardation, liver failure, susceptibility to sepsis and death in the newborn period. Unfortunately, the Peruvian Health System's NBS does not include CG in its diseases panel. **OBJECTIVE:** Emphasize the importance of early identification of CG. **METHODS:** Genetic assessment and counseling was performed by the Genetics Service of Instituto Nacional de Salud del Niño San Borja, Peru. Molecular diagnosis was performed by clinical whole genome sequencing (cWGS) through the philanthropic iHope program. **RESULTS:** One month old female infant was admitted to our institution with a diagnosis of "biliary tract atresia". The first presentation of symptoms began at 23 days of life with vomiting, progressive abdominal distention, hyporexia, hypoactivity. Neither basic (hypothyroidism, phenylketonuria, cystic fibrosis and congenital adrenal hyperplasia) nor expanded NBS panels include CG testing. Intraoperative cholangiography ruled out biliary tract atresia. Analysis of galactose metabolites in blood nor reducing substances in urine were not available in our institution. Organic acids in urine and other biochemical analyses were inconclusive. She was admitted to the intensive care unit with hepatic failure, hematological disorders, ascites, hypoglycemia, respiratory infections and sepsis. The cWGS test identified a homozygous pathogenic variant in the *GALT* gene, c.443G>A (p.Arg148Gln); both parents were found to be heterozygous. There was no family history of CG, no history of consanguinity, although both come from a small town in the south of Peru. Upon treatment, she showed gradual clinical improvement and was discharged from the intensive care unit**. CONCLUSIONS:** We report a delayed diagnosis of CG by cWGS in a Peruvian infant. Unfortunately, the lack of basic tests in our institution caused a delay in diagnosis and although the cWGS is not the first choice method, it was useful and allowed diagnosis. Therefore, universal access to basic tests for CG in the Peruvian health system is necessary, even though the CG is a rare disease, early detection and treatment have a favorable impact on patient morbidity and mortality.

P-135 - QUANTITATIVE ASSAY FOR DETERMINATING BIOTINIDASE DEFICIENCY IN DRIED BLOOD SPOTS ON FILTER PAPER

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INTRODUCTION: Biotinidase deficiency is an autosomal recessive inherited disorder of biotin recycling associated with secondary alterations in amino acid, carbohydrate, and fatty acid metabolism. **OBJECTIVE:** To develop a simple method for biotinidase quantification using dried blood spots (DBS) based on the method developed by Yamaguchi et al. **MATERIALS AND METHODS:** DBS were obtained from the Cuban Newborn Screening Program (NSP). Biotinidase activity was calculated using a paminobenzoate (PABA) calibration curve prepared in human blood adjusted to 55 % hematocrit, free of biotinidase activity plasma, and then impregnated on filter paper. Enzyme activity was expressed in nmol/min/mL. **RESULTS:** The assay was carried out within 20 hours. The lowest detectable biotinidase activity was 0.366 nmol/min/mL and the quantification limit was 1.097 nmol/min/mL. The recovery mean value from three samples prepared with different concentration of PABA and expressed in activity values of enzyme was 101.1 ± 5.6%. Intra and inter-assay variation coefficients were lower than 10 %. Linear calibration functions were obtained with a correlation coefficient (r) greater than 0.99. The linear activity range was between 1.17 and 7.10 nmol/min/mL. Therapeutic drugs in routine samples like sulfonamides gave purple color in the absence of biotinyl-PABA. A study with 231 DBS from the

Cuban NSP was carried out. A mean activity value of 5.85 ± 1.14 nmol/min/mL was obtained. The influence of the sample collection time was demonstrated, obtaining lower values of biotinidase activity in those DBS that were processed two months after collection and stored at 2-8 °C. Biotinidase activity in DBS determined by this assay was well correlated to that in serum. Biotinidase activity was determined in nine confirmed biotinidase deficiency DBS and five CDC controls using the ultramicro-assay and the enzyme activities values showed 100 % concordance with the clinical diagnosis**. CONCLUSIONS:** This method is precise and accurate and can be used for quantification of biotinidase activity in DBS in wide scale neonatal screening, although more newborns DBS should be studied to establish cut-off levels for partial and total biotinidase deficiency.

P-136 - COMPARISON BETWEEN TWO ANALYTICAL METHODS OF MEASUREMENT FOR THE NEWBORN SCREENING OF MAPLE SYRUP URINE DISEASE

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INTRODUCTION: Our Program performs the newborn screening (NS) through a two-stage analytical algorithm, with two different methods, whose accuracy and linearity were verified for both according to CLSI EP15-A3 and EP6-A. We consider important the comparison of results between the method used as reference and the new one, to define if the NS for maple syrup urine disease (MSUD) is positive or negative. **OBJECTIVES:** To determine if the methods used in the two stages for NS of MSUD are statistically comparable. **MATERIALS AND METHODS:** The cut-off value for the NS of MSUD was established in the period July to December 2021. Protocol "Measurement Procedure Comparison" CLSI EP9-A3: the concentration of branched chain amino acids (BCAA) in dried blood spots was determined by two methods: evaluated method, enzymatic colorimetric/Zentech (ZT) and comparison method, enzymatic fluorometric/In House (IH). 40 samples from patients with MSUD in treatment with medicalnutritional and biochemical follow-up in our Program were used. Samples concentrations were homogeneously distributed in the evaluated range and were processed in duplicate by both methods. For the statistical analysis we used EP Evaluator®12.0. **RESULTS:** •ZT Cut-off value, percentile 99.5: BCAA<6mg/dL; newborns evaluated: 7056; mean/median, BCAA mg/dL=1.5/1.4. •Comparison of analytical methods: concentrations range, mg/dL: 0.3 to 18.0 (IH) and 0.3 to 19.4 (ZT). Correlation coefficient=0.9760. Deming regression analysis, 95% confidence interval: intercept=0.06 (-0.18 to 0.30); slope=0.963 (0.909 to 1.018); standard error of the estimates (SEE)=0.13. Difference observed in the level of decision (DL), BCAA=6.0mg/dL (IH): 5.8mg/dL (ZT) was obtained; 95% confidence limits: 5.7mg/dL to 6.0mg/dL**. CONCLUSIONS:** Statistical comparison, ZT method respect to IH: There was none evidence found of constant systematic error between the analytical methods: the intercept confidence interval included zero. There was not a significant proportional systematic error: the slope confidence interval included 1. There was not significant difference in the DL: 6.0mg/dL was included in the confidence limits. We found an acceptable random error, taking into account the SEE. We conclude that the methods are statistically comparable, for which it is possible to perform NS for MSUD with the ZT method, using a cut-off value of 6.0mg/dL.

P-137 - MEDIUM-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD): NEWBORN SCREENING RESULTS IN URUGUAY

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INTRODUCTION: MCADD is the most common inherited defect of mitochondrial fatty acid oxidation and is potentially fatal. Affected cases, present between age three or 24 months. Severe lethal presentations in the first week of life have been reported. The cases identified by newborn screening (NBS) have excellent prognosis. Frequent feedings are instituted to avoid prolonged periods of fasting and an emergency regimen during intercurrent illness is given to the family. It has been estimated that before NBS programme, approximately 4% patients died in the first 72 hours. The *ACADM* gene A985G mutation accounts for almost 90% of the mutant alleles and 70% of cases are homozygous. Patients with this variant accumulate the highest levels of blood markers in the newborn period and are probably at risk for more severe disease. In

Uruguay, national MCADD NBS by MS/MS started in 2009 as a pilot programme, and it turns mandatory in 2013. **OBJECTIVE:** To present our results of NBS and clinical follow-up of the MCADD patients. **CLINICAL CASES:** Since 2009, 6 true positive cases have been confirmed by urine organic acids assay and molecular study. All sibs were studied and in one case the older brother was affected and also started follow up. At present the age of NBS true positive cases varies between 3 months to 13 years. Sex: 4 female and 2 males. Molecular study showed that variant A985G is present in all cases: 4 homozygous and two compounds heterozygous. Patients are scheduled in a clinical follow-up protocol and an emergency regimen is given. None of the cases presented acute decompensation even during acute fever episodes**. CONCLUSIONS:** Since 2009 the national NBS for MCADD, a potentially fatal disease, allowed us to start adequate management and follow-up and avoid potential severe decomposition of six asymptomatic cases and one sib.

P-138 - PRELIMINARY INCIDENCE OF STRUCTURAL HEMOGLOBINOPATHIES IN GUATEMALA

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INTRODUCTION: The structural hemoglobinopathies are alterations of the hemoglobin molecules, secondary to genetic mutations, which cause clinical manifestations due to an alteration of the transportation of oxygen. At world level, more than 275,000 live births are reported each year that present a disorder of falciform cells with the need of an early diagnosis. Central America reports the presence of the S hemoglobin (175 annual newborns) and C. **OBJECTIVES:** Determine the preliminary incidence of the structural hemoglobinopathies in newborns at the Hospital General San Juan de Dios and identify the hemoglobin variants. **MATERIALS AND METHODS:** 3006 newborns were included during the year 2017. Dried blood spots were used for the newborn screening and a test was performed to identify the hemoglobin variants by cation exchange high-performance liquid chromatography (HPLC) using the VARIANT nbs analyzer, Bio-Rad®. **RESULTS:** 23 cases (0.77%) presented an abnormal hemoglobin pattern. 22 cases (95.65%) corresponded to the S variant, of which 21 cases (91.3%) presented a heterozygous pattern (FAS) and 1 case (4.35%) a homozygous pattern (FS). 1 case (4.35%) presented a heterozygous pattern of the C variant (FAC). **DISCUSSION AND CONCLUSIONS:** The preliminary incidence of abnormal hemoglobin patterns was 7.65 per 1000 newborns. According to structural variant and the inheritance pattern, incidence of 6.98 per 1000 newborns with the FAS pattern and 0.33 per 1000 newborns with the patterns FS and FAC were determined. Due to the migration of African origin populations, the presence of S and C hemoglobins has been reported in non-endemic areas such as Central America increasing the incidence of diseases related to the presence of hemoglobin variants. This study was carried out in 2017, the year in which this diagnosis was implemented in the first public hospital in Guatemala. These preliminary results indicate that structural hemoglobinopathies are an important public health problem in Guatemala, evidencing the need to expand the coverage of their screening at a national level, because at the present time the different regions of the country are not contemplated, and a more representative sample is needed to establish the current status of these diseases.

P-139 - KNOWLEDGE AND ATTITUDES ABOUT SICKLE CELL DISEASE IN CAREGIVERS WITH AFFECTED CHILDREN IN THE HEMATOLOGY OUTPATIENT CLINIC OF A TERTIARY CARE HOSPITAL IN A DEVELOPING COUNTRY.

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INTRODUCTION: Sickle cell anemia is included within the structural hemoglobinopathies, is associated with high rates of morbidity and mortality. In the Dominican Republic, in 2015 a decree was presented ordering the start of neonatal screening, which has not yet been fulfilled. Knowledge is the pillar of prevention. **OBJECTIVES:** To evaluate the knowledge and attitudes about sickle cell disease (SCD) of caregivers with homozygous children who attend to the hematology outpatient clinic at the Robert Reid Cabral Third Level Children's Hospital before de implementation of neonatal screening in the Dominican Republic. **METHODS:** We performed a descriptive, observational, and cross-sectional research. The study population consisted of 180 patients and their relatives who attended to the outpatient clinic during the study period, the selected sample included 102 caregivers, who met the inclusion and exclusion criteria. The caregivers of children with SCD were assessed by questionnaire based on the Information Sheets for Parents of Children with Sickle Cell

Disease by the Utah Department of Health and by the New England Pediatric Sickle Cell Consortium. **RESULTS:** Most of the caregivers interviewed had little (53.9 %) and very little knowledge (22.5 %) about the SCD. Youngers and less educated caregivers had a lower level of knowledge. 58.8 % of caregivers knew the form of inheritance and only 4.9 % the probability of transmission. About complications of SCD 44.1 % had only partial knowledge and 39.2 % were unaware of them, in addition 48 % of mothers did not know any preventive methods. 56.9% of the parents were unaware of their sickle cell trait status before becoming pregnant. **DISCUSSION AND CONCLUSION:** In our research, the level of knowledge about the sickle cell disease in caregivers was very low. In countries where neonatal screening and good genetic and educational counseling exists, children with SCD use to have superior outcomes. Better methods and plans are needed to improve education, ongoing follow-up, and quality genetic counseling in these families, especially when the newborn screening program in our country begins.

P-140 - HYDROXIUREA EFFECTIVENESS AND ADHERENCE IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL ANEMIA

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INTRODUCTION: Hydroxyurea (HU) is a drug that has demonstrated improvement in the clinical severity of patients with sickle cell anemia, but in many cases its effectiveness is related to adherence and accessibility to treatment. Although HU is an inexpensive drug, many low-income countries still have problems acquiring it. **OBJECTIVE:** To determine the clinical and laboratory effectiveness and relate it with the degree of adherence to treatment with HU in patients with sickle cell anemia who attend to the hematology outpatient clinic at Dr. Robert Reid Cabral Children's Hospital. **METHODS:** An observational, descriptive, cross-sectional study was carried out during 2019. The population consisted of 99 children and adolescents diagnosed with sickle cell disease who attended to the outpatient clinic during the study period and had prescribed HU. 95 patients met the inclusion criteria. Clinical effectiveness was measured in proportion to the reduction in the number of vasa-occlusive crisis episodes per year, admissions, and complications. Laboratory effectiveness is reflected in the variation of blood count values before and after HU. To assess adherence to treatment, the information methodology provided by the SMAQ Compliance Test (The Medication Adherence Questionnaire) was used. **RESULTS:** 76.8% of the patients had a high effectiveness in the clinical response. 75.8% of the patients had a high and medium effectiveness in the laboratory parameters. 72.3% of the patients had presented more than three vasaocclusive crises per year and after HU only 8.5% continued presenting several crises per year. 62.1% of assessed patients have presented poor adherence to treatment with HU. The main cause of poor adherence was forgetting to take the medication followed by the difficulty of acquiring them due to the cost and accessibility. Most of the patients (61%) did not present side effects with treatment**. CONCLUSION:** Despite low adherence, HU turned out to be very effective and with few side effects. Social problems continue to be an important cause of poor adherence such as lack of supervision and poor access to medication. Better public health policies should be established to improve access to treatment in low-income patients.

P-141 - ACTIONS FOR THE PREVENTION OF SICKLE-CELL DISEASE IN ADOLESCENTS AGED 10-18 IN THE DOMINICAN REPUBLIC, 2009-2019

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INTRODUCTION: The World Health Organization (WHO) in 2006 urged Member States to design and implement national programs for the prevention and management of hemoglobinopathies. The National Program for the Detection, Education and Prevention of Sickle Cell Disease (PRONADEPFA) from Dominican Republic (DR), pioneer in neonatal screening of Sickle Cell Disease (SCD), carried out neonatal screening in 23,473 newborns during 1992-2003; 2,608 (11%) of them were carriers of a trait or any hemoglobinopathy: HbSS 0.23%, HbSC 0.09%, HbCC 0.02% standed out; HbAS 8.2% and HbAC 1.93%. PRONADEPFA stopped the newborn screening in 2004, but in 2009 started a community project to detect HbAS in adolescents living in slums of the DR, where poverty and teen pregnancy are prevalent, and to teach them about SCD and how to prevent it. **OBJECTIVES:** to communicate the contributions of PRONADEPFA in the prevention of SCD in adolescents 10-

18, in the DR during 2009-2019. **MATERIALS AND METHODS:** based on PRONADEPFA data, communities with the highest percentage of HbAS cases were selected. The study was performed in 8 schools located in Santo Domingo, Santiago, San Pedro de Macorís, Moca and Baní, cities belonging to the northern, southern, and eastern regions of the DR. Students 10-18 years old received educational talks about SCD's clinical manifestations, inheritance, and prevention. Prior parents' approval through informed consent was requested, and 1 ml of whole blood was collected from participants using Tapval purple cap tubes. HbAS detection was performed with Sickle Cell Induction Test using 2% sodium metabisulfite; positive cases were confirmed by alkaline and acid hemoglobin electrophoresis, respectively. **RESULTS:** 3,167 participants were educated; 2,654 subjects with the required previous consent were screened for HbAS. Frequency of HbAS was 8.2% (217)**. CONCLUSIONS:** This is the first report about a regional approach for the prevention of SCD in the DR. PRONADEPFA promotes information, awareness about SCD, and detection of HbAS in adolescents so they were properly oriented and genotyped before they start their sexual life, contributing to the reduction of morbidity and mortality due to SCD in the DR. These actions are linked to the guidelines proposed by the WHO for the prevention of hemoglobinopathies.

P-142 - CASE REPORT: HEMOLYTIC ANEMIA IN GLUCOSE 6 PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

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INTRODUCTION: Glucose 6 phosphate dehydrogenase (G6PD) is an enzyme that maintains the homeostasis of erythrocytes against oxidative chemical products, by the production of reduced nicotinamide adenine dinucleotide phosphate (NADPH). The enzyme is part of the pentose monophosphate metabolic pathway and catalyzes the oxidative step of glucose 6-phosphate to 6-phosphogluconate and reduces nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. The pathway supplies NADPH to the erythrocyte, a basic cofactor in glutathione metabolism that protects against oxidation. G6PD deficiency is an X-linked hereditary disease and enzyme deficiency in contact with oxidative chemicals causes erythrocyte lysis. **OBJECTIVE:** Presentation of two cases of acute hemolytic anemia in G6PD deficiency. **MATERIALS AND METHODS:** Review of clinical records with a diagnosis of G6PD deficiency and acute hemolytic anemia. **RESULTS:** We report 2 pediatric cases of hemolytic anemia in G6PD deficiency. First case, a 6-year-old male with a medical history of G6PD deficiency. Mother reports 9 days of unquantified fever and 5 days with arthralgia in the left knee. Physical examination revealed pain in the left popliteal fossa. On hospitalization, negative tests for dengue, streptococcal exoenzymes, polymerase chain reaction, and urinalysis; red blood cell count (RBC) with mild anemia 10.4g/dL, normal white blood cell count and under treatment with antibiotics and intravenous diclofenac. The patient persists with fever, transferred to the Children's Hospital. On the fifth day of hospitalization with RBC 10.1 g/dL and reticulocytes 7.8% and no finding of the febrile cause. Second case, a 1-year-old male, with no pathological personal history. Mother reports 1 day of unquantified fever treated with oral acetaminophen and diclofenac. Neonatal metabolic screening reports low G6PD and the mother reports use of camphor. On physical examination, scleral and integument jaundice. G6PD quantification was 2.4 U/g HB. RBC with severe anemia of 5.5 g/dL, reticulocytes 7%. He was hospitalized and requires a transfusion of 1 unit of packed red blood cells at 10 mL/kg. Post-transfusion RBC 8.7 g/dL and reticulocytes 5.3%**. CONCLUSION:** G6PD deficiency is a common enzymopathy in the population, detected in neonatal metabolic screening. Prevention of oxidative chemicals is important to prevent hemolytic anemia in these patients.

P-143 - APPROACH TO DIAGNOSIS IN POSITIVE NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY IN PUERTO RICO: UNDERSTANDING PHENOTYPE AND GENOTYPE CORRELATIONS DURING FIVE-YEAR

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BACKGROUND: Severe Combined Immune deficiency (SCID) is the most severe form of inborn immunodeficiencies, which are characterized in most cases by complete absence of T-cell-mediated immunity, and by impaired B-cell-function. Early diagnosis is important for prompt treatment since it is uniformly fatal without hematopoietic cell transplantation or gene therapy. SCID can be detected using T cell receptor

excision circle (TREC) assay. In August 2015 Puerto Rico (PR) added newborn screening (NBS) for SCID to the mandatory newborn screening panel using dried blood spot specimen. The estimated incidence in PR is of 1: 60,000 consistent with the incidence in USA. **OBJECTIVE:** Report the clinical, immunological, and molecular findings in Puerto Rican patients with a positive screening test for SCID. **METHOD:** A retrospective record review of positive newborn screening cases for SCID from Puerto Rican patients during August 2015-December 2020. Patients received immunological and molecular testing follow up at the Primary Immunodeficiency Clinic at the University of PR. **RESULTS:** A total of 125,440 infants were screened, identifying 18 cases with low TREC levels. Of these cases, 5 infants died (4 of which were preterm babies), 4 were lost to follow up, and 3 had normal follow up TREC levels after surgery for gastroschisis and omphalocele. The other 6 infants were referred to our clinic for diagnostic and follow up evaluation which led to the identification of 1 patient with Di George syndrome, 1 patient with RUNX1 deficiency, 1 patient Artemis deficient-SCID, 2 patients X-linked SCID (IL-2RG) and other non SCID lymphopenia who is still undergoing evaluation at our Immunology Clinic**. CONCLUSION:** NBS has allowed the early detection of infants with SCID and other lymphopenia disorders, which has permitted early diagnosis and management prior to developing symptoms or life-threatening complications. We confirmed 3 cases of SCID, 1 Di George syndrome and 1 RUNX1 deficiency. Variants of uncertain significance were obtained for the remaining low TREC level cases, where genetic testing has been part of the confirmation diagnosis. Describing these variants and associating them with the phenotypes will help us to understand the pathophysiology of SCID in Puerto Ricans.

P-144 - QUANTIFICATION OF THE BIOMARKERS LYSOSPHINGOMYELIN AND LYSOSPHINGOMYELIN-509 BY UPLC-MS/MS FOR THE SCREENING OF ACID SPHINGOMYELINASE DEFICIENCY (ASMD)

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Acid sphingomyelinase deficiency (ASMD, Niemann-Pick disease A/B) and Niemann-Pick type C (NPC) are sphingolipidoses that can share core clinical symptoms. These rare lysosomal storage diseases have an accumulation of sphingomyelin but with different genes involved. For ASMD, the variants occur in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene, while in NPC the *NPC1* or *NPC2* genes are impaired. Specific biomarkers can be monitored for the differentiation of ASMD from NPC, such as the quantification lysosphingomyelin (Lyso-SM), and lysosphingomyelin-509 (LysoSM-509). For the screening of ASMD, dried blood spots (DBS) from 16 patients diagnosed with ASMD deficiency were collected and compared with DBS from healthy subjects. The quantification of Lyso-SM and Lyso-SM-509 was performed by UPLCMS/MS (Xevo TQ-S micro) and the results were obtained in less than 3 min. All patients with ASMD deficiency had very high levels of both biomarkers. The average for lysoSM was 905 nmol/L (range= 265-3,356), reference range in controls= 37-119 nmol/L), and the average for lysoSM-509 was 27,895 nmol/L (range= 1,067-65,404), reference range in controls= 837-3,321 nmol/L). It is important to mention that the levels of Lyso-SM-509 found in NPC patients were lower than those obtained for ASMD patients, being 11,403 nmol/L (range= 3,819-22,747 nmol/L). Thus, the monitoring of LysoSM and LysoSM-509 for ASMD screening proved to be sensitive with a fast turnaround time (less than 3 min per sample). Besides that, it is important to highlight that the use of DBS for this procedure makes its measurement convenient for regions that have financial difficulties to have samples shipped on ice packs and/or across country borders. Finally, this procedure for ASMD can be used as a second-tier test in newborn screening.

P-145 - NEWBORN SCREENING FOR METACHROMATIC LEUKODYSTROPHY IN NORTHERN GERMANY

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Metachromatic leukodystrophy (MLD) is a rare, fatal autosomal-recessive genetic disorder caused by insufficient activity of the enzyme arylsulfatase A (ARSA) that results in intra-lysosomal accumulation of the ARSA substrate galactosylceramide I3-sulfate (sulfatide), inevitably leading to progressive demyelination and neurodegeneration in the central and peripheral nervous systems. There are three

variants of MLD commonly described in the literature based on the age at which symptoms appear: lateinfantile MLD, juvenile MLD, and adult MLD. Children affected by MLD display progressive neurologic symptoms, including ataxia, seizures, and quadriplegia, culminating in severe disability and early death. MLD diagnosis is often delayed or missed. We have initiated a prospective newborn screening study with the implementation of MLD into the current newborn screening panel (covering several different diseases) for all newborns in the German states. The total number of birth in this area is approximately 55,000 live births per year. A tiered screening approach is being applied where sulfatide levels are measured in dried blood spots, followed by genetic confirmatory testing (*ARSA*, *SUMF1*, and *PSAP* genes). A technical validation (for assay characteristics) has been performed utilizing the measurement of 500 random NBS samples. Five known infantile/adult MLD patient samples were also measured to define final cut-offs. Clearly elevated levels of C16: 0 and C16: 1-OH were found for all 5 MLD patients, C16: 1-OH significantly more. Final cut-offs for primary diagnostics were established in a pre-pilot study with circa 5,000 samples, including random controls older than 28 days. Data have shown that patient age group dependent cut-offs are critical, as the sulfatide concentrations were significantly lower in the NBS group compare to the >28 days subgroups. The combination of C16: 0 and C16: 1-OH sulfatide isoforms results in an improved positive predictive value compared to using only a single sulfatide. The study duration is planned for 12 months with an extension of three years. To date over 10,000 babies have been screened.

P-146 - ANALYTICAL VALIDATION AND POPULATION EVALUATION OF THE AUTOMATED ARCHITECT TSH CHEMILUMINESCENT MICROPARTICLE IMMUNOASSAY (CMIA) FROM ABBOTT ADAPTED TO BE USED IN NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

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INTRODUCTION: Analytical validation and population evaluation are required before implementation in routine of methods designed for determination in serum/plasma adapted for use in dried blood spots (DBS). **OBJECTIVE:** To present the analytical validation and population evaluation results corresponding to the automated Architect TSH kit (Abbott) designed for TSH determination in serum/plasma, adapted to be used in Newborn Screening for Congenital Hypothyroidism (CH), working on DBS.**MATERIAL AND METHODS:** Punching, elution and results calculation were made following the assay protocol adapted at Fundación Bioquímica Argentina. TSH determinations were made using the Architect TSH kit (CMIA) in two Architect $i2000_{SR}$ autoanalyzers (Abbott). Eluates measuring analytical range was experimentally determined. Recovery and precision were determined using control materials (CM) from NSQAP–CDC (3 levels, targets: 14.1, 23.4 and 48.9 µU/ml), and PerkinElmer (PE) (2 levels, targets: 15.1 and 60.5 µU/ml). For population evaluation, 810 normal TSH specimens from non-CH newborns (NB) and 17 abnormal TSH specimens (10 from non-CH and 7 from CH NBs) previously tested with AutoDELFIA Neonatal hTSH from PE were analyzed, TSH ranges [0.1-10.6] and [11.1-175.6] µU/ml, respectively. CMIA and PE results were correlated and compared. Preliminary and re-evaluated cut-offs were defined analyzing 810 and 28,249 NBs samples. For autoanalyzers responses comparison, 263 NB samples were tested in parallel. Reagents costs were also evaluated. **RESULTS:** Eluates measuring analytical range for DBS TSH calibration curves (0.7-273.0 µU/ml) was on average 0.0040-1.9000 µU/ml. Intra-assay CV's were < 8.6 % for PE-CM (4 runs, n=6). Inter-assay CV's were 13.2, 13.1 and 19.0 % for CDC-CM, and 11.1 and 10.4 % for PE-CM (20 runs, n=1). Analytical recovery using CDC-CM was 98.4, 86.0 and 92.1 %. Methods correlation was appropriate (TSH_{CMIA}= 0.730 TSH_{PE} + 0.213, r=0.934), showing a CMIA underestimation regarding PE. Preliminary and re-evaluated cutoffs were 7.0 and 8.5 µU/ml (99.3^{th} and 99.7^{th} percentiles, respectively). 807/810 non-CH NBs with normal PE TSH were normal by CMIA (99.63 %), and 10/10 non-CH and 7/7 CH NBs with abnormal PE TSH were abnormal by CMIA. Correlation between autoanalyzers was optimal: $TSH_{ARCHITECT\#2}$= 1.001 $TSH_{ARCHITECT\#1}$ + 0.083, r=0.997**. CONCLUSIONS:** Adapted Architect TSH assay showed appropriate analytical and diagnostic performance. Its functional sensitivity allowed optimal analytical response despite the specimen dilution. To highlight, reagent costs were much less expensive than those commercialized by other reagents manufacturers.

P-147 - PERFORMANCE EVALUATION OF A MULTIPLEX KIT FOR THE SIMULTANEOUS DETECTION OF IGM ANTIBODIES AGAINST TOXOPLASMA, RUBELLA AND HUMAN CYTOMEGALOVIRUS

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Intercientífica

INTRODUCTION: Serological diagnostics on newborn screening is extremely important for the prevention of congenital diseases, such as toxoplasmosis (Tox), rubella (Rub) and human cytomegalovirus (CMV). The traditional methods for diagnostics on newborn screening can detect a single analyte per assay. A multiplex assay can optimize the use of samples at the same time it decreases the time for results and use of consumables. **OBJECTIVE:** to evaluate the performance of a multiplex serological kit for the detection of IgM antibodies against three infectious agents simultaneously (Tox, Rub and CMV). **MATERIAL AND METHODS:** A total of 233 samples, balanced between positive and negative, characterized by the ELISA methodology were used as a reference. The samples were tested with a multiplex kit that uses a bead based technology (Luminex Corporation). The resulting data is expressed in Medium Fluorescence Intensity (MFI) and it was used on the R program with pROC package to verify sensitivity, specificity, area under the curve (AUC), agreement and the confidence interval at 95%. Precision (repeatability and reproducibility) was verified with CV. In addition, the analytical specificity of the method was verified using red blood cells only to demonstrate that no matrix component causes unwanted reactivity. **RESULTS:** the ROC analysis resulted in sensitivity of 98% for Tox, and 100% for Rub and CMV. The specificity was 100% for Tox and Rub and 83% for CMV. The AUC was 98.1% for Tox, 100% for Rub and 97.2% for CMV. The total agreement with the methodology used as reference was 98.8% for Tox, 100% Rub and 89.1% for CMV. The precision resulted in CVs below 15% in all tests between the triplicates, intra-assay and inter-assay studies. The results using red blood cells only were below the limit of detection, indicating no matrix effect**. CONCLUSION:** All the basic parameters to verify the performance of a new serological assay demonstrate that the multiplex kits perform with high agreement with reference ELISA methodology and with low imprecision. The kit is designed to run with dried blood spots, and the matrix comparison showed that there is no interference of red blood cells on the result.

P-148 - EXPANDED NEONATAL SCREENING PROGRAM IN THE MEXICAN ARMY HEALTH SERVICES. AN EXPERIENCE OF 8 YEARS.

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INTRODUCTION: In 2013, the Mexican Ministry of Health issued a new regulation that establishes the expanded neonatal screening as mandatory in Mexico, so that accordingly, the Mexican Army Health Services (SEDENA) decided to implement a new program for the detection of 68 congenital metabolic diseases. **OBJECTIVE:** To report the results obtained in the expanded neonatal screening program, implemented by SEDENA from December 2013 to November 2021. **MATERIALS AND METHODS:** Retrospective study of the neonatal screening database of the Mexican Army Health Services. All samples were obtained by heel puncture, impregnated on filter paper cards and analyzed using DELFIA/GSP®, tandem mass spectrometry, isoelectric focusing or high-performance liquid chromatography. **RESULTS:** A total of 60,028 newborns (NBs) were screened (29,237 female/30,791 male) in 38 military medical units distributed in 24/32 Mexican States. The average age of the sample collection was 7 days. 644 suspected cases were reported (repetition rate of 1.07%), 197 cases were confirmed (1: 305), with 435 false positives (0.72%), 7 deaths and 5 were not localized (0.78%). The most frequently detected diseases were: glucose 6-phosphate dehydrogenase deficiency (104) (1: 577); congenital hypothyroidism (50) (1: 1,201); congenital adrenal hyperplasia (16) (1: 3,752); cystic fibrosis (6) (1: 10,005); hemoglobinopathies (5) (1: 12,006), phenylketonuria (3) (1: 20,009); organic acidemia (6) (1: 10,005) and transient hyperthyrotropinemia (7) (1: 8,575). In addition, 398 carriers of hemoglobinopathies (1: 151) were not considered in the global statistics**. CONCLUSIONS:** The implementation of an expanded neonatal screening program in the Mexican Army Health Services and the correct management of the indicators have allowed the timely detection of inborn errors of metabolism, as well as a treatment set up before 16 days of life on average that allows to reduce complications, improve the quality of life and survival of patients.

P-149 - FIRST PRELIMINARY STUDY ON EXPANDED NEONATAL SCREENING OF INBORN ERRORS OF METABOLISM USING TANDEM MASS SPECTROMETRY (MS/MS) IN COLOMBIA

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INTRODUCTION: Inborn Errors of Metabolism (IEM) are congenital diseases, and their study generates epidemiological evidence that leads to defining strategies for an adequate diagnosis, management and treatment. The Malaria Vaccine and Drug Development Center (MVDC) with the advice of the Laboratory of Metabolism of Santiago de Compostela, the Asoclinic Laboratory and with funding from the Government of Valle del Cauca and the Ministry of Science and Technology, is the first Center to carry out Expanded Neonatal Screening by Tandem Mass Spectrometry (MS/MS) in Colombia. **OBJECTIVES:** Preliminary study to determine the prevalence of IEM dependent on amino acids (AA) and acylcarnitines (AC) using MS/MS in healthy and suspected newborns from Valle del Cauca. **MATERIALS AND METHODS:** A cross-sectional study is being carried out in healthcare centers from Valle del Cauca (Cali, Buenaventura, Palmira and Buga), for the screening of 30,000 healthy newborns and 1,500 infants with a suspicion of IEM. Heel blood discs are mixed with internal standards (isotopes) of AA, AC and Succinylacetone. The extracts are evaporated (N2(g)), derivatized (ButOH) and reconstituted for the quantification of 60 metabolites for the screening of 35 IEM (Amino acidopathies, organic acidurias and fatty acid-beta oxidation disorders). The samples are injected using a liquid chromatograph and measured by MS/MS (QTrap 3200, TQ 4500 and API 3200, Sciex). External quality control is performed with the CDC's NSQAP quality assurance. **RESULTS:** Until December 2021, 3,096 healthy newborns and 220 infants with suspicion of IEM had been screened. No confirmed cases of IEM have been detected so far. The values of the concentration of the metabolites and their ratios are within the percentiles P1, P5, P95 and P99 calculated, indicating normal magnitudes for newborns. The collected data meet the assumptions of homoscedasticity and normality of errors (Shapiro-Wilks, $p>0.05$)**. CONCLUSIONS:** In the samples studied in both, healthy newborns and infants with suspicion of IEM, no cases associated with IEM have been detected. Despite its limitations, this study currently gives children and their families the option of being tested in the country and in the long term the creation of an expanded national screening program.

P-150 - NEONATAL SCREENING OF INBORN ERRORS OF METABOLISM THROUGH TANDEM MASS SPECTROMETRY IN YUCATAN, MEXICO: A 14 YEARS EXPERIENCE.

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INTRODUCTION: Tandem mass spectrometry (MS/MS) has achieved a radical change in neonatal screening programs for congenital metabolic diseases since, with a single analytical procedure, specific biomarkers can be measured in order to detect about 40 diseases simultaneously, in the same dried blood sample on filter paper. **OBJECTIVE:** To show the results of the expanded neonatal screening program in the state of Yucatan, Mexico, for the detection of inborn errors of metabolism (IEM) using the MS/MS technique. **MATERIALS AND METHODS:** Retrospective study of 211,683 newborns (NBs), screened from December 2008 to October 2021, the samples were analyzed by MS/MS (NeoBase Nonderivatized® Kit Perkin Elmer). All suspected cases were confirmed by analysis of organic acids in urine by gas chromatography coupled to mass spectrometry (GC/MS) and quantification of amino acids in blood by high-performance liquid chromatography. **RESULTS:** 356 suspected cases were found, of which 349 were located (98.3 %). In 33 cases, the presence of an IEM was confirmed (1: 6,415), of which 17 were organic acidemias (1: 12,452) and 16 aminoacidopathies (1: 13,230). The most frequently found IEMs were glutaric acidemia type 1 (6) (1: 35,281), propionic acidemia (4) (1: 52,921), citrullinemia (4) (1: 52,921), tyrosinemia (3) (1: 70,561), 3-methyl crotonyl CoA Carboxylase (3) (1: 70,561), 3-hydroxy-3-methylglutaric acidemia (2) (1: 105,842), hyperphenylalaninemia (2) (1: 105,842), MSUD (2) (1: 105,842), and one case for methylmalonic acidemia, isovaleric acidemia, SCAD, VLCAD, argininemia, phenylketonuria, and glycine metabolism disorder (1: 211,683) respectively**. CONCLUSIONS:** The application of the MS/MS technique in the neonatal screening program in Yucatan has established that in the Yucatecan population IEMs have prevalence at birth of 1.56 x 10,000 NB (1: 6,415). This high prevalence highlights the importance of early detection to prevent

disability. It is important to emphasize the importance of having an optimal location of suspected cases (98.3 %), in order to know the prevalence at birth of these EIM.

P-152 - DETECTION OF NEWBORNS IN THE NEONATAL SCREENING PROGRAM OF THE HEALTH SERVICES OF THE MEXICAN NAVY: AN EXPERIENCE OF 9 YEARS.

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INTRODUCTION: The Expanded Neonatal Screening Program aims to detect congenital metabolic disorders in a timely manner, which could otherwise have serious clinical consequences. Today, newborn screening is part of the health care system from a large number of countries and institutions. Since 2012, the Mexican Secretariat of the Navy (SEMAR) has implemented a program to detect 78 inborn errors of metabolism in newborns. **OBJECTIVE:** To inform the results obtained by the Expanded Neonatal Screening Program of SEMAR from July 2012 to November 2021. **MATERIALS AND METHODS:** 22,835 blood samples were taken from the newborn (NB) heel in 32 medical units of SEMAR, located in 18 states of Mexico. All samples were analyzed by immunofluorometric assays (Auto DELFIA©/GSP©), tandem mass spectrometry, isoelectric focusing and high-performance liquid chromatography. **RESULTS:** 22,835 NBs were screened (11,002 girls/11,832 boys); 70% of the samples were taken between 4 ± 1 days of age, 344 samples were considered suspicious cases, 92.73% (319) were located and re-examined, 25 NBs were not located (7.27%). 98 cases were confirmed, with a false positive rate of 0.97% (221). The diseases detected were: congenital hypothyroidism (22), congenital adrenal hyperplasia (12), glucose 6 phosphate dehydrogenase deficiency (54), sickle cell anemia (3), cystic fibrosis (4), isolated 3-methylcrotonyl CoA Carboxylase deficiency (1), propionic acidemia (1) and galactosemia (1). 332 hemoglobinopathies carriers were also detected and were not considered in the global statistics. All confirmed cases began specialized medical treatment on average at 16 days of age. All affected families received genetic and reproductive counseling**. CONCLUSIONS:** In the population studied, the prevalence of metabolic congenital defects was 1: 233, being possible to establish that the two most prevalent are glucose-6-phosphate dehydrogenase deficiency (1: 423) and congenital hypothyroidism (1: 1,038). The expanded screening program allowed its early detection, diagnosis and intervention to prevent death or disability, actions that contribute to improving the quality of life of the newborns detected.

P-153 - PILOT PLAN FOR IMPROVEMENT OF NEWBORN SCREENING SAMPLES TRANSPORTATION IN COSTA RICA

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INTRODUCTION: In Costa Rica, neonatal screening began in 1990, improving year after year its coverage at the national level, achieving coverage close to 98% in recent years. All newborn screening assays are performed in the same laboratory facilities located in San José, Costa Rica's capital. The samples are collected through collaboration by a network comprised of more than 1000 health centers located throughout the country. Therefore, all newborn samples collected in these centers require appropriate transportation and delivery to the newborn screening laboratory facilities. The samples are transported and delivered by the National Postal Company (NPC), the national health system's messaging service, and by other alternatives. However, to improve and standardize the pre-analytical conditions of transport, a pilot plan is going to be performed from January to April 2022 with NPC through Express Mail Service (EMS). **OBJECTIVE:** To describe the selected indicators and quality criteria to evaluate the sample transport pilot project and elaborate a normalized methodology for packaging and transporting samples for neonatal screening. **MATERIALS AND METHODS:** The pilot plan includes 20 health centers located in different geographic areas of the country. There are 3 peripheral hospitals, 6 regional hospitals, and 11 health areas. An integral work team was formed to monitor the selected indicators and monitor the execution of the plan. A standardized methodology was defined for the entire sample transport process. **RESULTS AND CONCLUSIONS:** Two infographics have been obtained, prepared as a very useful didactic resource, and a detailed diagram of the entire sample transport process, which will serve as a guide for the development of similar pilot plans for screening programs in countries of the region. In addition, a preliminary 30% decrease in sample transit time and greater control and monitoring of the traceability of the sample shipment process,

and improved communication with sample collection centers have been obtained during the first month of this pilot plan.

P-154 - ASSISTANCE AT THE REFERENCE SERVICE IN NEONATAL SCREENING OF AMAZONAS BETWEEN 2020 AND 2021 DURING COVID-19 PANDEMIC

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INTRODUCTION: The Reference Service in Neonatal Screening of Amazonas (SRTN) assists patients screened for five diseases, which are phenylketonuria (PKU), congenital hypothyroidism (CH), cystic fibrosis (CF), congenital adrenal hyperplasia (CAH) and biotinidase deficiency (BD). Amazonas is a Brazilian state with 62 municipalities and access between them is by waterway or air transport. All newborn screening collections are sent to a single laboratory in Manaus and diagnosed patients are treated in a single service. During the pandemic, transport between municipalities was often suspended. The SRTN has not stopped caring for its patients, giving priority to first-time cases and facilitating drug prescriptions for patients under follow-up. **OBJECTIVES:** Describe the care provided to patients of the Reference Service in Neonatal Screening of Amazonas during the COVID-19 pandemic between 2020 and 2021. **MATERIAL AND METHODS:** This is a quantitative descriptive study of patients treated at SRTN during 2020 and 2021 using local data. **RESULTS:** In 2020, 30 first-time patients with CH were treated. The median age at first consultation was 90 days. Six first-time patients with CAH were seen, with median age of 22.5 days. Only 1 patient with PKU and 1 patient with CF were diagnosed and treated. No patient was diagnosed with BD. In 2021, 26 first-time patients with CH were diagnosed, with median age at first consultation of 56 days. 5 first-time patients with CAH were treated, with median age of 34 days. Attended 4 first-time patients with PKU, the median age at the first consultation being 45 days. Five patients with CF were treated, median age being 49 days. Only one patient was diagnosed with BD**. DISCUSSION:** During the pandemic, the SRTN maintained its multidisciplinary service and provided early diagnosis and follow-up for patients and its families, even with all the difficulties. Nevertheless, it is impossible to calculate the coverage of the service during the pandemic, due to lack of registration of live births in official sources. Despite this, all efforts were made to provide the best treatment to patients and minimize obstacles faced in their multidisciplinary follow-up.

P-155 - VIRTUAL TRAINING AND FOLLOW-UP SURVEILLANCE TO NEONATAL SCREENING COLLECTION CENTERS DURING THE COVID 19 PANDEMIC YEARS 2020-2021.

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INTRODUCTION: In Costa Rica, newborn screening sampling is carried out throughout the country by different public Health Centers from hospitals and primary and basic health services, as well as private health services. There is a considerable percentage of inadequate samples, historically has been around 4%. In 2019, nursing professionals were incorporated into the National Newborn Screening Program. They are responsible for training health personnel to carry out blood sampling for newborn screening and monitoring of collection centers. During the last 2 years (2020-2021), due to the COVID-19 pandemic, training and all educational activities had to be carried out through virtual platforms. **OBJECTIVE:** To evaluate the impact of virtual training and follow-up on neonatal screening collection centers during the COVID 19 pandemic years (2020-2021) through quality indicators for blood sample collection. **MATERIALS AND METHODS:** Descriptive and qualitative analysis was applied based on the statistical data of quality indicators for 82 newborn screening collection centers. In these centers a total of 1276 people were trained for newborn sample collection, using Zoom and Microsoft Teams virtual platforms. The centers selected for this study represent a high percentage of inadequate samples in past years. Quality indicators are described for 2020-2021. The percentage of inadequate samples is accounted for in each analyzed center, based on quality and quantity parameters of dried blood samples on filter paper sent to the National Newborn Screening Laboratory. **RESULTS:** An average of 50% decrease of inadequate samples (insufficient quantity and poor quality), and a 10% improvement in quality indicators: Transit Time and Age of Sample Collection and greater scope in training and sensitization to health personnel to carry out blood sampling for the newborn screening was observed in this

study. **CONCLUSIONS:** The use of virtual platforms implies greater coverage for training purposes since it allows the participation of more health personnel at the same training session, and it allowed training and follow-up surveillance during the COVID-19 pandemic years 2020-2021, reducing the number of unsatisfactory samples and improving some quality indicators.

P-157 - PROPOSAL OF INFORMATIVE MATERIAL FOR THE NEWBORN SCREENING PROGRAM IN GUATEMALA.

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INTRODUCTION: Newborn screening (NBS) was established at Hospital Roosevelt in 2003. Until 2017 newborns were screened at 24-48 hours of birth, in 2018 -due to the implementation of Total Galactose and Phenylalanine testing-, parents were asked to attend for sample collection from the 3rd to 7th day of birth, decreasing coverage. To improve the coverage of the NBS an initiative of informative material about NBS addressed to parents and health personnel was proposed. **OBJECTIVE:** To develop a proposal for informative material about the NBS to support the learning and knowledge of parents and health personnel. **MATERIALS AND METHODS:** Descriptive study, with a population of 300 pregnant, 30 health personnel, and 3 NBS expert professionals. Phase 1: Collect information about basic knowledge of NBS through surveys and interviews. Phase 2: Design of communication strategies and graphic content. Phase 3: Validation of the informative material by graphic designers, NBS professionals and pregnant. **RESULTS:** 81% of pregnant had a prenatal control, 69% were willing to perform an exam on the baby, 85% of pregnant did not know about NBS, and 30% had not interest in doing it. All of the interviewed health personnel considered pediatric follow-up and control after birth to be important and 73% did not have available the necessary materials to provide information and did not receive training about NBS. A brochure about generalities of NBS, diseases detected, NBS procedure and appointment sheet was developed. **DISCUSSION AND CONCLUSIONS:** Pregnant did not have a proper level of information about NBS and its benefits; therefore they did not go to the hospital for their NBS appointment. However, they had constant prenatal care and were in agreement to perform NBS tests. Health personnel were not able to provide information about NBS because they did not have the required knowledge. The informative material was developed using pictures that emphasize and reflect the normal process that was carried out on newborns without any damage. These studies are important to develop informative material according to the characteristics of the population and achieve greater coverage in NBS programs, having an approach from prenatal control, increasing the education of parents and health personnel.

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